Textbook of Cardiorenal Medicine

Peter A. McCullough
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Dedicated to:

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Preface

Cardiorenal medicine is an emerging multidisciplinary field that spans a wide spectrum of disease that affects both the cardiovascular and renal systems. It also uniquely highlights how one organ system can affect the other in both health and disease. Cardiorenal medicine has a stout scientific foothold in epidemiology, pathophysiology, diagnosis, prognosis, and management. The bourgeoning medical literature concerning cardiorenal medicine in these areas is testament to the growing base of new knowledge in this field.

The inaugural edition of Cardiorenal Medicine is the culmination of a bold and ambitious project that sought out experts across the globe to put their thoughts into text, tables, and figures for the reader to learn and gain new insight into this field of medicine. The term "cardiorenal medicine" harkens for collaboration and for careful understanding that living organisms are organized into systems, and that those systems inter-relate and rely on one another in both health and disease. It also intimates that multisystem disease such as diabetes mellitus greatly influences both organ systems and those changes in turn impact the next phases of disease in both organs. Lastly, cardiorenal medicine implies that in vitro diagnostics and therapeutics are very likely to have clinical implications and, in some cases, direct application to both organs.

This text is a tribute to each and every contributor who is an expert in his or her fields. We are indebted to Springer Publications and their assiduous pursuit of materials for publication with all the sudor of publisher working through a global pandemic. It also commemorates a lifetime of professional dedication and tireless effort by Dr. Claudio Ronco of Vicenza and Padua, Italy. Professor Ronco was the original inspiration for this text and through his vision we are "carpe diem" or seizing the day of science where cardiologists, nephrologists, intensivists, and primary care physicians can come together in the best interests of medical science for the benefit of their patients and generations to come.

Dallas, TX, USA — Peter A. McCullough

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1 Implications of Chronic Kidney Disease on the Epidemiology of Cardiovascular Disease

Peter A. McCullough and Aaron Y. Kluger

1.1 Introduction

The heart and the kidneys are inextricably linked via hemodynamic, neural, hormonal, and cellular signaling systems. The kidneys are the most vascular organ in the body receiving a quarter of cardiac output at rest despite a distal location from renal arteries branching from the aorta. Thus, follows that kidney disease is strongly associated with cardiovascular illness and in fact, may be considered more than a cardiovascular risk factor and better termed as a cardiovascular risk state. Additionally, when either organ sustains injury or begins to fail, there appears to be a consequential affect on the other organ in either an adaptive or maladaptive response that we now recognize as a "cardiorenal syndrome(s)" [1]. This chapter will review the connections between the heart and the kidneys from epidemiological, biological, and clinical perspectives with the aim of gaining greater appreciation for this important interface in both acute and chronic care.

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1.2 Cardiovascular Risk in Chronic Kidney Disease

The Chronic Kidney Disease Prognosis Consortium (CKD-PC) was established in 2009 by Kidney Disease: Improving Global Outcomes (KDIGO) organization in an attempt to understand the risks of declining renal filtration function represented by the estimated glomerular filtration rate (eGFR) and the presence of albumin in the urine indexed to the filtered creatinine concentration (urine albumin:creatinine ratio [ACR]). In a series of manuscripts, this group demonstrated in a very large, pooled database (1,555,332 subjects in 45 cohorts), that the severity of chronic kidney disease (CKD) was related to the risks of all-cause mortality, cardiovascular death, acute kidney injury, progressive CKD, and end-stage renal disease (ESRD) [2]. These relationships can also be shown in a "heat map" of risk. It is important to understand that when both eGFR and elevated ACR overlap, there appears to be magnified risks for all outcomes. Data from the National Kidney Foundation Kidney Early Evaluation Program (KEEP) and the National Health and Nutrition Examination Survey suggest that the majority of individuals with CKD in the younger age groups are identified by albuminuria while those in the older age strata have reduced eGFR (<60 mL/min/1.73 m^2) as the CKD marker. Importantly, the overlap between the two markers is less common than one alone in

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these large populations. However, when both reduced eGFR and albuminuria are present in the same patient the predicted and observed rates of cardiovascular events are markedly increased over a relatively short (<5 years) duration. Thus, it is critical that in every patient, both the eGFR be calculated from the age, gender, race, and serum creatinine using standardized equations and that the urine ACR be checked on a first morning voided specimen. Structural kidney disease detected by imaging studies including polycystic kidney disease also are characterized as CKD in the absence of eGFR and ACR abnormalities. The CKD-PC was limited in terms of nonfatal cardiovascular outcomes; therefore, we must turn our attention to other sources of information to understand the connections to coronary atherosclerosis, myocardial disease, valvular disease and arrhythmias.

The term "reverse epidemiology" has been applied to patients with ESRD for many risk factors, particularly body weight. What this means is that in the general population, increased adiposity as expressed with the body mass index is consistently associated with cardiovascular events and reduced survival. However, in ESRD, increased BMI confers improved survival. This suggests that increased adiposity is the inverse of cachexia. That is, as chronic disease progresses, cachexia and reduction in weight is along common pathway towards inanition and death. Thus, retention of adiposity is associated with survival. Reverse epidemiology has also been observed with total cholesterol and albumin which are proxies for nutritional intake and are epidemiologically inversely related to the degree of cachexia.

1.3 Coronary Heart Disease

Data from many studies suggests that the CKD milieu promotes the early initiation and accelerated course of coronary atherosclerosis. Because CKD is strongly associated with traditional coronary risk factors including hypertension, diabetes, dyslipidemia, and smoking, the combination of these factors may be reflected by CKD and thus its relationship is amplified by positive confounding. However, when adjusting for these factors, CKD has been consistently associated with nonfatal myocardial infarction and cardiovascular death [3]. A prominent feature of coronary atherosclerosis in patients with CKD and ESRD is accentuated calcification which occurs in all cases of atherosclerosis when reviewed at necropsy. Initially, calcium deposits on cholesterol crystals in the subendothelial space [4]. However, the progression of atherosclerosis involves a multitude of local and systemic factors which stimulate vascular smooth muscle cells to undergo osteoblastic transformation into osteocyte-like cells which deposit calcium hydroxyapatite crystals into both the subendothelial and medial compartments of blood vessels. Many factors have been implicated in CKD to accelerate this process including low-density lipoprotein cholesterol, non-high density lipoprotein cholesterol, vascular calcification factor, osteoprotegerin, and most notably phosphorus [5]. As eGFR falls, there is retention of phosphate which can stimulate the Pit-1 receptor on vascular smooth muscle cells thereby facilitating the osteoblastic transformation [6]. Of note, neither dietary calcium or the plasma concentration of calcium have been independently associated with calcific deposits in the coronary arteries. As CKD progresses, coronary artery disease is commonly identified on a variety of clinical studies, frequently as longer lesions and in more proximal vessels [7]. Fortunately more extensive calcification while it is related to the burden of coronary disease, is also associated with more stable lesions, thus, CKD patients often have stable but extensive CAD leading to episodes of both silent and symptomatic coronary ischemia.

It has been suggested that there are both traditional and non-traditional risk factors that may contribute to more accelerated atherosclerosis in persons with CKD. The traditional risk factors include: elevated LDL-C, hypertension, diabetes mellitus, smoking, family history of premature coronary heart disease (first degree relative female before age 55 and male before age 45 years). Nontraditional risk factors in CKD have been variously mentioned in the literature

and include blood markers of mineral and bone disorder (hyperphosphatemia, elevated calcium-phosphorus product, osteopontin, hyperparathyroidism, fibroblast growther factor-23), C-reactive protein, uremia, asymmetric dimethylarginine and reduced nitric oxide availability, anemia, hyperuricemia, increased unbound iron (catalytic or poorly liganded iron), homocysteine, fibrinogen, and increased coagulation proteins. None of these factors has been sufficiently tested in prospective studies to be considered a therapeutic target for prevention in CKD patients with atherosclerosis.

1.4 Heart Failure

Chronic kidney disease promotes the three major pathophysiologic mechanisms by which the left ventricle can fail: pressure overload, volume overload, and cardiomyopathy. Because hypertension is both a determinant and a consequent of CKD, the vast majority of CKD patients have longstanding histories of elevated blood pressure and increased cardiac afterload resulting in left ventricular hypertrophy and increased left ventricular mass [8]. Salt and water retention result in chronic volume overload. Nephrotic syndrome and loss of oncotic forces results in worsened fluid retention and edema. Uremia and retention of many substances (indoxyl sulfate and p-cresol) results in impaired myocyte function in both systole and diastole. It has become recently understood that production of fibroblast growth factor-23 from bone in response to CKD phosphate retention, has off-target effects on the left ventricular myocardium resulting in increased left ventricular mass and cardiac fibrosis. The resultant myocardial tissue has a reduced capillary density compared to that of persons with normal renal function. Considerable evidence is accumulating that "CKD cardiomyopathy" is manifest by impaired systole and diastole with biomarker and imaging evidence of cardiac fibrosis. The observation that galectin-3 levels correlate with type III aminoterminal propeptide of procollagen, matrix metalloproteinase-2, and tissue inhibitor of metalloproteinase-1 suggests that myocardial macrophage infiltration enhances turnover of extracellular matrix proteins in patients with CKD [9]. Thus, patients with CKD are at very high risk for the development of heart failure associated with markedly impaired cardiorespiratory function and the cardinal features of fatigue, effort intolerance, edema, and clinical findings including pulmonary congestion and elevation of B-type natriuretic peptides (BNP and NT-proBNP) [10]. When acutely decompensated heart failure is present, then a viscous cycle of worsened renal filtration function, venous and renal congestion, and further retention of salt and water can occur. This is commonly termed cardiorenal syndrome type 1 [11].

It has become increasingly recognized that hemodialysis itself may contribut to myocardial disease through process of "myocardial stunning" where there are transient wall motion abnormalities that are related to episodes of hypotension during hemodialysis. The greater the number of segmental wall motion abnormalities, the worsened survival over time (Fig. 1.1). Recent analyses suggest short daily hemodialysis in the home setting is associated with fewer episodes of intra-dialytic hypotension, regression of left ventricular hypertrophy, and a 41% lower risk of heart failure, fluid overload, and cardiomyopathy [12]. At very low ultrafiltration rates over longer periods of time, the removal of fluid from the intravascular space may better match the rate of plasma refill from the extravascular space, and thus, avoiding hypotension and myocardial stunning.

1.5 Valvular Calcific Deposits and Complications

Accelerated aortic valvular and mitral annular calcification and fibrosis is common in patients with CKD and nearly universally present in patients with ESRD. The murmur of aortic valve sclerosis is found in the majority of patients while the mitral annular disease is usually silent and detected only by echocardiography or other forms of imaging. The aortic valve sclerosis and calcification can progress to symptomatic aortic

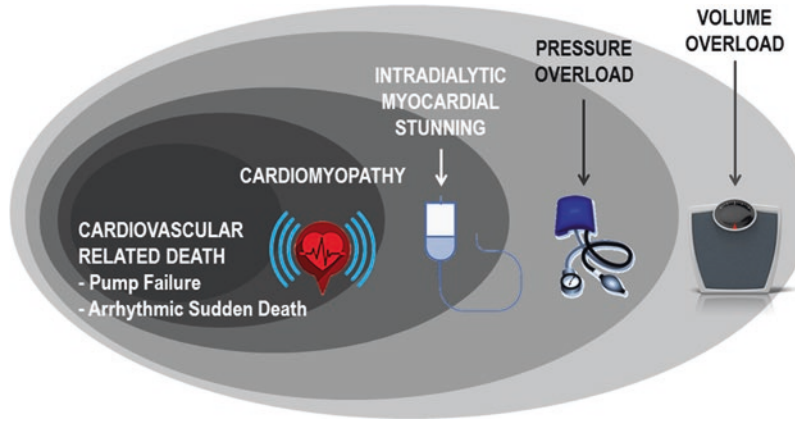

Fig. 1.1 Pathophysiologic rationale for myocardial stunning in ESRD on hemodialysis

stenosis while the mitral annular disease can result in very mild functional stenoses or regurgitation by Doppler but rarely requires surgical attention. Recent studes have linked elevations in lipoprotein (a) which occur in ESRD to the development of calcific aortic stenosis [13]. Both valvular lesions can be the substrate for acute infective endocarditis in ESRD patients with temporary dialysis catheters and occurs at a rate of 6–8% per year. Staphylococcus aureus is the main cause (75%) of vascular access-related bacteremia among patients receiving long-term hemodialysis. When endocarditis occurs in this setting, the operative mortality rate can be in excess of 50% [14]. Most patients with CKD should undergo echocardiography at some point in their care in order to evaluate not only for the extent of valve disease but also to assess left ventricular systolic and diastolic function.

1.6 Arrhythmias

Patients with CKD have the myocardial and hemodynamic determinants of all forms of arrhythmias. In the United States Renal Data System database, 62% of cardiac deaths (27% of all deaths) are attributable to lethal arrhythmias [15]. Atrial fibrillation occurs at an elevated rate in patients with CKD and is associated with an increased risk of cardioembolic stroke compared to those with normal renal function at all levels of the CHA_2DS_2-VASc score. Recent data are supportive of apixaban (either 2.5 mg or 5 mg p.o. bid) potentially in place of warfarin for CKD patients with nonvalvular at high risk of stroke or systemic embolism [16]. Because of accelerated myocardial fibrosis and the presences of both macrovascular and microvascular disease, reentrant ventricular tachycardia is believed to be the prelude to ventricular fibrillation followed by asystole and sudden death. Increased premature atrial and ventricular beats when seen on monitoring can be harbingers of atrial fibrillation and ventricular tachycardia, respectively. Electrolyte shifts, and particularly changes in potassium concentration that occurs in CKD and is accentuated with forms of dialysis are also believed to play a role in ventricular arrhythmias and sudden death, most likely due to ventricular fibrillation. The role of implantable cardio defibrillators is controversial at the time of this writing given shortened survival and the risks of device and lead infection in ESRD [17]. Each guidelines-based approach in the population of patients with heart disease and normal renal function is complicated by increased adverse events and even iatrogenic death in patients with CKD and ESRD [18]. Thus, therapy must be individualized and very frequent monitoring is required.

1.7 Summary

The connection between kidney and heart disease can be viewed in four domains: coronary atherosclerosis, myocardial disease, valvular abnormalities, and arrhythmias. Chronic kidney disease

plays a role in the epidemiology, pathogenesis, presentation, outcomes, and management of each manifestation of CVD. Future research is needed to better understand the unique mechanisms at work in patients with CKD that promotes and worsens CVD outcomes. Practical strategies are needed to guide clinicians towards most appropriate medical and procedural management of this high-risk population.

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2 Prevalence and Progression of Cardiovascular Calcification in the General Population and Patients with Chronic Kidney Disease

Paolo Raggi and Antonio Bellasi

2.1 Coronary Artery Calcium as a Marker of Atherosclerotic Vascular Disease in the General Population

Atherosclerosis development is almost universal during human life [1] and coronary artery calcium (CAC) has been known for centuries to be an intrinsic component of the disease. CAC is accumulated through active processes of calcification resembling hydroxyapatite bone formation and not simple precipitation of crystals [2]. To date, it is still unclear whether CAC is deposited in an attempt to heal the atherosclerotic plaque, or whether it is part of an ongoing process of inflammation and damage of the subintimal arterial layer. However, it has become very clear that the presence of CAC is a harbinger of poor outcome. The demonstration that CAC carries an adverse prognostic value was obtained with fluoroscopy [3] even before the introduction of fast computed tomography, but it was only with the latter that non-invasive quantification of CAC became possible [4].

CAC seen on cardiac CT imaging can be quantified with 3 different scores. The Agatston score [4] is the product of the area of a calcified lesion by the peak density within the lesion. Although this score is exquisitely sensitive to the calcium content of a plaque, it is poorly reproducible and it is therefore not recommended for sequential scanning. The volume score [5] is the sum of all voxels within a calcified plaque with an attenuation (i.e radiological density) greater than 130 Hounsfield units. This score was introduced to overcome the limited reproducibility of the Agatston score and it is recommended for sequential CT studies. Finally, the mass score [6] is an actual measure of calcium content in the plaque, and it requires the positioning of a calcium phantom underneath the patient while acquiring the CT scans, but it is rarely used.

In the general population the extent of CAC measured on CT imaging is closely associated with the burden of atherosclerosis, and it is generally believed that CAC represents 15–20% of the total plaque burden [7, 8]. CAC can be seen as the final product of a long time exposure to risk factors for atherosclerosis [9, 10], and as such it is loosely correlated with the Framingham risk score (FRS) [11]. However, a substantial number of patients at risk of atherosclerotic events have no CAC on a screening CT [12, 13], and their event rate is extremely low [13, 14].

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The impact of risk factors is not equal among men and women and among subjects of different ethnic groups [15]. For example black patients have a lower prevalence and smaller amounts of CAC compared to white patients [16–19], despite having more risk factors for atherosclerosis than Whites [20]. However, black patients with CAC tend to have a worse prognosis than Whites [16].

The investigators of the Multi Ethnic Study of Atherosclerosis (MESA) performed CAC screening in 6814, 45–84 year-old patients of White, Hispanic, Black and Chinese ethnicity [21]. The prevalence and magnitude of CAC were higher in Whites, followed by Chinese, Hispanic, and black patients [22]. As shown in several other databases, the prevalence and extent of CAC were higher in men than in women of all ethnicities, and a good proportion of patients had no CAC despite the presence of risk factors. Women have smaller arteries than men [23–26], and the volume of atherosclerosis and CAC that can be accommodated in their arteries are therefore smaller than that of men. Additionally, women tend to develop atherosclerosis 10–15-year later than men and this is reflected in the delayed appearance of CAC on cardiac CT screening [27].

Nomograms of CAC scores have been used to describe the age and sex prevalence of subclinical atherosclerosis in several studies [27–29]. Raggi et al. [30] demonstrated that CAC nomograms help to assess risk among patients with a low absolute CAC score, but a high score relative to subjects of similar age and sex. In a study of 632 asymptomatic subjects referred for CAC screening and followed for 32 ± 7 months, patients with high absolute CAC scores had a high risk of myocardial infarction. However, the majority of patients had a small absolute CAC score, but investigators noted that the majority of these patients had a high score percentile. This suggested that they had accumulated a critical burden of atherosclerosis too quickly and too large for their age.

The utility of CAC as a marker of risk for future cardiovascular events has been tested in numerous studies in the general population. Probably the most representative are 2 large population studies; the MESA -mentioned above- and the Heinz Nixdorf Recall (HNR) study conducted in the Ruhr area in western Germany. Both studies showed that increasing CAC scores are associated with a progressively increased risk of cardiovascular events [31, 32], and CAC adds incrementally to traditional risk factors for atherosclerosis for the prediction of events [32, 33]. The same investigators incorporated CAC scores in a new risk score algorithm derived from the MESA and validated with data from the HNR data and the Dallas Heart Study (DHS) [34]. They showed that incorporating CAC scores into a prediction model increased its ability to identify patients at risk of events (C-statistics improvement from 0.75 to 0.80; $p < 0.0001$), with excellent discrimination and calibration.

Several other methods to assess extent of CAC besides the classic methods described above were shown to be predictive of events. Some of the reported methods include: number and location of calcified lesions in the coronary artery tree [35], distribution of calcified lesions along the course of the coronary arteries [36], coverage of the coronary artery length with calcific plaques [37], and presence of low attenuation (i.e. density) plaques [38]. The latter is of particular interest for the purpose of comparing risk assessment by means of CAC in the general population and in patients affected by CKD. For the general population the presence of low attenuation plaques may be indicative of plaques with a larger lipid content, hence fragile and more prone to fracture. In patients with CKD, the pathophysiology of calcium accumulation in the vasculature is likely very different and, as discussed later in this chapter, risk increases with increasing plaque density [39].

The utility of CAC screening in the general population extends to its very high negative predictive value. Among 19,898 patients without CAC at screening, the 10-year mortality rate was 0.87%, while it rose to 7.8% among the 18,767 with a CAC score > 10 [40]. Esteves et al. showed that without CAC on a screening chest CT, 99% of the simultaneously performed nuclear stress tests were negative for inducible myocardial ischemia [41]. Based on several other publications

showing a similar trend, the recent guidelines of the American Heart Association and American College of Cardiology on treatment of dyslipidemias added for the first time a consideration for "de-escalation" of treatment in patients at intermediate risk in the absence of CAC [42]. On the other hand the presence of CAC should increase the level of risk and stimulate an intensification of treatment [42].

In view of its excellent specificity for the presence of atherosclerosis in the arterial wall, some investigators thought that sequential CAC imaging might be useful to assess effectiveness of anti-atherosclerotic therapies. Initial observational studies with statins seemed to prove that these drugs delay progression of CAC [5, 43]. However, further randomized trials disputed these initial observations [44, 45], and careful metanalyses even showed an increase in CAC score in patients treated with lipid lowering agents [46, 47]. As a consequence, current guidelines discourage use of sequential CAC imaging in the general population for the mere purpose of gauging effectiveness of therapeutic interventions. As discussed in more detail in the next section, the situation is different in patients with CKD likely due to the different pathophysiology of vascular calcification in those patients.

2.2 Cardiovascular Calcification in Chronic Kidney Disease

2.2.1 Pathogenesis

Cardiovascular calcification (CVC) is highly prevalent in patients with CKD [10, 48] and it involves both arterial conduits and cardiac valves (Figs. 2.1 and 2.2). As such, it is regarded as an important marker of CV risk in this fragile population [49].

Accelerated CV senescence has been postulated as one of the mechanisms potentially responsible for development of CVC and CV risk in patients with CKD [50]. It is notable that CVC becomes more prevalent and severe as renal function declines, independent of age [51]. Additionally this marker of vascular damage is less closely associated with atherosclerotic risk factors than in the general population [52]. Calcified coronary artery plaques are larger and atherosclerotic plaques contain more calcium than in the general population [53].

Although it is unclear if medial calcification develops in the coronary arteries, considered to be medium size arterial conduits, a few reports suggested that in patients with advanced CKD subintimal and medial calcification may coexist. The two most likely coexist in larger size arteries such as the carotid arteries and the aorta [2]. While sub-intimal calcification has been traditionally associated with atherosclerosis, medial calcification seems connected with non-traditional CV risk factors such as inflammation, oxidative stress, advanced glycation end products (AGEs) accumulation, derangement of bone and mineral metabolism, uremic toxins and deficit of inhibitors of CVC [2, 48, 50].

Several in-vitro and in-vivo data suggest that abnormalities of calcium and phosphate homeostasis may influence the development of CVC [54]. In physiologic conditions, inhibitors such as phyrophosphate, matrix-GLA protein (MGP) or fetuin-A prevent minerals from aggregating, forming insoluble crystals of hydroxyapatite that precipitate in soft tissues including the blood

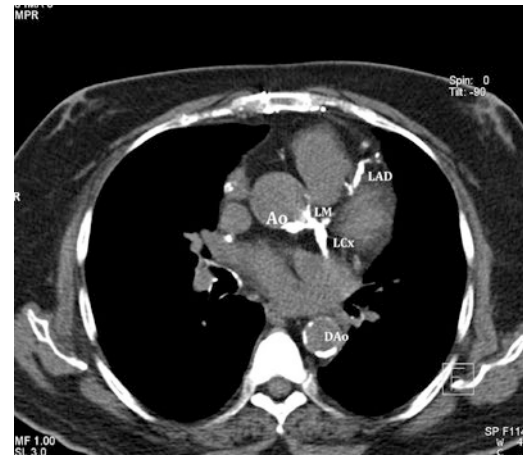

Fig. 2.1 Axial computed tomography image of the heart showing heavy calcium deposits in the ascending aorta (Ao), left main trunk (LM), left anterior descending artery (LAD), left circumflex artery (LCx) and descending thoracic aorta (DAo)

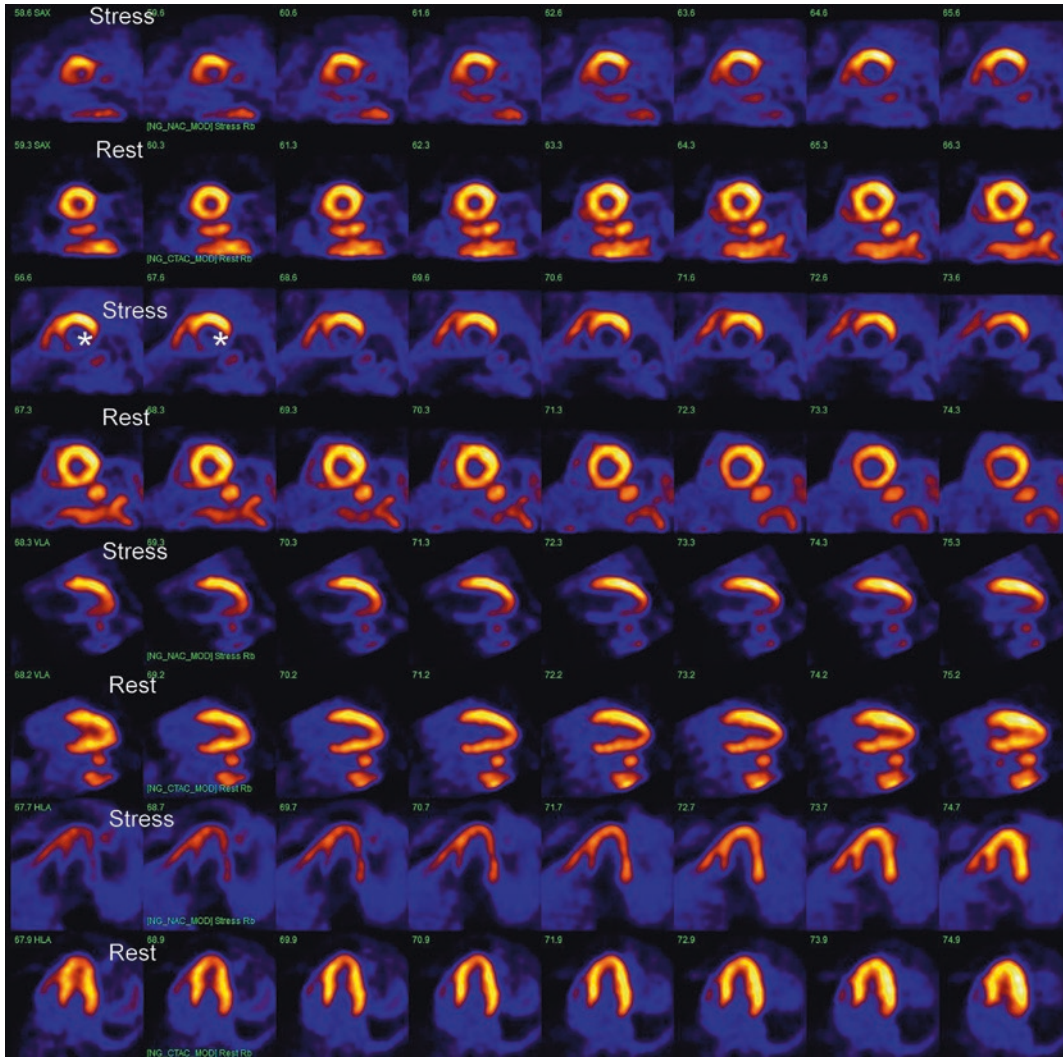

Fig. 2.2 Positron emission tomography (PET) stress test in the same patient as above showing a large perfusion defect after stress involving the entire inferior wall of the left ventricle (part of the defect is indicated by the asterisks). The perfusion defect is entirely reversible at rest. Note that the distribution of coronary calcium and areas of ischemia often do not correspond; therefore it is incorrect to use distribution of coronary artery calcium to predict inducibility and location of myocardial ischemia

vessel walls [2, 48, 54]. Preclinical data show that incubation of vascular smooth muscle cells (VSMCs) with high levels of calcium and phosphate in the media induces an osteochondrogenic phenotypic switch and VSMCs become capable of secreting bone matrix in the context of the arterial wall, triggering deposition and progression of CVC [2]. Some researchers suggested that passive precipitation of hydroxyapatite nanocrystals may occur due to chronically elevated serum concentrations of minerals, promoting activation of resident macrophages, pro-inflammatory cytokine secretion and cellular apoptosis, in an attempt to eliminate calcium-phosphate crystals [48].

CKD is characterized by a state of chronic subclinical inflammation due to an imbalance of pro- and anti-inflammatory cytokines [50].

Over-expression of pro-inflammatory factors such as tumor necrosis factor alpha (TNFα) or interleukin 6 (IL-6) reduces the synthesis of anti-inflammatory factors. Fetuin-A and alpha-klotho are among the deficient factors that may be implicated in CVC inception and progression. Fetuin-A is essential for calcium-phosphate crystals solubilisation and formation of calciproteins in plasma. In contrast, alpha-klotho modifies the binding of fibroblast growth factor 23 (FGF23) to its receptor in the kidney increasing urinary phosphate wasting [48]. Although the roles of calciproteins and alpha-klotho/FGF23 are not completely understood, their impact on mineral metabolism may account for some of their presumed effect on CVC deposition and progression [48]. Of note, the effect of the altered Klotho/FGF23 axis on CVC may be independent of calcium-phosphate homeostasis since Klotho modulates other signalling pathways such as FGF-receptor 1 and mTOR [48]. Future efforts are required to establish the contribution of these factors in the development of CVC in patients with CKD due to the conflicting clinical data currently available.

Oxidative stress and accumulation of AGEs have also been implicated in the pathogenesis of CVC [48]. Besides promoting calcium/phosphate removal from the bone through activation of the RANK/RANKL system in osteoblasts, experimental data suggest that AGEs may induce VSMC osteogenic differentiation through p38-mitogen-activated protein kinase (MAPK) as well as Wnt/β catenin signalling. Additionally, AEGs may act synergistically with some uremic toxins and induce the synthesis of pro-inflammatory cytokines (IL-1, IL-6, TNFα) linked to endothelial dysfunction and vascular calcification [48].

Uremic toxins that accumulate as renal function declines may also affect vascular health [48]. As an example, indoxyl sulfate triggers the expression of the sodium-phosphate co-transporter Pit-1 that enhances the uptake of calcium and phosphorus by VSMCs and appears to mediate their osteogenic differentiation. In addition, indoxyl sulfate suppresses the hepatic synthesis of Fetuin-A [48].

Finally, vitamin K (an essential cofactor for MGP carboxylation and activation) and pyrophosphate (an inhibitor of calcium-phosphate crystals formation) are often deficient in CKD patients further increasing susceptibility to development of CVC in these patients [55].

2.2.2 Epidemiology and Clinical Significance of Cardiovascular Calcification in CKD

Patients with CKD have an exceptionally high risk of cardiovascular (CV) events [56]. Although there is an incomplete understanding of the reasons behind such risk, epidemiological studies have repeatedly reported a linear and independent association between degree of renal function impairment and risk of CV events [56]. One in two patients with end stage renal disease (ESRD) receiving dialysis dies from a CV event [56, 57]. Risk algorithms validated in the general population to predict major CV events (MACE) underperform in patients with CK [58], and these patients suffer a poorer outcome after a CV event [56] than subjects with normal renal function.

In comparison with the general population, patients with CKD suffer from the impact of non-traditional risk factors such as derangements of bone and mineral metabolism and the accumulation of uremic toxins. The most frequent cardiovascular conditions of patients with CKD are sudden cardiac death, arrhythmias and congestive heart failure, while ischemic heart disease is relatively less common [56].

Epidemiological studies showed that CVC is associated with adverse outcomes in patients with CKD and that the prevalence of CVC increases with declining renal function. In a cohort of 572 non-dialysis dependent CKD (NND-CKD) patients Gorriz and coworkers documented a stepwise age-independent increase in prevalence and severity of vascular calcification [59]. The authors assessed CVC by means of simple imaging tools such as planar X-rays of the abdomen, hips and hands, and detected calcifications in one or more territories in 79% of the study participants; in 47% of the patients CVC was graded as severe

[59]. The MESA investigators reported a higher prevalence and severity of CAC among 1284 subjects with non dialysis dependent-CKD compared to 5269 subjects with normal renal function enrolled in the study [51]. In the Dallas Heart Study, CKD (defined as presence of microalbuminuria and GFR <60 mL/min*1.73 m^2) compared to normal renal function, was associated with an almost threefold increase in risk of extensive CAC (Odds Ratio of CAC greater than 100 AU 2.85; 95% confidence interval, 0.92 to 8.80 in CKD vs. no-CKD subjects) [60].

The prevalence of CVC continues to increase after initiation of dialysis and up to 80% of patients on maintenance dialysis exhibit some degree of CVC [61, 62]. It is also notable that unlike the general population, white and black patients, as well as men and women receiving maintenance hemodialysis show no difference in markers of vasculopathy (namely thoracic aorta calcification, CAC and arterial stiffness) despite differences in baseline clinical characteristics [52]. These data suggest that renal replacement therapy (RRT) is toxic for the CV system independent of clinical characteristics that may differentiate patients in the general population. Whether restoration of renal function and dialysis cessation after kidney transplantation reduce the risk of CVC is still under scrutiny. Research data in this direction are limited, and likely confounded by the concomitant use of various immunosuppressants [63].

A large amount of observational data accumulated over the years, demonstrated that CVC is associated with an adverse outcome in patients with CKD. Simple imaging modalities such as vascular ultrasound and planar X-ray to show presence of CVC in the radial, femoral, iliac arteries [64–67], abdominal aorta [68, 69], and CAC on chest CTs [70, 71] have all shown the power of CVC as a marker of risk in CKD.

The value of CAC as a marker of risk in CKD patients is also supported by large collaborative epidemiological studies. In the Chronic Renal Insufficiency Cohort (CRIC) study, CAC predicted myocardial infarction, congestive heart failure and all-cause mortality, independent of baseline CV risk evaluated by traditional risk score algorithms [72]. In addition, inclusion of CAC score in a risk algorithm led to a small albeit significant increase in the accuracy of cardiovascular events prediction [72]. In the MESA study CAC was associated with and adverse outcome both in patients with normal and impaired renal function independent of age, sex, race and comorbid conditions [51]. Additionally, CAC was a better predictor of outcome than markers of arterial stiffness (ankle-brachial index) and carotid intima media thickness [51].

Similar findings have been reported in CKD patients receiving maintenance hemodialysis or peritoneal dialysis (PD) and after kidney transplantation [10, 63, 73]. Presence or extent of vascular calcification predict unfavorable events irrespective of baseline risk or comorbidities [10, 63, 73].

In contrast, as seen in the general population, the absence of CVC is a harbinger of an excellent prognosis. Block et al. [62] showed that CAC measured within a few weeks of dialysis initiation was a significant predictor of mortality after adjustment for age, race, gender, and diabetes mellitus with an increased mortality proportional to baseline score ($P = 0.002$) [71]. However, the absence of CAC was associated with an excellent prognosis and a low mortality rate at 5 years (3.3/100 patient years vs. 14.7/100 patients years for CAC > 400). In a series of 179 patients receiving PD, subjects without CAC had a significantly lower risk of all-cause mortality, cardiovascular mortality and cardiovascular events, even after adjustment for demographic and comorbid factors [73].

Deposition of hydroxyapatite in the arterial wall is linked with other markers of cardiovascular risk. As with vascular calcification, a stepwise increase in arterial stiffness with increasing CKD stage has been documented in non-dialysis dependent-CKD patients [74, 75]. In a series of 132 patients new to dialysis, Di Iorio et al. reported a significant association of CAC and arterial stiffness (assessed via pulse wave velocity) as well as abnormal myocardial repolarization (assessed via QT dispersion on EKG) [76]. Similarly, Raggi and coworkers showed that patients on maintenance hemodialysis with evidence of valvular, thoracic and abdominal aorta

calcification have reduced aortic compliance [77]. Observational data confirmed the cardiovascular risk inherent with decreasing arterial compliance [78, 79].

Finally, calcification of the cardiac valves has been associated with an unfavourable outcome in CKD. The prevalence of aortic and mitral valve calcification is higher in CKD subjects than the general population. Cardiac valve calcification leads to disturbed leaflet motility, increase transvalvular pressure gradients as well as left ventricular hypertrophy and, in some cases, left atrium enlargement [80, 81]. All of these factors are predictors of an adverse prognosis. Of interest, the increased risk associated with valvular calcification appears independent of its reported association with coronary artery or aortic calcification [67, 82].

The debate on the pathogenetic and teleological meaning of calcium deposition, repair mechanism vs. promoter or participant in vascular damage, is still ongoing. However, some data support the notion that plaque mineral content is associated with an adverse outcome. In a series of 140 consecutive hemodialysis patients, higher plaque density was independently associated with increased mortality before and after adjustment for confounders [39]. In addition, plaque density mitigated the risk associated with CAC burden (significant interaction effect) [39]. These results are in conflict with data reported in subjects with preserved renal function. In fact, the MESA investigators [38] reported an inverse -rather than direct- association of plaque density and survival in subjects from the general population. Reverse epidemiology is a plausible explanation. Indeed, a large number of CKD patients expire in the course of CKD mainly due to CV events. Hence, CKD subjects receiving dialysis may not be comparable to individuals with normal renal function albeit matched for age and sex.

2.2.3 Progression of Cardiovascular Calcification in CKD

In consideration of the prognostic significance of both vascular and valvular calcification, a great effort has been devoted to develop therapies to delay or reverse CVC in patients with CKD. Lipophilic statins seem to promote rather than inhibit calcification progression [83], possibly due to inhibition of vitamin K synthesis [83]. Indeed, vitamin K is an essential factor for MGP activation that is a potent inhibitor of CVC. Several ongoing trials are testing the effect of vitamin K supplementation on CVC progression. In this regard, trials designed to compare the effects of new direct oral anticoagulants (DAO) with vitamin K antagonist (warfarin) in patients with atrial fibrillation are also much awaited since they will shed light on whether vitamin K metabolism modulation impacts CVC progression [84].

The most frequently and best-investigated therapies to affect CVC so far have been those involving phosphate binders (Fig. 2.3). Calcium supplements are associated with CVC progression in the general population [85] as well as CKD patients [86, 87]. Although calcium supplements are commonly used as phosphate binders in advanced CKD or dialysis dependent patients, several studies showed that they can expose patients to an excess calcium load, positive calcium balance and promote calcium crystal deposition in soft tissue and vessels [88]. In a randomized controlled study of patients with moderate to advanced CKD, subjects receiving calcium acetate showed a trend toward CAC progression compared to placebo or calcium-free phosphate binders [89]. A considerable amount of data has been accumulated on the effect of calcium containing vs. calcium free phosphate binders on CVC progression in patients on maintenance hemodialysis. A recent metanalysis showed that use of calcium based binders is associated with a significant CAC progression; the increase in Agatston score was 95 (95% confidence interval: 43–146) units higher among patients treated with calcium-containing phosphate binders [87]. This was associated with a significant 22% increased risk of all-cause mortality [87].

Though based on preliminary observations, the effect of calcium supplements may be modified by the concomitant use of other drugs that modulate calcium metabolism such as calcimi-

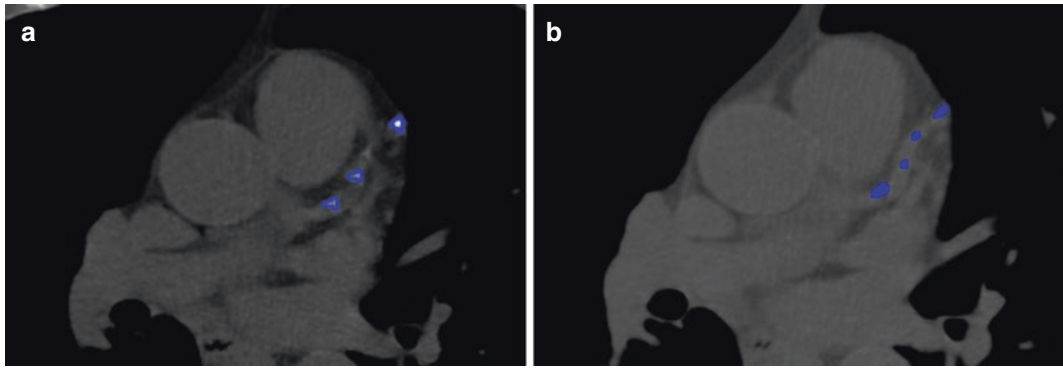

Fig. 2.3 Comparison of axial computed tomography images of the heart taken 1 year apart, showing progression from 3 (panel **a**, baseline scan) to 4 calcified lesions (panel **b**, follow-up scan) along the length of the left anterior descending artery

metics or vitamin D [90]. In a post-hoc analysis of the ADVANCE trial [91], patients with evidence of aortic valve calcification at study inception showed a significantly smaller progression of CAC when treated with cinacalcet and low doses of vitamin D compared to flexible doses of vitamin D [92]. In a post-hoc analysis of the INDEPENDENT study [93], the concomitant use of calcium-free phosphate binders and cincacalcet was associated with a better survival compared to the combination of calcium based binders and cinacalcet or vitamin D [94]. Based on the numerous studies showing the undesirable effect of calcium based therapies, guidelines on mineral metabolism management in patients with CKD recommend the use of limited amounts of calcium-based phosphate binders in all stages of renal impairment [95].

Newer compounds designed to slow the progression of vascular calcification are currently under clinical development and hold promise for the future. A new inhibitor of CVC, SNF472, has progressed from phase 1 clinical development and is being studied in an ongoing phase 2 trial that will hopefully shed light on its potential inhibition of CAC progression [96]. This compound shares chemical properties with bisphosphonates and pyrophosphate and preclinical data suggest that CVC regression may occur in animals treated with SNF472 [96]. Other drugs are of potential interest to reduce vascular calcification deposition and progression. Although we are not aware of any trial in humans, an increase mineralization in bone coupled with reduced hydroxyapatite deposition in the vasculature has been described in preclinical models treated with sotatercept, an anti-anemia compound that inhibits the activin-A receptor. Similarly, it has been shown that bortezomib and everolimus may potentially prevent CVC progression by increasing Wnt/B-catenin signalling and Klotho synthesis, respectively. Finally, sclerostin, and DKK1-secreted frizzled related proteins (Wnt inhibitor antagonists) are under preclinical development and future efforts are needed to establish their role in inhibition of CVC progression [97].

2.3 Conclusions

Only a portion of the exceptional cardiovascular morbidity in patients with CKD can be explained by traditional risk factors. During the past several years, it has become apparent that CVC contribute substantially to the adverse prognosis of patients with CKD, and that alterations of mineral metabolism and bone turn-over are closely linked with the development of vascular and valvular calcification. However, it is noteworthy that a proportion of patients, even after years of advanced CKD and renal replacement therapy, do not develop CVC and have a remarkably lower probability of events compared to patients with CVC. Some interventions directed at limiting

exposure to known or purported noxious stimuli have been shown to slow the development of CVC and its adverse effects. More research is undoubtedly necessary to advance this agenda and continue to expand on the successes of earlier endeavors.

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3 Spectrum of Ventricular Dysfunction in Chronic Kidney Disease

Amarinder Bindra and Yong Ji

Chronic kidney disease (CKD) is the presence of structural and functional abnormalities of the kidneys with gradual loss of kidney function and progressive decrease in glomerular filtration rate (GFR). It is associated with significant number of comorbidities and cardiovascular diseases where a significant percentage of patients suffer from adverse cardiovascular events or mortality before progressing further into the stages of CKD. The heart and the kidney are two intricately linked organs through hemodynamic functions involving various regulatory pathways. These pathways include the sympathetic nervous system, renin angiotensin aldosterone system, and other various neuro-hormonal systems which can serve as a compensatory mechanism but may lead to progressive structural changes to the heart beginning in the earlier stages of CKD.

As the population begins to age with higher percentage of people living beyond 60 years old, the prevalence of hypertension (HTN), diabetes mellitus (DM), obesity, and other comorbidities increase causing age related pathological changes to the kidney and the heart driven primarily by progressive vascular injury. CKD has traditionally been linked with cardiovascular diseases, particularly sharing a close relationship with accelerated atherosclerosis. Now with more advanced diagnostic modalities, evidence of structural changes to the heart or the process of cardiac remodeling is becoming more transparent. CKD has been shown to have a strong association with ventricular systolic and diastolic function through various mechanisms. In this chapter, we will discuss how CKD has a direct and indirect contribution to the process of cardiac remodeling and changes in cardiac geometry and structure leading to a spectrum of ventricular dysfunction.

With declining kidney function there has been an increase in the prevalence of heart failure (HF). In the ARIC Study, Kottgen et al. showed that the incidence of heart failure (HF) was threefold higher in individuals with eGFR <60 mL/min [1]. In a prospect cohort study of 433 end stage renal disease (ESRD) patients who were followed from start of ESRD therapy to mean of 41 months, 31% of the patients had cardiac failure, 15% had systolic dysfunction, 32% had LV dilatation, and 74% had left ventricular hypertrophy at the start if therapy [2]. Identifying individuals with CKD and newly diagnosed HF is important as prognosis is poor in these patients as the mortality rate three years after diagnosis of HF in ESRD patients was 83% [3]. Specifically LV cavity and mass index were independently

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associated with death after two years [2]. The timing of cardiac dysfunction occurrence in those with CKD that is independent of other comorbidities is not yet well known; however, the course has been shown to occur sooner if patient has significant concurrent comorbidities including HTN and DM.

There is increasing data to support the role of echocardiography as a noninvasive method in the evaluation of cardiac function in advanced CKD patients. Two-dimensional echocardiography (2D-echo) is an important diagnostic modality for assessment of RV and LV structure and function by providing measurements of ventricular diameters and volumes, wall thickness, and ejection fractions. But 2D-echo can also provide useful information regarding atrial and ventricular filling pressures. Trans-mitral pulsed wave doppler flow in echocardiography is used to measure diastolic function, particularly by measuring the E (early diastolic filling phase) velocity which can be influenced by the load on the left atrium (LA) and heart rate (HR) [4]. One can also assess the early diastolic velocity along the longitudinal myocardial axis (e′) at the level of the mitral annulus by using the tissue doppler imaging (TDI). Although there are some pitfalls, the ratio of E/e' have been traditionally used to measure filling pressures and some have used it as a marker of prognosis in patients with CKD [5]. Increasing stages of renal failure have been shown to correlate with LA size and Left Ventricle (LV) systolic and diastolic dimensions. Interestingly, worsening diastolic function measured by shortening of deceleration time, E wave, and E/A ratio was noted in more than 50% of patients in ESRD with formed AV fistula and their diastolic diameter of the LV improved after HD (hemodialysis) sessions [6]. Also noted through echocardiography was increase in LV muscle mass, interventricular septal thickness in end diastole and systole, and right ventricle (RV) diameter with increased stage of CKD. 2D-Echo has expanded our understanding of the morphological changes associated with CKD and its physiological consequences.

One of the key cardiac pathophysiological features in patients with CKD is LVH. Study by Park et al. showed a strong association of higher LV mass, increased LVH, and abnormal LV geometry in those with eGFR <30 mL/min [7]. Specifically, higher albuminuria have also been associated with higher LV mass, and lower eGFR has been linked with LV size and systolic and diastolic function [8]. In the general population, prevalence of LVH is predicted to be approximately 15–21%, but near 50–70% in the intermediate stages of CKD, and 90% in ESRD [9]. Patients who have classic risk factors such as diabetes, hypertension, are at increased risk of developing renal failure leading to accelerated atherosclerosis and vascular disease, renin-angiotensin- aldosterone (RAAS) activation, and volume and pressure overloaded state which all contribute to the development of compensatory LVH. There are various proposed mechanisms of the progression and stages of ventricular remodeling.

Traditionally cardiologists have tried to describe HF syndrome with purely hemodynamic concepts and targeted therapy towards correcting hemodynamic derangements—Fig. 3.1. However, explanation of heart failure with just hemodynamic stressors has been shown to be inadequate leading to further suggestions and investigation of alternative mechanisms involved in the disease process. When often discussing the pathophysiology of the heart, we discuss the

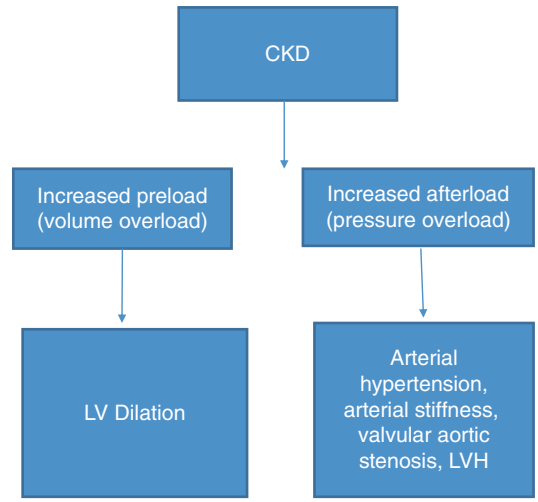

Fig. 3.1 Hemodynamic model

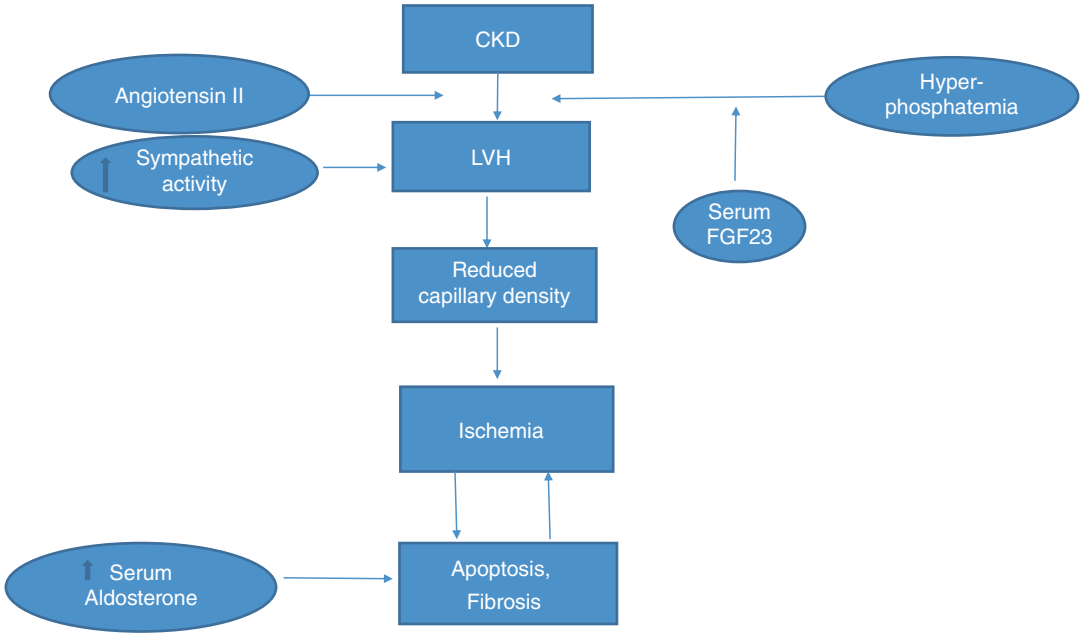

Fig. 3.2 Micro vascular model

preload, afterload, and measurement of pressure, volume, and flow. When targeting treatment options we often think about cardio output, pulmonary capillary wedge pressure, and systemic vascular resistance.

One of the more popular hypothesis involves the neuro-hormonal mechanism, where the activation of the sympathetic nervous system and RAAS produces a harmful effect on the heart by exacerbating further hemodynamic abnormalities and has a direct toxic effect on the myocardium. Activation of these systems leads to systemic vasoconstriction, stimulates sodium and water retention, further increasing neuro-hormonal activity through a vicious cycle by increasing atrial distension and progresses to secondary baroreceptor dysfunction. Studies have shown that elevated nor-epinephrine and angiotensin has direct deleterious effects on the myocytes which produces increased LV remodeling and progressive LV dysfunction. As seen by early trials targeting the blockade of RAAS and sympathetic nervous system with use of ACEI or beta adrenergic blockers, these agents demonstrated favorable effects on disease progression and mortality [10].

However the neuro-hormonal axis pathway is unlikely to explain the involvement of the pro-inflammatory cytokines in patients with heart failure (Fig. 3.2). Plasma levels of TNF-alpha and IL-6 were elevated in patients as their functional heart failure classification deteriorated [11]. Chronic inflammation, oxidative stress, and endothelial dysfunction in patients with CKD have been shown to increase morbidity and mortality in patients with cardio vascular disease by creating a milieu that increases their risk. CKD also has been correlated with both a systemic inflammatory and oxidative stress state which may increase HF risk.

Patients with CKD are more susceptible to reduction in capillary density in myocardium making them vulnerable to ischemia, and fibrosis. In the hypertrophied myocardium, capillary density is reduced causing an imbalance of oxygen supply and demand leading to exaggerated extracellular and collagen synthesis [12]. Amann et al. demonstrated this myocyte capillary mismatch particularly in patients with uremia [13]. The imbalance of exaggerated collagen synthesis and collagen degradation leads to fibrosis making patients more susceptible to diastolic dysfunction

[14]. Long term, the increasing pressure load may promote cardiac remodeling, increasing the release of myo-fibroblasts leading to the development of interstitial myo-fibrosis.

In the context of hemodynamics, LVH can be viewed as a compensatory mechanism for the high cardiac work load secondary to increased afterload and increased preload. CKD patients may lead to decreased aortic compliance, arterial hypertension leading to an increased afterload state. In conjunction, loss of nephrons and decrease in GFR leads to further salt retention and accumulation of fluid leading to increased preload causing LV dilatation. Both of these changes contribute to worsening hypertension and further volume pressure overload. This eventually leads to the upregulation of RAAS activity which not only increases aldosterone production and sympathetic pathway but also leads to excess angiotensin II. Angiotensin II, along with the release of pro-fibrotic factors such as galectin-3, TGF-beta, endogenous cardiac steroids, by the activation of RAAS pathway, promotes myocardial hypertrophy, fibroblast proliferation, and interstitial accumulation of collagen [15]. This cycle is further intensified by uremic toxins which also has been shown to contribute to cardiac fibrosis by producing TGF-beta, tissue inhibitor of metalloproteinase (TIMP-1), and alpha-1 collagen which contributes to fibrosis [16].

Other biomarkers such as fibroblastic growth factors like FGF-23, which plays a key role in regulation, growth, and differentiation of cardiac myocytes, have been investigated and linked to LV remodeling [17]. In the general population, higher FGF-23 concentrations were associated with LVH, but this correlation was stronger in those with CKD [18]. Study by Nerpin et al. demonstrated pathological hypertrophy in isolated rat cardiomyocytes after FGF receptor-dependent activation of the calcineurin-NFAT signaling pathway, along with increased prevalence of LVH in mice after intra-myocardial and IV injection of FGF-23 [19]. CKD leads to accumulation of phosphate which leads to increase in FGF-23 which has phosphaturic properties and is also involved in blocking vitamin D3 synthesis with prolonged levels leading to cardiac remodeling and LVH.

Secondary hyperparathyroidism and hyperphosphatemia in patients with CKD have also been shown to contribute to increased LV mass, LVH, and impaired LV diastolic dysfunction [20, 21]. This was supported with tissue Doppler imaging, where calcium-phosphate levels were correlated with diastolic myocardial function in patients with CKD [22]. Vitamin D deficiency has been proposed to also contribute to myocardial hypertrophy and extracellular matrix production via increased c-myc protein levels [23].

Patients with CKD have different features of inter-myocardial fibrosis in which endocardial and epicardial fibrosis predominate which is distinct from patients with hypertensive heart disease or chronic ischemic heart disease. Study by Mall et al. showed that uremia was a determinant of inter-myocardial fibrosis independent of HTN, DM, anemia, heart weight, and prevalence or absence of dialysis [24]. Myocardial infiltration of monocytes and macrophages can lead to diastolic dysfunction. Macrophages produce Galectin-3 which interacts with extracellular matrix proteins and binds to cardiac fibroblasts and increase collagen in myocardium and was shown to be an independent predictor of mortality in patients with CKD [25]. However, other studies have shown not shown any correlation of Galectin-3 with HF, but eGFR <30 mL/min correlated with twofold higher levels.

LVH is associated with both LV systolic and diastolic dysfunction, but diastolic dysfunction has been demonstrated to occur in early stages of CKD where subtle changes in echocardiographic parameters of LV filling pressures can be seen [26]. It is estimated that approximately 15% of patients with CKD starting dialysis therapy have LV systolic dysfunction while prevalence of diastolic dysfunction is much higher and more apparent in earlier stages of CKD [27]. In a study by Franczyk-Skora et al. looking at HF disturbances in CKD, LV EF was the lowest in stage V CKD and the highest in stage II CKD. However, there has been varying data in regards to impairment in systolic function in patients with CKD with up to 15%–28% variance in patients on

dialysis [6]. LVH, CAD, microvascular abnormalities, neuro-hormonal imbalances, myocardial fibrosis, all contribute to the development of LV systolic and diastolic dysfunction.

The Acute Dialysis Quality Initiative XI Workgroup have proposed a new classification of HF in patients with structural heart disease. Using this proposed criteria, Hickson et al. evaluated for structural heart disease in patients with ESRD and concluded that impaired LVEF and RV dysfunction had a twofold increased risk of death with RV functioning having the strongest association with mortality [28]. Among the 567 patients who had structural heart disease, 78% had grade II or above diastolic dysfunction, 49% had LVH, 34% had RV systolic dysfunction. RV dysfunction is believed to be from a chronic volume overload state further exacerbated by arteriovenous fistulas which increases the preload, or the rate or volume of blood returning to the heart which can also increase the SV load on the LV contributing to LVH and diastolic and systolic dysfunction. HD has been associated with increased risk of RV dysfunction particularly in those with brachial AVF [29]. Patient also undergoing HD compared to PD are at higher risk of RV dysfunction [30]. Momtaz et al. demonstrated lower RV systolic indices which includes RV fractional area change, tricuspid plane systolic excursion, and peak systolic velocity at lateral tricuspid annulus, were significantly lower in HD patients [30]. Compared to earlier stages of CKD, patients with stage V had much greater RV diameter [6]. RV dysfunction leads to impaired LV diastolic and systolic function, and this interdependence has been demonstrated in various cardiac diseases [28]. Chronic dialysis treatment has also been associated with increased pulmonary pressures which was however not significantly associated with RV or LV dysfunction [30].

As demonstrated in this chapter, the impact CKD has on cardiac geometry and structure through cardiac remodeling is multi-dimensional. Activated neuro-hormonal pathways indirectly contributes to the remodeling process through a compensatory mechanism caused by an increased preload and afterload state meanwhile having a direct toxic effect on the myocardium leading to both right ventricular and left ventricular dysfunction. The pro-inflammatory and oxidative stress state exhibited in CKD further exacerbates ventricular function by making the myocardium more vulnerable to ischemia by causing an imbalance of oxygen supply. It also exaggerates extracellular and collagen synthesis leading to fibrosis supported by the presence of elevated growth factors linked to ventricular remodeling. As mentioned, secondary hyperparathyroidism and vitamin D deficiency in patients with deteriorating kidney function have also been linked with ventricular dysfunction. Echocardiography has been proven to be a valuable noninvasive imaging modality to confirm the changes in the geometric dimensions in the heart during the remodeling stages including increased LA size, LVH, LV mass, while being able to assess the diastolic and systolic functions of the ventricles. It is now well established that chronic kidney disease is not only the consequence of cardiovascular disease, but also the cause of significant ventricular dysfunction through various pathways and mechanisms.

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The Myocardium in Renal Failure

4

Kerstin Amann

In patients with chronic kidney disease (CKD), the exceedingly and disproportionally high prevalence and mortality of cardiovascular (cv) disease are a major clinical problem [1]. In these patients, cv disease is approximately 20 times more frequent than in age- and sex-matched segments of the non-renal population and up to 3 times more frequent than in other cv risk groups, such as diabetes mellitus. However, it is of major importance that particularly young CKD patients exhibit up to 1000 times higher risk of cv disease compared to matched segments of the non-renal population. In addition to this negative epidemiology, it is important to emphasize that cv disease in CKD patients, specifically coronary artery disease, myocardial interstitial fibrosis, and myocardial capillary supply, is different in several aspects from what is seen in non-renal patients. Therefore, these alterations are much more complex and difficult to treat than in non-renal patients. Certainly, some treatable CKD-specific factors such as anemia, hyperphosphatemia and hypercalcemia, hyperparathyroidism, and others contribute to the problem, but they are clearly not sufficient to explain the broad spectrum of cv disease in renal patients. Consequently, it has been shown that some therapeutic strategies for cv disease that are extremely effective in non-renal patients lack comparable efficacy in CKD patients, i.e., statins [2]. Moreover, traditional surgical vascular procedures such as angioplastic or cardiac bypass surgery are associated with worse outcome and worse prognosis in CKD patients compared to a non-renal group with otherwise similar additional risk profile [3].

Initially, it was assumed that higher cv morbidity and particularly cardiac death in CKD patients are due to more frequent and particularly accelerated atherosclerosis with more pronounced coronary artery sclerosis and higher risk of myocardial infarction. It has been shown recently, however, that the majority of cv events, i.e., up to 60%, is not caused by myocardial infarction but is due to sudden cardiac death [4] most likely due to arrhythmias, which may be explained by a characteristic cv pathology with specific CKD-associated changes that will be discussed in more detail in the following.

First, in CKD patients there is marked and early onset left ventricular hypertrophy (LVH) that is present in approximately 60% of patients even before the start of dialysis. Second, patients with CKD suffer from pronounced myocardial fibrosis that develops early on, is much more pronounced than in other cardiac diseases, i.e., in hypertensive heart disease, and has important functional consequences in terms of increased myocardial stiffness and increased arrhythmo-

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genicity. Third, myocardial arterial and capillary supply is also altered in CKD, i.e., intramyocardial arteries show increased wall thickening and angioadaptation to increased heart weight is markedly impaired leading to lesser capillary supply in the setting of LVH. In summary, these specific myocardial structural changes in CKD favor a so-called myocyte-capillary mismatch with increased intercapillary distances and as a consequence decreased myocardial blood and oxygen supply that renders the heart more susceptible to ischemic injury and arrhythmias [5, 6].

Specific animal models have been instrumental in further exploiting the aforementioned structural alterations in CKD, their pathogenesis, and their functional consequences. Here, particularly the well-established animal model of the subtotally nephrectomized rat (SNX) which develops mild to moderate stable and long-lasting renal failure excellently mimics cv pathology in CKD patients [7]. Using this model a specific time course of cv alterations was detected with an early and specific activation of cardiac interstitial fibroblasts as soon as 2 weeks after induction of renal failure representing the first step in the development of myocardial fibrosis. One to two weeks later progressive myocardial hypertrophy develops whereas significant capillary rarefaction (approx. 20–25%) and arterial changes can be seen only after 8–12 weeks of renal failure. All these cv lesions progress as renal failure progresses (Fig. 4.1).

From a clinical point of view, LVH is certainly the most prominent cv alteration in CKD since it is per se associated with increased mortality and it represents a strong independent predictor of mortality (HR 3.6. in a multivariate analysis) [8]. Earlier work [9] showed that LVH is already present in more than 80% of patients who enter a dialysis program and even in 17% in younger patients without significant comorbidities [10]. Of note, the time on hemodialysis correlates with increased LVH prevalence in CKD patients [11]; however, it is reported to be somewhat less in peritoneal dialysis [12]. Furthermore, apart from higher frequency of LVH and LV failure in CKD and ESRD, there is also an increased prevalence of lung diseases, i.e., COPD and sleep apnea [13], which may further contribute to cv death. In the PEPPER study [14] 90% of patients with CKD stage 4 and 5 showed increased left ventricular filling pressure indicative of left ventricular failure and there was a small group of 10% of patients who presented with so-called "unexplained pulmonary hypertension." Thus, LVH in CKD is specifically associated with systolic and more importantly diastolic dysfunction and a specific type of coexisting heart failure (HF), i.e., a combination of left and right HF.

From a pathophysiological perspective there a numerous systems and factors that could contribute to high cv disease in CKD patients. Among those are pathways of inflammation and oxidative stress, cellular immune-mediated mechanisms, stress-mediated and (neuro)hormonal responses, metabolic and nutritional changes including bone and mineral disorder, altered hemodynamic and acid-base or fluid status, modification of proteins (LDL, HDL, albumin, etc. as examples) as well as anemia. Recently, a completely and most likely very important new field of research has emerged, namely the involvement of fibroblast growth factor 23 (FGF 23) in the pathogenesis of LVH and myocardial fibrosis in CKD [15, 16]. First, in clinical studies FGF23 was found to be directly related to LVH and mortality in hemodialysis patients. Then, in a series of elegant experimental studies FGF23 was shown to induce LVH in renal failure via the FGF receptor 4 on cardiomyocytes and this could be prevented by antibodies against this receptor [17, 18].

Another potentially interesting and important mechanism in the SNX model of renal failure was a significant loss of cardiomyocytes due to increased myocyte apoptosis, activation of cyclin D2, PCNA, and a reduction in CDK inhibitors [19]. This significant loss of myocytes may of course lead to a progressive loss of cardiac contractility and consequently heart failure [20]. Interestingly, in the SNX model this loss of cardiomyocytes could be completely prevented by chronic ACE inhibitor and rapamycin treatment [20, 21], which may of course also be applicable in CKD patients.

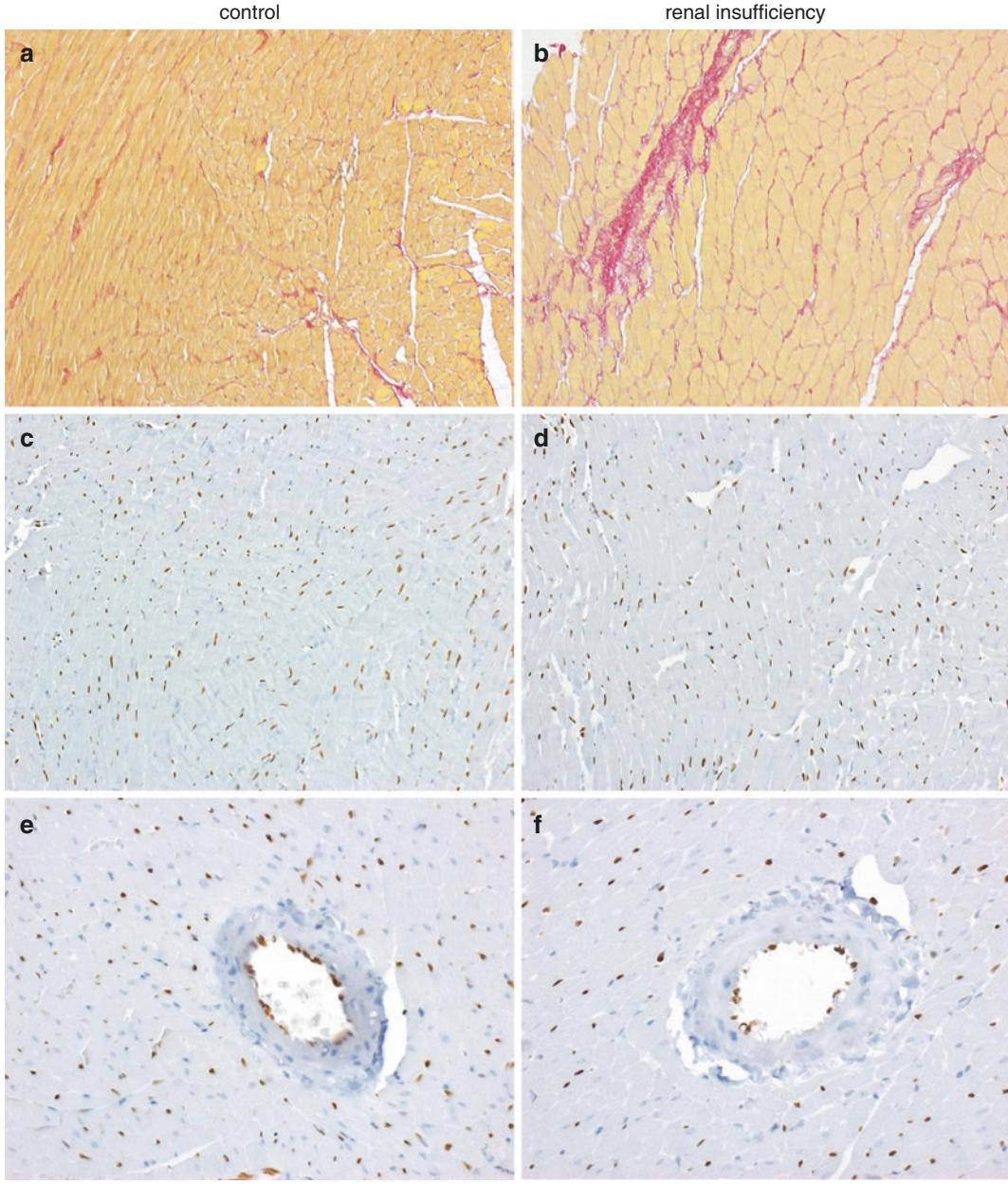

Fig. 4.1 (**a**, **b**) Representative myocardial fibrosis in subtotally nephrectomized rats (SNX) with moderate renal insufficiency (**b**) and control rats (**a**). Sirius red stain, magnification ×20. (**c**–**f**) Representative examples of lower myocardial capillary supply in SNX rats (**d**, **f**) compared to controls (**c**, **e**). Immunohistochemistry using an antibody against the endothelial cells marker ERG. Magnifications: ×20 (**c**, **d**), ×40 (**e**, **f**)

In addition, impaired angioadaptation to ischemia in the myocardium and also in the skeletal muscle of SNX rats was found pointing to a potential role of pro- or antiangiogenic factors in the development of cv disease in renal failure. In particular, the impaired capacity to form new capillary vessels in the hypertrophied myocardium contributes importantly to the burden of cv disease in CKD. Capillary angiogenesis is usually an adaptive process in response to ischemic

processes such as arterial stenosis/occlusion or heart hypertrophy, which aims to restore the perfusion of the affected organs. In the SNX rat model the 25% reduction in myocardial capillary supply after 8 weeks of renal failure was associated with a significantly greater myocardial infarction compared to non-renal control animals (30 ± 6.7 vs. 18.8 ± 6.6%) indicating lower ischemia tolerance or in other words increased susceptibility of the myocardium to ischemic damage [22]. This has also been confirmed in clinical studies in CKD patients [23, 24]. Furthermore, the elegant work of McIntyres group [24, 25] documented repeated episodes of reduced cardiac function, i.e., cardiac stunning, together with higher levels of troponin, in 2/3 of adult patients and even in children during dialysis. A significant impairment of angioadaptation with reduced formation of neovessels after ischemia was also shown in the skeletal muscle [26], which may contribute to higher morbidity and worse prognosis from peripheral arterial occlusive disease in CKD patients [27]. Unfortunately, the pathomechanism of impaired angioadaptation in CKD is not fully understood. Animal data indicate, however, that a diminished or even disturbed adaptive upregulation of vascular endothelial growth factor (VEGF) and its receptors in the heart and also within the ischemic skeletal muscle may play a crucial role [28]. Moreover, impaired mobilization of bone marrow derived cells in CKD may also impair angiogenesis [29]. In patients with CKD [31] a potential role of the soluble VEGF receptor (sFlt-1) that acts as a VEGF antagonist thus inhibiting the ischemia-induced angiogenesis was found [30]. In line with this in vitro findings suggest an antiangiogenic effect of CKD serum as well as increased apoptosis of endothelial cells and decreased NO production [31]. Also, the proangiogenic gene regulation by hypoxia-induced factors (HIF) may be of particular importance for adaptive angiogenesis after ischemia since significantly lower basal levels of HIF gene expression could be found in the skeletal muscle of SNX rats [32]. This finding may prompt new treatment perspective using drugs that target the stabilization of HIF.

In addition to structural and functional alterations of the myocardium itself in CKD, there are also major structural changes of extracardiac arteries and veins which are not the focus of this review. In general, a more pronounced and progressive type of atherosclerosis with specific patterns of calcification and lipids that was already noted by Lindner and Charra more than 40 years ago in dialysis patients [33] can be regarded as a hallmark of vascular changes in CKD. Moreover, marked fibrous or fibro-elastic thickening of elastic and muscular arteries with loss of elastic fiber content leading to increased vascular stiffness (i.e., premature aging of the vasculature in predialysis and dialysis patients [34, 35] and more pronounced peripheral artery disease) has also been described even in children with CKD assuming that the effect of age-associated risk factors is neglectable. It is of interest, however, that in these young population there is a slight tendency towards lower vascular wall thickness after renal transplantation, i.e., some sort of regression of vascular thickening might take place when renal function is improving [36].

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Impact of Renal Failure on Valvular Heart Disease

5

Natalia Rocha and Katherine Panettiere-Kennedy

5.1 Introduction

It is apparent that kidney function and cardiovascular health are interconnected and share a similar risk factor profile. The metabolic derangements associated with chronic kidney disease (CKD) are known to lead to calcification of vascular beds and heart valves [1–3]. Valvular calcification as evidenced by aortic sclerosis and mitral annular calcification (MAC) has been extensively shown to be a marker of heightened cardiovascular risk in the general population [4, 5]. It may be considered as a subclinical manifestation of cardiovascular disease (CVD) due to its graded association with increased risk of cardiovascular events such as stroke, coronary artery disease, and cardiovascular death after adjusting for traditional risk factors [4–7].

A contemporary study utilizing an extensive echocardiographic registry found higher prevalence of aortic stenosis and mitral regurgitation among participants with CKD when compared to those without CKD after adjusting for age and comorbidities [8]. The authors suggest that these differences are predominantly due to gradual calcification of the aortic leaflets and mitral apparatus leading to restriction in motion. Interestingly, even mild degrees of CKD were associated with higher prevalence of valvular abnormalities, suggesting that the calcification process starts early in the natural history of CKD. They additionally noted that presence of at least mild aortic stenosis (AS) or mitral regurgitation (MR) was associated with worse outcomes among those with CKD when compared to those without [8].

In addition to being more prevalent in the setting of end-stage renal disease (ESRD), valvular calcification also appears to proceed more rapidly in these patients [9], and those with faster progression of disease appear to have worse outcomes [10]. Certain metabolic, hemodynamic and echocardiographic findings such as high parathyroid hormone level, increased left atrial volume, and higher stroke volume seem to correlate with faster progression of stenosis, which suggests the need for more frequent imaging assessment in patients meeting these criteria [10].

The presence of abnormal kidney function adds specific nuances to the diagnosis and treatment of valvular heart disease (VHD). As will be discussed in more detail, CKD affects the outcomes of essentially all valve surgeries including surgical and percutaneous approaches and thus, the most commonly used thoracic surgery risk prediction scores (EUROSCORE I, EUROSCORE II and STS Score) include an

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appraisal of level of kidney function. Unfortunately, as patients with advanced CKD and ESRD have historically been excluded from major cardiovascular trials, it is unclear whether their results can be extrapolated such that general guidelines can be applied to this population.

This chapter will focus on the pathology, diagnosis, and treatment of valvular heart disease in patients with CKD, with emphasis on mitral annular calcification and aortic sclerosis.

5.2 Pathology

The predominant mechanism responsible for valvular heart disease in patients with CKD appears to be progressive calcification of left-sided valves [1]. The concept of valvular calcification as a passive, age-related consequence of calcium deposition is no longer accepted. Rather, it is currently viewed as an active inflammatory process analogous to, but likely more intricate than atherosclerosis [11].

Several factors known to contribute to the development and progression of valvular calcification are more prevalent or more severe in the setting of CKD. Anemia, volume overload, hypertension, and the presence of arteriovenous fistulas—common outcomes of CKD—can all increase mechanical stress on the valves [12]. Altered calcium-phosphate metabolism, hyperparathyroidism, increased FGF-23, and reduced klotho are also common in patients with kidney dysfunction, and known to be associated with valvular calcification as well [13, 14]. Interestingly, calcium-based phosphate binders are also associated with progression of aortic calcification and are no longer considered preferred binding agents for this reason [15–17].

Progressive sclerosis of the aortic valve more commonly leads to aortic stenosis, while mitral annular and leaflet calcification lead to similar rates of either mitral stenosis or regurgitation. One or both valves can be affected, and the combination of aortic stenosis with mitral regurgitation can be particularly challenging to manage.

5.3 Prevention

Though research regarding prevention of valvular disease progression in CKD is still preliminary, several potential therapeutic targets have been identified. As calcification is believed to be the primary process involved in CKD-related valve disease, it is not surprising that attenuation of calcium load has been one of the more promising avenues of investigation. In a randomized clinical trial, HD patients were assigned to receive either sevelamer or a calcium-based phosphate binder and were evaluated by CT scans at baseline and 1 year. Among patients treated with sevelamer, 45% displayed slowing of total valvular and vascular calcification, versus only 28% of those treated with a calcium-based phosphate binder. Additionally, among those treated with sevelamer, 26% displayed regression of calcification, versus only 10% of those treated with a calcium-based phosphate binder [18]. It should be noted that these results were only significant when valvular and vascular calcification scores were combined, and thus benefit has yet to be shown for valve protection specifically. Based on this evidence, however, KDIGO recommends restricting the dose of calcium-based phosphate binders in CKD patients when possible (evidence level 2B) [17].

Another area of investigation is reduction in parathyroid hormone (PTH). With this approach in mind, a randomized trial assigned HD patients with secondary hyperparathyroidism to receive either standard therapy with flexible vitamin D dosing (control group), or the calcimimetic cinacalcet along with fixed low-dose vitamin D. Change in aortic and mitral valve calcification were measured at 52 weeks, and the authors found a treatment difference of −44.7% in aortic valve calcification, but no statistically significant treatment difference in mitral valve calcification [19]. Although these results are not overwhelming, they show some promise, and further investigation into PTH as a target of therapy is warranted.

It is known that the vitamin K antagonist warfarin increases vascular calcification via interference with vitamin K-dependent matrix Gla-protein, an inhibitor of vascular cal-

cification [20]. This relationship has prompted studies evaluating the impact of directly acting oral anticoagulants and vitamin K supplementation on calcification. A randomized animal study found that mice treated with warfarin but not rivaroxaban displayed a significant increase in cardiac valve calcification when compared with control mice [21], and a multicenter retrospective observational trial in humans similarly found that patients treated with rivaroxaban displayed a lesser degree of aortic valve calcification over a 16-month period than those taking warfarin [22].

Regarding vitamin K supplementation, an open-label proof-of-concept study assigned patients with asymptomatic or mildly symptomatic aortic valve calcification to vitamin K or placebo, and found that patients taking vitamin K showed only 10% progression of aortic valve calcification, versus 22% in the placebo group [23]. However, in addition to having a small sample size, high dropout rate, and open-label status, this study excluded patients with CKD. Clearly, research in this area is preliminary and no conclusions can be drawn, particularly regarding CKD patients. However, taken together these studies offer some initial support to the hypothesis that there is a role for vitamin K in prophylaxis of valve calcification.

Finally, bisphosphonates are under consideration as a prophylactic agent based on the observed association between osteoporosis and aortic valve calcification. A pilot retrospective study of patients with aortic stenosis found that the progression of calcification as measured by mean gradient change was slower in patients treated with bisphosphonates than those not treated with bisphosphonates [24]. However, these results were only significant for patients with mild and not moderate or severe aortic stenosis, and the study was limited to patients with preserved renal function. Another retrospective study of women over 60 with osteoporosis did not find any significant impact of bisphosphonate treatment on rate of valvular calcification [25]. Currently, this method of prophylaxis has only biologic plausibility, and further research is required to determine if it has clinical promise in the prevention of valvular calcification in CKD patients.

5.4 Diagnosis and Follow Up

Because early stages of valvular calcification are usually asymptomatic, the presence of a cardiac murmur on physical exam can be the first clue that a patient has valve disease. In CKD patients, signs and symptoms of valvular heart disease such as dyspnea, orthopnea, and lower extremity edema can be falsely attributed solely to volume overload due to advanced kidney disease, which may delay cardiac workup and hinder diagnosis. Other more specific signs and symptoms such as irregular heart rhythm from atrial fibrillation, chest pain, and syncope frequently occur late in the natural history of the disease, and relying on these signs to prompt cardiac evaluation would delay diagnosis as well.

Transthoracic echocardiography (TTE) is the modality of choice for the detection and follow-up of valvular heart disease and its consequences. It permits integral evaluation of the structure of the valvular apparatus, degree of calcification, evidence of stenosis or regurgitation, as well as chamber sizes and the presence of pulmonary hypertension [12]. K/DOQI guidelines recommend performing echocardiographic evaluation as a screening tool for valvular heart disease in every patient within the first 1–3 months of dialysis initiation, once dry weight has been achieved [26]. If no disease is found, screening should be repeated every 3 years or sooner if the patient develops new symptoms such as dyspnea despite maintainance of dry weight, angina, or unstable hemodynamics during hemodialysis treatments, all of which would be concerning for the development of valvular heart disease (Fig. 5.1).

For patients with CKD not yet on dialysis, TTE is considered an appropriate screening test in asymptomatic patients when there is reasonable suspicion for valvular heart disease [27]. The follow-up of non-aortic valvular disease in patients with CKD should follow the same guidelines as the those of the general population, regardless of dialysis status. While asymptomatic

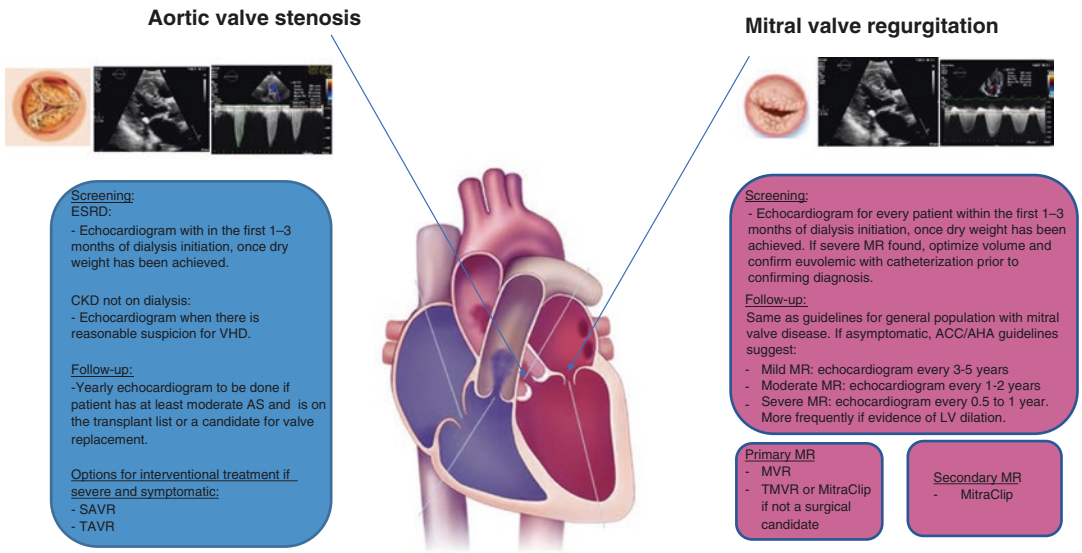

Fig. 5.1 Algorithm for screening, follow-up, and treatment of the most common forms of valvular heart disease in chronic kidney disease (CKD). *ESRD* indicates end stage renal disease, *VHD* valvular heart disease, *AS* aortic stenosis, *SAVR* surgical aortic valve replacement, *TAVR* transcatheter aortic valve replacement, *MR* mitral regurgitation, *MVR* mitral valve replacement, *TMVR* transcatheter mitral valve replacement

patients with moderate aortic stenosis in the general population should have an echocardiogram repeated every 1–2 years to assess for progression [28], K/DOQI guidelines recommend yearly echocardiogram follow-up in asymptomatic patients on dialysis with at least moderate AS who are on the transplant waitlist or those on dialysis who would be suitable candidates for aortic valve replacement, due to the higher rate of progression of stenosis (level of evidence C) [26]. It is important to highlight that K/DOQI guidelines utilize aortic valve area ≤ 1.0 cm^2 to define moderate AS, rather than aortic valve peak velocity and mean gradient, which are used in the American Society of Echocardiography (ASE) guidelines [28].

Interpretation of follow-up echocardiograms should take into account the patient's dry weight or date of last hemodialysis (HD) treatment/time of last peritoneal dialysis (PD) treatment in order to enhance interpretation and avoid confounding due to expected hemodynamic shifts between sessions. This is especially important in patients found to have significant mitral regurgitation since high left ventricular filling pressures can increase the severity of MR. For this reason, a final diagnosis of severe MR and surgical indication should be made only after documentation of normal filling pressures on right heart catheterization [29].

For the assessment of aortic stenosis, other imaging modalities have emerged as complementary tools to echocardiography. In about 25% of patients with AS undergoing echocardiography, there is discordance in the assessment of severity (i.e., AVA <1 cm^2 suggesting severe disease, with peak velocity <4 m/s and mean gradient <40 mmHg suggestive of non-severe disease), preventing an accurate diagnosis. Computer tomography aortic valve calcium score (CT-AVC) has been shown to have excellent discrimination of severe AS while also providing prognostic information in the general population [30]. Additionally, this imaging modality does not

require the use of intravenous contrast, which is ideal for patients with kidney dysfunction. Unfortunately, patients with advanced kidney disease have mostly been excluded from the largest studies of CT-AVC, and for this reason, it is unclear whether the current cut-offs used to define severe AS have similar diagnostic accuracy in the advanced CKD or ESRD population.

The use of magnetic resonance imaging (MRI) for the assessment of aortic stenosis is limited to patients whose echocardiographic studies are of inadequate quality. While MRI is superior to CT for the assessment of myocardial fibrosis and accurate chamber quantification, taking these measurements requires the use of gadolinium-based contrast agents which are contraindicated in patients with advanced kidney dysfunction due to the risk of nephrogenic systemic fibrosis (NFS) [31].

As will be detailed below, the use of computer tomography with contrast remains the imaging modality of choice in the periprocedural assessment prior to transaortic valve replacement (TAVR).

For regurgitant lesions of the aortic and mitral valves, ascertainment of severity is critical as it guides clinical decisions for intervention. Although echocardiography remains the pillar of diagnosis, cardiac MRI is superior in the determination of regurgitant volume and fraction using phase-contrast imaging, which does not require the use of contrast [32–34]. In addition to determining the degree of severity, the evaluation of MR should include an appraisal of the etiology since management differs significantly as will be detailed further in this chapter.

5.5 Treatment

5.5.1 Aortic Valve Stenosis

For patients with diagnosis of severe AS who require valve replacement, are deemed likely to benefit from intervention, and have an estimated life expectancy >1 year, the current therapeutic options include surgical aortic valve replacement (SAVR) and TAVR. A Heart Valve Team should be involved in this decision following individualized risk-benefit assessments, including surgical risk and feasibility of TAVR (specially by transfemoral approach), as well as other factors. It is known that CKD impacts the outcomes of both SAVR and TAVR, and an appraisal of kidney function is an essential step in determining the patient's operative risk when creating a treatment plan.

The indication for TAVR has evolved since its first FDA approval. It was initially reserved for patients with prohibitive surgical risk (2011), then those with high-risk (2012) [35, 36], and subsequently for those with intermediate-risk (2016) [37]. After landmark studies among low-risk patients demonstrated that TAVR is at least not inferior to SAVR in regard to death and stroke, the FDA expanded the use of both the Sapien 3 and CoreValve TAVR systems to low-risk patients, increasing the already widespread use of this less invasive approach (Table 5.1) [38, 39].

A propensity score-matched analysis including patients with CKD IV and V as well as end-stage renal disease patients undergoing SAVR and TAVR found higher in-hospital mortality with SAVR when compared to TAVR. Compared with those in the TAVR group, those undergoing SAVR also had higher rates of AKI, dialysis requirements, and post-surgical complications such as need for blood transfusion, atrial fibrillation, perioperative stroke, and shock. The patients in the SAVR group additionally endured longer hospital stays and higher costs, while those in the TAVR group displayed higher rates of pacemaker placement [40].

While it is clear that CKD patients stand to benefit from TAVR procedures, advanced chronic kidney disease (GFR <30 mL/min/1.73 m^2) is still considered a major non-cardiovascular comorbidity during the pre-TAVR assessment due to its known negative impact in post-TAVR

Table 5.1 Characteristics of selected trials of TAVR and MitraClip

Type of valve disease	Name of trial	Intervention	Primary outcome measured	Baseline renal status
Aortic stenosis TAVR	PARTNER 1 [73]	TAVR vs. SAVR in high operative risk	All-cause mortality at 1 year	Excluded if creatinine >3 mg/dL
	PARTNER 2 [37]	TAVR vs. SAVR in intermediate operative risk	All-cause mortality or disabling stroke at 2 years	Excluded if creatinine >3 mg/dL or RRT
	PARTNER 3 [38]	TAVR vs. SAVR in low operative risk	Composite of death from any cause, stroke, or rehospitalization (related to the procedure, valve, or heart failure) at 1 year after procedure	Excluded with eGFR <30 mL/min or requirement for RRT
	CoreValve extreme [74]	TAVR vs. SAVR in extreme operative risk	All-cause mortality or major stroke at 12 months	Excluded if ESRD of CrCl <20 cc/min
	CoreValve [75] high risk	TAVR vs. SAVR in high operative risk	All-cause mortality or major stroke at 12 months	Excluded if ESRD of CrCl <20 cc/min
	SURTAVI [76]	TAVR vs. SAVR in intermediate operative risk	All-cause mortality or disabling stroke at 2 years	Excluded if ESRD of CrCl <20 cc/min
	Evolut low risk [39]	TAVR vs. SAVR in low risk operative risk	Death or disabling stroke at 2 years	No exclusion criteria for renal disease
Mitral regurgitation MitraClip	Everest 2 RCT (primary and secondary MR) [60]	MitraClip vs. MVR for primary or secondary MR	Efficacy: freedom from death, from surgery for mitral-valve dysfunction, and from grade 3+ or 4+ MR at 12 months Safety: composite of major adverse events within 30 days	Excluded if creatinine >2.5 mg/dL
	Mitra-FR (secondary MR) [77]	MitraClip + medical therapy vs. medical therapy alone	All-cause mortality and unplanned hospitalizations for HF	Excluded if RRT
	COAPT (secondary MR) [78]	MitraClip + medical therapy vs. medical therapy along	Hospitalizations for HF within 24 months of follow-up	No renal exclusion criteria

SAVR surgical aortic valve replacement, *TAVR* transcatheter aortic valve replacement, *MR* mitral regurgitation, *MVR* surgical mitral valve replacement, *RRT* renal replacement therapy, *ESRD* end-stage renal disease, *eGFR* estimated glomerular filtration rate, *CrCl* creatinine clearance, *HF* heart failure

outcomes. A large nationwide German study including in-hospital data from all patients who underwent TAVR between 2010 and 2013 showed that those with CKD (defined by diagnostic and procedural codes for acute and chronic conditions) had higher rates of in-hospital complications, higher in-hospital mortality, and longer lengths of hospital stay when compared to those without CKD [41].

As mentioned previously, TAVR is associated with lower risk of AKI compared to SAVR, however, kidney injury remains a prevalent complication of TAVR and it is associated with worse outcomes [42]. The etiology of AKI after TAVR is multifactorial and includes pre-procedure as well as intra-procedure factors.

Pre-procedural variables associated with higher risk of AKI include older age, pre-existing CKD, diabetes, peripheral vascular disease, and contrast exposure from pre-TAVR planning. The 2017 expert consensus pathway on TAVR management recommends that the patient's baseline kidney function guide the selection of imaging modality for assessment of vascular access

suitability. Patients with GFR >60 mL/min/1.73 m^2 or ESRD who are not expected to recover kidney function should undergo TAVR CT angiography to evaluate suitability of vascular access, aortic valve morphology, accurate sizing of the annulus and outflow tract, as well as the risk of certain intra and post-procedure complications such as coronary obstruction [43]. The use of intravenous contrast in this modality is required and may increase the risk of acute kidney injury. Fortunately, strategies to reduce contrast exposure such as the use of the Very Low Intravenous Contrast Volume CT protocol and others have been shown to be feasible in the comprehensive pre-TAVR assessment, and should be attempted when possible [44].

Patients in AKI or ESRD with expected recovery should avoid contrast exposure. In these cases, a non-contrast CT of the chest, abdomen, and pelvis or a non-contrast magnetic resonance angiogram should be obtained with the goal of determining the degree of aortic valve calcification and tortuosity of the peripheral vessels [45]. MRI without gadolinium contrast is another alternative for patients with acute kidney injury or CKD with GFR <30 mL/min/m^2, as it can accurately provide anatomic information needed for most aspects of the pre-TAVR assessment, apart from vascular access planning which will require the use of contrast [31, 46]. An emerging alternative for proper assessment of vascular access mapping prior to TAVR in patients with advanced kidney disease is the use of Ferumoxytol-enhanced (FE) magnetic resonance. Ferumoxytol is a novel magnetic resonance contrast agent without risk of NSF, which has been shown to provide reliable vascular mapping and aortic annular measurements in patients with CKD [47, 48].

Intra-procedure factors associated with AKI include hemodynamic fluctuations due to hypotension from bleeding, rapid ventricular pacing, and the use of general anesthesia which is more frequently required for the transapical (TA) approach [49]. Additionally, atherosclerotic emboli created during catheter manipulation of the aorta and deployment of the valve can travel to the renal vascular beds causing renal injury [50].

The choice of access route for TAVR can have a significant impact on the post-procedure incidence of kidney injury. When compared to the transfemoral (TF) approach, the TA approach is associated with higher risk of AKI. This difference is partially explained by patient demographics, as those selected to undergo the TA approach usually have a higher burden of risk factors for AKI as well as more severe and diffuse atherosclerotic disease, and thus are more prone to kidney injury. Furthermore, the use of monitored anesthesia care with moderate sedation for the TF approach is becoming more prevalent, leading to shorter procedure lengths and recovery times as well as less hemodynamic instability and AKI [51, 52].

Regardless of the type of valve intervention selected, it is imperative to stratify patients in regard to their AKI risk, and to consider involving a nephrologist early on for assistance in employing prevention strategies to minimize kidney injury [50].

5.5.2 Aortic Regurgitation

Patients with severe aortic regurgitation (AR) who are symptomatic or have echocardiographic evidence of left ventricular (LV) dysfunction or dilation should be referred for SAVR [28]. A surgical risk assessment should be performed in a similar fashion as for AS, taking into account major organ system dysfunction (which includes CKD stage 3 or worse), frailty assessment, and other procedure-specific impediments.

5.5.3 Mitral Valve Stenosis

Mitral valve stenosis (MS) in patients with CKD or ESRD occurs most commonly due to progression of MAC. Although rare in the general population, significant MAC leading to MS is not uncommon among patients who have been on hemodialysis for several years [53]. When advanced, MAC can lead to reduction in diastolic annular dilation and restriction of leaflet motion causing significant impediment of LV inflow and consequent symptoms.

Treatment of severe calcific MS should start with optimizing volume status and controlling heart rate if atrial fibrillation is present. For patients who are symptomatic despite medical therapy, choice of treatment is controversial and should include a thorough assessment of the risk/benefit ratio for surgical valve replacement. Guidelines for interventions for MS are based on outcome data generated from patients with rheumatic MS and in general, should not be extrapolated to the population with calcific MS. Due to significant calcification with risk of embolization, and because the commissures are usually spared in calcific MS, percutaneous balloon valvuloplasty is not indicated in this group. Instead, mitral valve replacement (MVR) is the intervention of choice in patients with acceptable surgical risk, though this approach carries several of its own technical challenges related to the procedure and the interaction between annular calcification and the prosthesis [54, 55].

5.5.4 Mitral Regurgitation

Patients with MAC leading to severe MR may benefit from mitral valve repair or replacement. Repair of calcific MR has been shown to be feasible and safe even in the elderly, with superior outcomes when compared to valve replacement [56, 57]. Analogous to surgical AVR, outcomes of MVR are significantly affected by kidney dysfunction, and high-risk patients are often deemed ineligible for surgery [58]. In addition, technical challenges associated with the presence of MAC frequently impede surgery in this population.

For patients with severe primary MR and prohibitive surgical risk, percutaneous edge-to-edge leaflet repair with MitraClip can be considered if anatomy is favorable. Despite the fact that kidney disease is highly prevalent among patients undergoing MitraClip, the main initial trials assessing this technology have failed to include a significant number of patients with CKD. The EVEREST (Endovascular Valve Edge-to-Edge Repair Study; NCT00209339) trial excluded those with "renal insufficiency" [59], while EVEREST II (NCT 00209274) had 3.3% of patients with CKD [60]. Subsequent higher risk cohorts such as the EVEREST II High-Risk Study (NCT01940120) [61] and the European Sentinel Registry [62] included a greater proportion of patients with abnormal kidney function, although these were smaller studies (Table 5.1).

A study utilizing the Society of Thoracic Surgeons (STS)/ACC Transcatheter Valve Therapy (TVT) registry including 5141 patients who underwent MitraClip procedure between November 2013 and June 2016 stratified patients by creatinine clearance and found that impaired kidney function was associated with all-cause mortality and new dialysis requirement [63]. The authors reported a 1-year all-cause mortality of >30% among participants with stage 4 and 5 CKD, and this association held even among patients who achieved acceptable reduction in severity of MR. Similarly, a study among a cohort of patients treated with MitraClip in 3 separate multicenter studies (EVEREST II, EVEREST II High-Risk and REALISM Continued Access) assessed renal function before and after mitral valve repair and reported a correlation between baseline kidney dysfunction and 1-year mortality. Interestingly, the authors showed that a reduction in MR severity with MitraClip was associated with improvement in renal function at 1 year among those with baseline renal dysfunction [64]. Additional studies are needed to further investigate the true impact of reduction in MR severity on kidney function and its morbidity consequences in order to determine which CKD patients would benefit from this approach.

Transcatheter mitral valve replacement (TMVR) is being evaluated as an alternative for circumstances in which the mitral valve pathology is not amenable to percutaneous repair. Unfortunately, due to potential anchoring issues, significant paravalvular leakage, and higher rates of left ventricular outflow tract obstruction, the presence of MAC is an exclusion criterion for all current TMVR systems [65, 66]. A multicenter TMVR global registry study among patients with severe MAC and extremely high surgical risk showed that the procedure is feasible but associated with high mortality at 30 days and 1 year [67]. In addition, as with studies of most cardio-

vascular therapies, patients with renal disease are underrepresented in clinical trials of TMVR and for this reason it is unclear if this population would benefit from the procedure. Further assessment of TMVR outcomes among patients with MAC with and without kidney disease in clinical trials is needed, as this might be a useful strategy for selected patients in the future.

Whenever MR occurs as a consequence of ventricular dysfunction it is referred to as secondary MR. Contemporary guidelines agree on the recommendation to first address the underlying cause and optimize heart failure treatment with medication as well as with cardiac resynchronization therapy when appropriate. However, the treatment arsenal for secondary MR *refractory* to medical therapy is currently evolving, and guideline consensus has not been reached between the American College of Cardiology/American Heart Association (ACC/AHA) and European Society of Cardiology/European Association for Cardio Thoracic Surgery (ESC/EACTS). ESC/EACTS states that MitraClip may be considered in selected high-risk patients with primary or secondary MR while the ACC/AHA guidelines reserve this indication for primary MR only [68, 69].

The COAPT trial (NCT01626079) was a landmark study of patients with severe MR and symptomatic HF, which showed superiority of transcatheter mitral valve approximation with MitraClip on background guideline directed medical therapy (GDMT) versus GDMT alone, in regard to rate of heart failure hospitalization and mortality (Table 5.1) [70]. Among those included in the trial, approximately 70% had CKD with creatinine clearance <60 mL/min. It is unclear if the cohort with CKD had worse outcomes when compared to those with normal kidney function, which would be interesting to investigate. It would also be interesting to assess if the hemodynamic changes associated with a decrease in severity of MR with MitraClip would result in improvement in kidney function on a short and long-term basis and if this would in turn impact patient outcomes. Given the prevalence and clinical importance of kidney disease among patients with functional MR and symptomatic heart failure, this technology has the potential to benefit a large cohort of extremely high-risk individuals.

5.6 Choice of Valve Type

When valve replacement is required, the determination of whether a bioprosthetic or mechanical valve is more suitable should be shared between the patient and the Heart Valve Team. This determination should take into account valve durability and the potential need for reoperation, need for chronic anticoagulation, as well as patient values and preferences. In general, mechanical valves have the convenience of being more durable, but have the disadvantages of requiring lifelong anticoagulation and carrying a higher potential risk of strokes and thromboembolism.

Patients with CKD not on dialysis should follow the general population guidelines for prosthetic choice. Both the ACC/AHA [69] and ESC guidelines [68] underline the importance of shared decision making when choosing prosthesis type. The ACC/AHA recommends giving preference to mechanical valves in patients younger than 50 years old while the ESC recommends a higher cutoff of 60 years for aortic valves and 65 years for mitral valves. The evidence to suggest the above age cutoffs is derived from large database studies. It is unclear whether they apply to the population with more advanced CKD.

While former ACC guidelines have recommended the use of mechanical valves in ESRD patients due to theoretical accelerated deterioration of bioprosthetic valves, contemporary epidemiological data as well as smaller case series studies have described no difference in survival outcomes or valve durability between patients receiving mechanical versus bioprosthetic valves. The K/DOQI guidelines state that both mechanical and bioprosthetic valves can be used among patients on dialysis with similar outcomes (Level of evidence B). However, in patients with history of life-threatening bleeding and without other indications for chronic anticoagulation, bioprosthetic valves are likely preferable [26].

The potential expansion in the feasibility of valve-in-valve procedures for degenerated bio-

prosthetic valves in the future should be considered as an additional factor in the shared decision making. For now, this discussion should be limited as data on long-term outcomes is not yet available.

5.7 Management Post-Surgery: Anticoagulation

Patients with abnormal kidney function are at significantly higher risk of bleeding with and without the use of chronic anticoagulation and antiplatelet agents. Additionally, CKD is known to promote a hypercoagulable state which can increase the risk of prosthetic valve failure [71]. For this reason, it is paramount to assess the patient's individual risk of thrombosis and bleeding before making decisions that will impact their medication profile.

Lifelong continuous anticoagulation with vitamin K antagonists (VKA) with a target INR level is required after implantation of mechanical valves regardless of level of kidney function. The specific INR goal depends on the type of valve and the presence of additional risk factors for thromboembolic events [69]. The routine use of daily low dose aspirin is also recommended by the ACC/AHA guidelines [69] but not the ESC guidelines [68]. Direct oral anticoagulants are not currently approved for use in patients with mechanical valves.

For patients with bioprosthetic valves, it is reasonable to use the combination of VKA for the first 3–6 months along with continuous use of low dose aspirin in patients with reasonable bleeding risk [69].

There is currently no consensus among different guidelines regarding the appropriate antithrombotic regimen after TAVR. In the absence of other indications for chronic oral anticoagulation, it appears that a combination of clopidogrel and low dose aspirin is reasonable at least for 3–6 months after valve implantation followed by low dose aspirin alone. In the presence of other indications for anticoagulation, an oral anticoagulant such as VKA is indicated without a concomitant antiplatelet agent. Several clinical trials are ongoing to address the fine balance between antithrombosis and bleeding risk after TAVR procedures, as well as in the setting of various other clinical scenarios such as underlying atrial fibrillation and recent coronary stenting [72]. As expected, trials involving direct oral anticoagulants largely exclude patients with severe kidney dysfunction. Fortunately, trials comparing different combinations of VKA, aspirin, and clopidogrel such as AVATAR (Anticoagulation Alone Versus Anticoagulation and Aspirin Following Transcatheter Aortic Valve Intervention; NCT02735902), POPular-TAVI (Antiplatelet Therapy for Patients Undergoing Transcatheter Aortic Valve Implantation; NCT02247128) and AUREA (Dual Antiplatelet Therapy Versus Oral Anticoagulation for a Short Time to Prevent Cerebral Embolism After TAV; NCT01642134), do not have a specific exclusion criterion regarding level of kidney function. Ideally these trials will recruit a reasonable sample size of patients with advanced CKD and shed light on the specific nuances of this high-risk population.

5.8 Conclusions

Valvular heart disease is highly prevalent in the population of patients with CKD and ESRD, and has significant impact on morbidity and mortality. There are numerous special considerations involved in the diagnosis and management of VHD in the population with advanced kidney disease and ESRD, and these should be appreciated in order to improve detection and provide appropriate and timely treatment.

The approach to treatment of aortic stenosis and mitral regurgitation is currently undergoing an exciting transition. Patients with advanced CKD are often considered poor candidates for valve surgeries because the presence of abnormal kidney function affects virtually all post-operative outcomes, and these patients could potentially benefit from less invasive, percutaneous

approaches. Recently, landmark trials of transcatheter valve therapies have promoted an expansion of the use of these techniques and this is a promising development for CKD patients. However, patients with advanced CKD and ESRD have historically been excluded from major cardiovascular trials, and thus, it is unclear whether the results of these studies can be extrapolated to this population. Further studies with broader renal inclusion criteria are needed in order to investigate the clinical utility of these interventions in this particular population.

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6 Arrythmias in Chronic Kidney Disease: Working Towards a Clinical Approach in Atrial Fibrillation

Justin Ashley and Manish M. Sood

6.1 Introduction

The arrythmia burden of patients with chronic kidney disease (CKD) and end stage renal disease (ESRD) is high [1, 2] and pose unique risks to patients' health and well-being. The interrelationship between CKD, ESRD and arrythmias is complex [1]. Both CKD and cardiovascular disease (CVD) in general are influenced independently by common disease processes such as diabetes mellitus and hypertension [3]. CVD and CKD disease processes also directly affect each other in various neuro-hormonal, cellular and biochemical pathways [1, 4]. Accordingly, it is not surprising to find that the rates of arrythmia in patients in CKD are disproportionately higher when compared to the general population [1, 4–6]. For example, ventricular arrythmia and sudden cardiac arrest is roughly four times more prevalent in the CKD population than in the general population [2]. These startling figures have significant mortality implications. Ventricular arrhythmia and cardiac arrest comprise 40% of known causes of death among patients on dialysis [2] and are believed to account for 48% of unexplained deaths in the dialysis population. Despite these sobering realties, supraventricular arrythmias, particularly atrial fibrillation, impose a larger burden of morbidity and mortality in the CKD and ESRD population.

In this article, we will focus specifically on atrial fibrillation (AF); the epidemiology of AF and its most serious complication of thromboembolic stroke; evidence and issues regarding anticoagulation therapies and lastly, clinical considerations in patients with CKD.

6.2 CKD, Atrial Fibrillation, and Stroke

Atrial fibrillation is the most common arrythmia is in the general population [7, 8] with a general prevalence of about 10% [2]. The prevalence of atrial fibrillation in the CKD and ESRD population is significantly higher at approximately 25% of the population [2]. The prevalence of atrial fibrillation increases with increasing age with

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greater than one-third of adults older than 80 years old with atrial fibrillation [7, 8] as well as other comorbidities such as diabetes, hypertension, and, most significantly, heart failure [2]. Patients with stage 3–5 CKD and heart failure have a 50% prevalence of atrial fibrillation [2]. The risk for developing de novo atrial fibrillation in CKD is associated with stages of kidney function (as measured by the estimated glomerular filtration rate, eGFR) and degree of albuminuria [4, 6]. One recent retrospective study [6] found that albuminuria (measured as albumin-creatinine ration [ACR]) and eGFR are independent risk factors for developing atrial fibrillation in chronic kidney disease. Indeed, for each 1 mL/min per 1.73 m^2 increase of eGFR, the investigators found the incidence of AF decreased by 0.4% [6]. Similarly, the incidence of atrial fibrillation increased by 0.6% per each 1 mg/mmol increase in urine albumin-creatinine ratio. Further, the greatest increase in risk of atrial fibrillation was observed when a patient transitioned from no albuminuria to microalbuminuria. The increased prevalence of atrial fibrillation in the CKD and ESRD populations are particularly worrisome as it carries significant morbidity and mortality concerns.

Chronic kidney disease and atrial fibrillation are intricately linked disease processes that share similar adverse outcomes [9]. Independently, CKD is associated with increased rates of hospitalization [10], cardiovascular complications [11, 12] and death [10]. Similarly, atrial fibrillation is related to increased risk of cardioembolic stroke [8, 13, 14], congestive heart failure (CHF) [15], myocardial infarction (MI) [16], and ultimately a detriment to one's quality of life [17]. Unsurprisingly, early evidence also demonstrates that comorbid patients with both CKD and atrial fibrillation have particularly poor clinical outcomes [9]. One recent retrospective study [9] assessing patients with eGFRs <90 mL/min/1.73 m^2 and a diagnosis of atrial fibrillation found that patients had a higher incidence of CHF, MI, and progression to ESRD when compared to CKD patients without atrial fibrillation. Further, the risk of mortality was 2.5-fold greater in the CKD and atrial fibrillation group [9]. The risk of CHF, MI, and ESRD were increased with reduced eGFR. Another study demonstrated an 80% 5-year mortality risk for a patient with ESRD and atrial fibrillation when compared to ESRD patients in sinus rhythm [18].

The relationship between atrial fibrillation, chronic kidney disease, and cardioembolic stroke is of particular clinical concern [4, 19]. Independently, atrial fibrillation increases the risk of stroke by a factor of five [20, 21]. Similarly, chronic kidney disease increases the risk of stroke independent of atrial fibrillation [20, 22]. In 2017, the prevalence of cerebrovascular accidents in the United States in the CKD population was 17.5% (as opposed to 6.9% in the general population). One large, retrospective cohort study [20] found that patients with CKD and atrial fibrillation experienced a doubling in the event rate of stroke or thromboembolism when compared to patients who had atrial fibrillation alone. Similarly, a meta-analysis of 33 prospective studies [22] demonstrated that the relative risk of stroke significantly increased among patients with an eGFR <60 mL/min/1.73 m^2 (RR 1.75; 95% CI 1.10–2.78). This effect was further pronounced when a patient had an eGFR <60 mL/min/1.73 m^2 and albuminuria (RR 2.20; 95% CI 1.45–3.3). Further complicating this picture, patients with CKD and ESRD are at increased risk of bleeding [20, 23, 24] making the management of stroke risk unclear in this unique population [3, 4, 25, 26].

6.3 Anticoagulation in Atrial Fibrillation and CKD: Shifting Paradigms to Novel Anticoagulants

Traditionally, Vitamin K antagonists (VKAs) such as warfarin have been the mainstay for stroke prevention in atrial fibrillation [27]. However, warfarin presents multiple clinical

obstacles that must be negotiated in CKD and ESRD populations [4]. Firstly, warfarin involves frequent drug monitoring to achieve an international normalized ration (INR) of 2.0–3.0. The problem is compounded in CKD and ESRD populations as these patients are at particular risk of vitamin K deficiencies [28]. As a result, these patients are often out of the therapeutic window (Time in Therapeutic Range [TTR])—the most important predictor of warfarin effectiveness and safety [29, 30]. Secondly, warfarin has well documented drug interactions that must be considered. Thirdly, early evidence suggests that warfarin increases the risk of calcific uremia arteriopathy (formerly calciphylaxis) and accelerated vascular calcification in dialysis [31]. Finally, there remains no clear evidence regarding the effectiveness of warfarin as a means for stroke prevention in patients with advanced CKD and ESRD. Indeed, warfarin may expose patients to risk of hemorrhage [24, 31–33]. Accordingly, there remains a need to identify new anticoagulants in CKD and ESRD patients that are both safe and efficacious.

Approved in 2008, the introduction of Non-Vitamin K oral anticoagulants (NOAC) were designed to address the many pitfalls associated with traditional VKAs. These anticoagulants work by directly antagonizing either factor II or Xa in the coagulation cascade [23]. Dabigatran is a direct thrombin inhibitor, a protease enzyme that is responsible for the conversion of fibrinogen to fibrin—the final step in the coagulation cascade [23, 34]. Other popular NOACs such as rivaroxaban, apixaban, and edoxaban work by inhibiting factor Xa, the rate limiting step in the clotting cascade [34]. Multiple clinical trials [35–38] and real-world studies [39–43] have identified NOACs as safer (i.e., major bleeding and all-cause mortality) and more efficacious (i.e., preventing ischemic stroke and systemic emboli) medications in the general population when compared to warfarin [35, 36, 38]. Further, these NOACs have been demonstrated to show a more predictable pharmacological profile as they have less dietary and medication interactions and have a shorter half-life [27]. This predictability and short half-life translates into less frequent blood testing and improved patient adherence.

The majority of the landmark trials assessing the efficacy and safety NOACs were conducted relatively recently. These studies are primarily responsible for the paradigm shift in the management of atrial fibrillation from VKAs to NOACs. Subsequently, the American Heart Association (AHA) and the Canadian Cardiovascular Society (CCS) have recognized both warfarin and NOACs as equivalent therapies in the management of non-valvular atrial fibrillation [44, 45]. Further, NOACs are recommended for patients who are unable to maintain a therapeutic INR.

Despite the promise of NOACs in the management of atrial fibrillation, NOACs have many challenges themselves. Specifically, unlike warfarin, NOACs do not have a standardized test to monitor effectiveness of therapeutics [34]. Nor is there a readily available antidote [3]. Secondly, all NOACs are, in various proportions, renally excreted (Table 6.1). Accordingly, as patient's CKD and estimated glomerular filtration rate (eGFR) declines the clearance of the NOAC decreases, and it is possible that these drugs reach supra-therapeutic levels in the body [46], increasing the risk for major bleeding. To address this, NOACs often have standard and reduced dosing to reflect patients with normal and reduced eGFRs (Table 6.1) [47–50].

The major trials that evaluated NOACs excluded patients with CrCl <25–30 mL/min and on dialysis; patients as discussed above have the highest risk of AF and stroke [20, 23, 51, 52]. Ultimately, this leaves the understanding of the role of NOACs in CKD and ESRD incomplete. Further, little data is available in regards to which anticoagulant is available and most appropriate for patients with CKD and ESRD. However, there is an early growing body of evidence to suggest that NOACs are safe and efficacious in patients with CKD and ESRD.

Table 6.1 Renal clearance and dosing of NOACs in patients with CKD

NOAC	Renal clearance	Renal dosing	
		Health Canada	USA FDA
Dabigatran	80%	*AF* CrCl = 30–50 mL/min: 150 mg oral twice daily CrCl <30 mL/min: Contraindicated *Treatment and prevention of VTE* CrCl 30–50 mL/min has not been studied—cannot recommend	*AF and VTE* CrCl >30 mL/min: 150 mg oral twice daily CrCl = 15–30 mL/min: 75 mg oral twice daily CrCl <15 mL/min: Contraindicated
Rivaroxaban	30%	*AF* CrCl = 30–49: 15 mg PO once daily CrCl <30 mL/min: not recommended *VTE* CrCl = 50–80 mL/min: 15 mg PO BID × 21 d then 20 mg PO daily CrCl = 30–49 mL/min: 15 mg PO BID × 21 d then 20 mg PO daily CrCl <30 mL/min: Not recommended	*AF* CrCl >50 mL/min: 20 mg PO daily CrCl = 15–50 mL/min: 15 mg PO daily CrCl <15 mL/min: Contraindicated
Apixaban	25%	*AF* 5 mg PO BID unless 2/3 are met: 1. Age ≥80 years 2. Body weight ≤60 kg 3. Serum Cr >132 μmol/L If met: then 2.5 mg PO BID CrCl <25 mL/min: contraindicated *VTE* 10 mg PO BID × 7 d followed by 5 mg PO BID No dose adjustment in patients with CrCl >30 mL/min CrCl <29 mL/min: contraindicated	*AF and VTE* 5 mg PO BID unless 2/3 are met: 1. Age ≥80 years 2. Body weight ≤60 kg 3. Serum Cr >132 μmol/L If met: Then use 2.5 mg PO BID CrCl <25 mL/min: contraindicated
Edoxaban	50%	*AF and VTE* 60 mg PO daily unless 1 ≥ of following criteria met: 1. CrCl 30–50 mL/min 2. Body weight ≤60 kg 3. Concomitant use of P-gp inhibitors (except amiodarone and verapamil) If met: then 30 mg PO daily CrCl <30 mL/min: contraindicated	*AF and VTE* CrCl 15–50 mL/min: 30 mg PO daily CrCl <15 mL/min: contraindicated

AF atrial fibrillation, *BID* twice daily, *CI* contraindicated, *Cr* creatinine, *CrCl* creatinine clearance in mL/min, *d* days, *FDA* Food and Drug Administration, *PO* oral, *USA* United States of America, *VTE* venous thromboembolism

6.3.1 NOACs Versus Warfarin

The majority of the trials assessing the safety of NOACs in the general population have been reviewed elsewhere [27, 34, 51, 53]. There has also been a growing body of evidence that has assessed the safety of and efficacy of NOACs for stroke and systemic embolism in the chronic kidney disease population. In general, data from meta-analysis have identified NOACs as non-inferior or superior therapies in the prevention of stroke and systemic embolism with a similar or improved safety profile (in regard to major bleeding) when compared to warfarin.

The efficacy of NOACs have been assessed in two recent meta-analyses [26, 54]. Harel et al. (2014) [54] analyzed eight RCT that compared three NOACs (rivaroxaban, dabigatran, and apixaban) against VKAs in participants with atrial fibrillation and a creatinine clearance (CrCl) <50 mL/min. The study found that the risk of stroke was similar between NOACs and VKAs. Another meta-analysis of five major

NOAC RCTs [26] performed a subgroup analysis of patients with a CrCl<50 mL/min and the efficacy of three treatment modalities: Warfarin, Low Dose NOACs (Dabigatran 110 mg and Edoxaban 30 mg or 15 mg for renally dose reduced), and High or single dose NOACs (Dabigatran 150 mg, Apixaban, Rivaroxaban, Edoxaban 60 mg or 30 mg for renally dosing). The meta-analysis identified a 21% reduction in the odds of stroke or systemic embolism in the full dose NOAC strategy when compared to patients on warfarin. Encouragingly, the low dose NOAC strategy demonstrated a 29% reduction in stroke compared to warfarin [26]. These results suggest that NOACs as a class of medications are non-inferior or potentially superior to warfarin in preventing strokes and systemic embolism in patients with atrial fibrillation and chronic kidney disease.

In regard to safety, four recent meta-analyses continue to demonstrate NOACs as safer or equivalent therapies to warfarin [26, 54–56]. Ando and Capranzano (2017) [26] identified a significant reduction of major bleeding with NOACs versus warfarin in a dose dependent fashion. Similar results were identified by Bai et al.'s (2016) meta analysis of three RCTs [55] which identified a 19% reduction in composite bleeding outcomes for NOAC users compared to warfarin. Harel et al. (2014) [54] and Raccah et al. (2016) [56] found that the risk of intracranial hemorrhage was significantly reduced in patients with CKD on NOACs when compared to warfarin [54] although other safety parameters (major bleeding or clinically relevant bleeding) were not significantly different. Cumulatively, these meta-analysis continue to affirm that NOACs, as a class of drugs, offer either an equivalent [54, 56] or superior safety [26, 55] and efficacy profile than VKAs in patients with CKD.

These meta-analysis lend credence to the idea that NOACs are generally safer that VKAs in the management of stroke prevention in patients with atrial fibrillation and CKD. However, as identified above, these studies offer little insight into how individual NOACs compare to warfarin.

6.3.2 Individual NOACs and Post-Hoc Analyses

Recent post-hoc, sub-group analyses of the major NOAC trials [46, 57–60] have identified individual NOACs as safe and effective therapies for patients with reduced creatinine clearance. For example, the Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation (ROCKET-AF) RCT [38] was re-analysed to assess whether rivaroxaban (versus warfarin) was still a safe and effective drug in patients who experience worsening renal function (WRF) defined as a >20% decrease of creatinine clearance (CrCl) during the course of the study [46]. Patients with WRF randomized to rivaroxaban had an approximately 50% reduction in the risk of stroke or systemic embolism when compared to warfarin with similar rates of major bleeding. A similar re-analysis of the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) RCT [36] found that patients randomized to apixaban had improved outcomes regardless of CrCl [58]. Further, investigators found a non-significant reduction in the relative risk of ischemic stroke and major bleeding in patients with WRF. Finally, re-analysis of the Randomized Evaluation of Long-Term Anticoagulant Therapy (RELY) trial [35] found that either dosing strategies of dabigatran (110 or 150 mg twice daily) was safer and more effective than warfarin in patients with CKD and atrial fibrillation for stroke prevention [59]. These studies demonstrate individual NOACs are non-inferior or superior to warfarin in regards to reducing both stroke reduction and major bleeding.

6.3.3 Network Meta-Analyses

A major limitation of these post-hoc analyses are primarily a function of low patient numbers in sub-groups. Further between the meta-analyses that assess NOACs in general and the individual post-hoc analyses, these studies provide little insight into which NOACs should be used in the CKD and potentially ESRD populations. To date,

there have been no NOAC head-to-head trials [26, 54–56]. Two of the meta-analyses try to address these issues by way of network analyses [26, 56]. This is a statistical method that allows researchers to take data from different RCTs and create indirect comparisons of NOACs against each other as well as warfarin. Through this method, Ando and Capranzano [26] was only able to identify dabigatran 150 mg twice daily as the statistically superior therapy in regards to stroke reduction in the CKD population compared against warfarin and other NOACs. Of note, apixaban was identified as the second most effective NOAC. In regards to safety and major bleeding, Dabigatran 150 mg twice daily was found to offer the highest risk. Instead, the network analyses [26, 56] identified apixaban and low dose edoxaban (30 or 60 mg twice daily) as the only statistically superior NOACs for safety. These network analyses point towards apixaban as potentially the NOAC that strikes the finest balance between efficacy and safety in stroke prevention for CKD patients with atrial fibrillation.

6.3.4 Post-Marketing Observational Surveillance Studies

The RCTs, post-hoc analyses, and meta-analyses have contributed heavily to establish the safety and efficacy of NOACs in the CKD population. However, interpreting the data of these studies are problematic. Firstly, the conditions and rigors inherent to RCTs can render them poor reflections of the modern clinical setting. Post-marketing observational surveillance studies complement RCTs as they provide information on real world prescribing practices, safety and clinical outcomes outside the confines of RCTs [41]. Secondly, the NOAC RCTs in particular are limited due to the underrepresentation of elderly patients with CKD and exclusion of patients with ESRD [41, 51, 54]. This is particularly problematic as are these patients are the most at risk atrial fibrillation, stroke, and death [2]. With improved methodologies and statistical methods, post-marketing observational surveillance studies have been instrumental for demonstrating the safety and efficacy of NOACs in the real world and for the most vulnerable patients [61].

Post-Marketing surveillance studies have also assessed NOACs individually. Apixaban is particularly intriguing as it is currently the only FDA approved NOAC for patients with CrCl<15 mL/min [62]. One retrospective cohort study assessed apixaban use in hospitalized patients with ESRD on HD identified a weak association between higher cumulative apixaban exposure, number of HD sessions, hospital length of stay and increased risk of major or clinically relevant bleeding [62]. The results of these studies challenged the FDA guidelines and encourage prudence in the use of apixaban in patients with ESRD. However, other observational studies have found apixaban to be similar in safety and efficacy to warfarin [63–65]. A small, retrospective cohort study of patients with ESRD found apixaban non-inferior to warfarin in regards to stroke reduction but noted a non-statistically significant 9% reduction in risk of bleeding [63]. Another study [64] found no difference between apixaban and warfarin for ESRD patients on HD in regards to both stroke prevention and clinically relevant bleeding. Finally, one study found that rates of ischemic stroke with apixaban within a 1 year period was higher than patients on warfarin [65]. However, apixaban still offered a safer profile in regards to bleeding.

Post-marketing observational surveillance studies have identified similar results for rivaroxaban and dabigatran. In a study of patients with atrial fibrillation either on rivaroxaban or warfarin, Weir et al. [66] found that rivaroxaban had lower rates of stroke (approximately 60%) compared with warfarin. A subgroup analysis of different creatinine clearances found that rivaroxaban was particularly beneficial in the group with CrCl <50 mL. The investigators found rivaroxaban to be non-inferior to warfarin in regards to major bleeding. Two other studies found rivaroxaban and dabigatran to be non-inferior to war-

farin in regards to both efficacy and safety [54, 65]. Of note, an important real-world study found that the use of dabigatran and rivaroxaban in ESRD increased the risk of major hemorrhage and death. These studies continue to reinforce the relative safety and efficacy of rivaroxaban and dabigatran in CKD in relation to warfarin.

6.4 Working Towards a Clinical Approach to Stroke Prevention CKD and Atrial Fibrillation

Patients with chronic kidney disease are at increasing risk of atrial fibrillation as a function of both decreasing eGFR and proteinuria [2, 6, 20]. Although atrial fibrillation places patients at increasing risk of ischemic stroke [2, 3], patients with CKD are also at greater risk of increased bleeding and hemorrhage [24, 33]. Clinicians are frequently tasked with finding the right balance for their patients. However, the evidence in this area is often conflicting or difficult to interpret as this vulnerable population is often poorly represented or excluded altogether in clinical trials [3, 25]. Further, the evidence base is still incomplete as head-to-head trials comparing warfarin against NOACs are yet to be completed [3]. Ultimately, the uncertainties in this area make developing a clinical approach to stroke prevention in atrial fibrillation a difficult area to navigate.

With the current available evidence, NOACs offer an acceptable balance of efficacy and safety for patients with mild to moderate CKD [13, 25, 26, 44, 55, 66]. As discussed above, NOACs demonstrate superior or non-inferior profiles to warfarin. Given the intricacies and difficulties of warfarin, NOACs potentially offer a safe method to prevent stroke in patients with mild to moderate CKD and atrial fibrillation. Careful attention must still be given to patients with declining eGFR either acutely or chronically as NOACs are renally cleared and can accumulate leading to supratherapeutic levels. In regards to which NOAC should be considered, the combination of RCTs, meta-analyses, and post-surveillance marketing studies seem to point to apixaban as a generally safe approach [8, 25, 26, 34, 36, 56].

The most difficult decisions for clinicians is whether to initiate anticoagulation in the severe CKD, ESRD, and HD populations [4, 33, 67]. Currently, no major guidelines recommend NOAC use in patients with ESRD or hemodialysis [8, 13, 45] and recommend warfarin if anticoagulation is considered. However, current research continues to identify VKAs may confer no benefit of stroke prevention while increasing the risk of hemorrhage [68–70]. Given the state of the evidence for NOACs and warfarin in CKD and ESRD, the most recent guidelines from Kidney Disease: Improving Global Outcomes (KDIGO) urge clinicians to use prudence when prescribing anticoagulation for patients with CrCl <30 mL/min (Table 6.2) [19, 71]. Apixaban, edoxaban, and rivaroxaban all have recommended dosing for CrCl between 15–30 mL/min. Dabigatran and edoxaban are explicitly not recommended for any patient with a CrCl <15 mL/min whether or not the patient is on dialysis. Conversely, KDIGO suggests reduced dosing for apixaban and rivaroxaban (Apixaban—2.5 mg twice daily, Rivaroxaban—15 mg daily) while acknowledging that these recommendations are based on a paucity of data. Warfarin use for patients with a CrCl 15–30 mL/min is identified as an area of clinical equipoise [19].

Risk scores to aid in determining who benefits from anticoagulation are commonly used clinical tools in the general population with atrial fibrillation [4]. However, it is currently unclear as to the degree atrial fibrillation contributes to stroke risk in the hemodialysis population [72]. Currently, KDIGO endorses the use of CHA_2DS_2-VASC score for patients with CKD and ESRD. This has been challenged by recent reviews [72] arguing that both the $CHADS_2$ and CHA_2DS_2-VASC demonstrate poor concordance in general as well as poor validation in patients with CKD and ESRD. Other risk scores such as R_2CHADS_2 (includes CrCl <60 mL/min) and ATRIA (eGFR <45 mL/min/1.73 m^2) incorporate renal impair-

Table 6.2 KDIGO oral anticoagulant recommendations for patients with advanced CKD and ESRD

eCrCl (mL/min)[a]	Warfarin	Apixaban[b]	Dabigatran	Edoxaban	Rivaroxaban
15–30	Adjusted dose for INR 2–3 could be considered	2.5 mg PO b.i.d. could be considered	Unknown (75 mg PO b.i.d.)[c,d]	30 mg QD[e] could be considered	15 mg QD could be considered
<15 not on dialysis	Equipoise based on observational data and meta-analysis	Unknown (2.5 mg PO b.i.d.)[c]	Not recommended	Not recommended	Unknown (15 mg QD)[c]
<15 on dialysis	Equipoise based on observational data and meta-analysis	Unknown (2.5 mg PO b.i.d.)[c]	Not recommended	Not recommended	Unknown (15 mg QD)[c]

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INR international normalized ratio
Doling of direct oral anticoagulants (DOACs) based solely on limited pharmacokinetic and pharmacodynamic data (no randomized efficacy or safety data exist)
[a]Cockcroft-Gault estimated creatinine clearance
[b]Apixaban dose needs modification to 2.5 mg b.i.d. if patient has any two of the following: serum creatinine ≥1.5 mg/dL, age ≥80 years, or body weight ≤60 kg
[c]DOAC doses listed in parenthesis are doses that do not currently have any clinical safety or efficacy data. The doses of DOACs apixaban 5 mg b.i.d.[b], rivaroxaban 15 mg QD and dabigatran 75 mg b.i.d. are included in the United States Food and Drug Administration approved labelling based on limited dose pharmacokinetic and pharmacodynamics data with no clinical safety data. We suggest consideration of the lower dose of apixaban 2.5 mg PO b.i.d. in CKD GS/GSD to reduce bleeding risk until clinical safety data are available
[d]Dabigatran 75 mg available only in the USA
[e]The dose was halved if any of the following: estimated CrCl of 30–50 mL/min, body weight of ≤60 kg, or concomitant use of verapamil or quinidine (potent P-glycoprotein inhibitors)

ment in their calculation. However, these scores treat kidney function as binary. Therefore, they fail to capture the increasing risk of stroke with worsening renal function [6]. Further, the factors that truly influence stroke risk in chronic kidney disease are yet to fully be elucidated including uremic effects on hemostasis and atherogenesis [72], albuminuria [73], and mineral bone disease [72, 74].Ultimately, deciding not only which patients should be anti-coagulated but which anti-coagulant to use is a clinical conundrum that warrants further exploration.

Again, the limited existing data (largely from observational studies) identifies NOACs as a potentially safe option [64–66, 75]. However, caution must be taken in NOAC choice. Indeed, one post-marketing surveillance study found dabigatran and rivaroxaban increase the risk of major bleeding compared to warfarin in the HD population [76]. Accordingly, the safest NOAC to prescribe in HD is likely apixaban [64].This is further reflected in the FDA's decision to identify apixaban as the only approved NOAC in patients with ESRD and on HD [3]. This decision is largely founded on early pharmacokinetic and pharmacodynamic studies and must be interpreted cautiously. Ultimately, the decision to anticoagulated a patient with CKD and atrial fibrillation will have to be individualized to each patient and with clinical vigilance [8, 13, 45].

6.5 Conclusion

In summary, the arrythmia burden in the CKD and ESRD population is high and carries with it a significant risk for morbidity and mortality. Atrial fibrillation—the most common arrythmia in the general population—has an increased prevalence in the CKD population and carries with it significant cardiovascular risks, particularly carioembolic stroke. The vitamin k antagonist, warfarin, is currently the mainstay of stroke prevention in the CKD population. However, there is an early developing body of evidence drawn from retrospective studies, post-hoc analyses, and meta-analyses that have identified NOACs as non-inferior alternatives to warfarin with an

improved safety profile. This data is still in its infancy and is limited in the role of NOACs in ESRD and HD patients as well as head-to-head comparisons of NOACs. Currently, early evidence suggests that apixaban may best balance stroke reduction with risk of bleeding. Ultimately, current guidelines recommend careful clinical judgement when prescribing anticoagulation in the ESRD and HD populations and on a case-by-case basis.

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Type 1 Cardio-Renal Syndrome

7

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7.1 Introduction

Co-existence of renal dysfunction is common in patients with heart failure (HF) and often leads to adverse clinical outcomes [1]. The term "cardio-renal" was introduced as early as 1913 by Dr. Thomas Lewis, who described a unique form of paroxysmal dyspnea in the setting of concomitant cardiac and renal dysfunction [2]. The following year, Dr. Alfred Stengel proposed the classification of cardio-renal diseases into three distinct forms: (1) primary valvular or myocardial disease with secondary renal disease; (2) primary arterial or arteriolar disease with secondary renal and myocardial disease; and (3) primary renal disease with secondary myocardial and vascular disease [3].

After a century of medical progress, our contemporary classification scheme for cardio-renal syndrome (CRS) remains largely descriptive of such temporal bi-directional relationships between cardiac and renal dysfunction without specifying precise mechanistic culprit(s) [4]. Nevertheless, there is general agreement that adverse interactions between the kidneys and circulatory components promote increased circulating volume, exacerbate HF symptoms, and accelerate subsequent disease progression [5]. In contrast, contribution of various non-cardiac factors that have been proposed some half a century ago may still be under-recognized [6]. This chapter will review the classical mediators of cardio-renal injury through which acute HF aggravates renal dysfunction leading to Type 1 CRS, and outline the directions for further investigation beyond our current management strategies.

7.2 Definition of Acute (Type 1) Cardio-Renal Syndrome

Clinicians have largely considered acute (or "Type 1") CRS as equivalent to the working definition outlined in a National Institute of Health

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workshop for acute CRS as "an extreme form of cardio-renal dysregulation in which therapy to relieve congestive symptoms of HF is limited by further decline in renal function." [7] There are several key words in this definition: (1) "dysregulation" refers to the dysfunctional cross-talk between the heart and the kidneys to maintain salt and water homeostasis; (2) "congestive symptoms" refers to the volume overloaded state related to HF; and (3) "limited by further decline in renal function" refers to the refractoriness to standard diuretic regimen (sometimes considered as "diuretic resistance"). In simpler terms, the intention to treat congestive HF by aggressive diuresis was deemed inadequate as a result of ineffective renal responses.

It is important to emphasize here that considerations of "abnormal renal function" still relied on indirect biomarkers that estimate glomerular filtration or function (e.g. clearance of creatinine/cystatin C, and leakage of albumin/protein) rather than biomarkers of tubular function (e.g. clearance of urea or toxins, and handling of electrolyte homeostasis). On the other hand, reliable insights into renal hemodynamics remained limited. Therefore, the precise processes and mechanisms in which the kidneys endure injury remain unclear in the setting of acute CRS [8].

7.3 Factors Contributing to the Development of Acute CRS

Contributing factors to the development of acute (Type 1) CRS include hemodynamic disturbance, neurohormonal activation, and inflammation (Fig. 7.1).

Impaired Cardiac Output. In the setting of acute HF, reduced cardiac output can lead to impaired renal blood flow and perfusion, which has long been proposed as the primary driver of renal dysfunction and subsequent injury [9]. Indeed, acute kidney injury (AKI) is more prevalent and severe with impaired cardiac output, being reported more than 70% in cardiogenic shock [10]. Improvement in serum creatinine levels shortly after implantation of left ventricular assist devices also highlights the pathophysiological importance of hemodynamic disruption in CRS [11]. However, this once-prevailing concept of "arterial underfilling" as the single perpetrator of CRS cannot be fully explained by clinical observations, since the majority of patients presented with acute HF also have relatively preserved cardiac output [12–15]. It is likewise important to note that a rise in serum creatinine may not be the primary abnormality to reflect

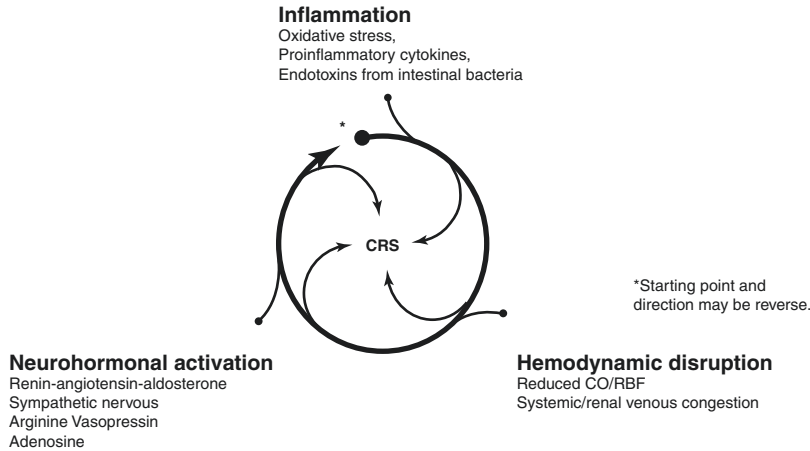

Fig. 7.1 Key Contributors to Cardio-Renal Syndrome. Despite efforts to establish a hierarchy, there seems to be no such hierarchy among cardio-renal connectors. Inflammatory reaction, an activated neurohormonal system and hemodynamic disruption become connected during the subclinical stage of CRS, starting a vicious cycle but staying in a subclinical stage for a period

underlying hemodynamic derangements, as hypochloremia may also be triggered by underlying low cardiac output state [16–18].

Systemic Venous Congestion. Over the past decade, there is growing understanding of an inverse relationship between central venous pressure (CVP), renal blood flow (RBF), and glomerular filtration rate (GFR) in the setting of HF [19]. Like impaired cardiac output, elevated CVP can lead to increased renal interstitial hydrostatic pressure, resulting in a decreased net filtration pressure, and progressive renal dysfunction [20]. This can be exacerbated in the setting of acute decompensated HF, whereby increased CVP on admission as well as insufficient reduction of CVP during hospitalization can be stronger hemodynamic determinants for the development of worsening renal function compared to diminished cardiac index [21]. Recent mechanistic demonstrations with saline loading experiments have further confirmed the impact of increasing "venous impedance" at the level of the kidney on attenuation of diuresis and natriuresis [22, 23]. These observations may imply that beyond impaired renal perfusion in low cardiac output state, the inability to mobilize venous congestion despite aggressive diuresis can also trigger acute (Type 1) CRS.

Raised Intra-Abdominal Pressure. One of the commonly-overlooked contributors of acute CRS is extra-cardiac hemodynamic alteration in the abdominal cavity [24]. Especially in the setting of overt right-sided HF with significant venous congestion or in post-operative/obstructive settings with ileus or organ swelling, abdominal congestion in the form of splanchnic venous and interstitial congestion can manifest via compromised capacitive function of the splanchnic vasculature and deficient abdominal lymphatic flow resulting in interstitial edema [24]. Increased intra-abdominal pressure detectable via bladder manometry, in extreme cases of abdominal congestion, is correlated with renal dysfunction in advanced refractory congestive heart failure [25].

Pre-existing Renal Insufficiency. The most common scenario whereby acute (Type 1) CRS occurs is due to pre-existing renal dysfunction, which may cause worsening pressure and/or volume overload. Furthermore, chronic uremia can induce left ventricular hypertrophy, promote cardiac fibrosis, and induce systemic oxidant stress [26]. Up to one third of patients hospitalized with acute decompensated HF have concomitant AKI (here referred to rise in biomarkers of glomerular filtration accompanying oligouria), and 60% of patients with acute HF who did not have AKI on admission eventually developed AKI during hospitalization [27]. The co-occurrence of AKI in patients with acute HF worsens survival in those patients [28]. While we do not fully understand the mechanisms leading to increased cardiovascular complications among chronic kidney disease (CKD) patients, worsening renal function in patients with HF is primarily caused by reduced renal perfusion pressure following hemodynamic derangement as the primary culprit. However, when renal dysfunctions become clinically noticeable in the setting of HF, over-activation of neurohormonal systems and systemic inflammation occurs concomitantly with progressive deterioration of cardiac function, making it difficult to single out the culprit among the cardio-renal mediators.

Neurohormonal Mediators. The concept of neurohormonal system activation because of circulatory perturbations plays a large part in our expanded understanding of renal physiology and sodium homeostasis [29]. Activated renin-angiotensin system (RAS) and the sympathetic nervous system (SNS) are prototypical cardio-renal mediators that have diverse influences on hemodynamic components such as right atrial/ventricular compliance, venous capacitance, and returning volume of venous blood [30]. Teleologically, over-activated RAS restores renal perfusion pressure by sustaining intraglomerular pressure and promoting volume expansion [31]. However, while angiotensin restores intraglomerular pressure by constricting efferent arterioles, ensuing vasoconstriction of systemic resistance vessels results in increased afterload and detrimental cardiac function [31]. Excessive urinary sodium and chloride loss caused by aggressive diuresis may induce renin release that increases renal sodium avidity, which is a natural response to dehydration [32]. Avid sodium reabsorption

and water retention in the presence of an overactive RAS further aggravates HF and sets up the vicious cycle of CRS [8, 33, 34].

An over-activated RAS can also worsen renal dysfunction through non-hemodynamic mechanism [8]. For example, angiotensin II stimulates production of proinflammatory mediators (e.g. tumor necrosis factor [TNF]-α, interleukin-6, monocyte chemoattractant protein-1, nuclear factor kappa-light-chain-enhancer of activated B cells [NF-κB]) and mobilizes inflammatory cells in the glomeruli. Following cell proliferation, fibrosis and apoptosis eventually progress in the heart and kidneys [35]. Of note, mineralocorticoid in concert with angiotensin II stimulates macrophages in the kidney to secrete galectin-3, a HF biomarker in recent spotlight, which in turn induces proliferation of pericytes, deposition of collagen, and eventual renal fibrosis [36].

Although its deleterious effects in renal injury are less elucidated than in HF [31], the over-activated SNS also contributes to the development of renal dysfunction [37]. First, efferent sympathetic nerves are activated by ischemia/reperfusion injury, a common clinical cause of AKI in various clinical settings [38]. Renal ischemia increases glomerular expression of tyrosine hydroxylase, a rate limiting enzyme of noradrenaline production, suggesting morphological alterations of adrenergic nerve terminals in glomeruli of ischemic AKI [39]. The activated SNS facilitates renal fibrogenesis, tubular vasoconstriction, and reduces GFR in manners dependent on endothelial dysfunction and inflammation, acting jointly with elevated angiotensin II and increased oxidative stress [38]. Adrenergic receptors and endothelin receptors are a superfamily of G protein coupled receptors (GPCR). Transverse aortic constriction elevated renal GPCR signaling and endothelin expression in mice, and then led to deterioration of renal function. In addition, pharmacologic inhibition of GPCR alleviated renal dysfunction [40].

Sympathetic nerve denervation can increase basal renal flow, urine flow rate, fractional sodium excretions, and GFR in rats after renal ischemia/reperfusion injury. The denervated rats had less congestion in the medullary portion, lower level of inflammation, and reduced tubular damage than rats with intact sympathetic activity [41, 42]. In mice with transverse aortic constriction, sympathetic renal denervation did not only blunt the increase in norepinephrine level but also blocked reno-cardiac signaling, which was essential for cardiac hypertrophy in response to pressure overload [43]. Recently, a few small-sized human studies reported renal denervation improved cardiac and renal function [44, 45]. Despite skepticism, observations of renal sympathetic over-activity in patients with CRS support continuing innovative investigational strategies for renal sympathetic denervation [31].

Inflammatory Mediators. Ample evidence has supported the inflammatory process as an important pathology of both cardiovascular disease and CKD. In humans, the circulating level of TNF-α was elevated in severe HF with cachexia and was associated with adverse clinical status as well as RAS system activation [46, 47]. When HF with reduced ejection fraction (HFrEF) patients had acute decompensation, biomarkers for inflammatory response such as high sensitivity C-reactive protein, myeloperoxidase, TNF-α, and galectin-3 continued to increase even after clinical improvement, which implied a unique role of inflammation in the pathophysiology of HF exacerbation [48]. In addition, activation of the complement system occurs in HFrEF, where dysregulated alternative pathways of the complement system can worsen the disease severity [49]. Increase in interleukin-6 may also be mechanistically linked with cardio-renal dysregulation [50].

When we induced chronic HF in mice after coronary artery ligation, the peripheral fraction of pro-inflammatory monocytes/macrophages increased with profound splenic remodeling, representative of augmented antigen processing. In particular, splenectomy resulted in cardiac reverse remodeling and attenuated tissue infiltration of inflammatory cells, while adaptive transfer of splenocytes into naïve mice led to resumption of immune-cell mediated injury, which suggested the central role of the mononuclear cell phagocyte network in chronic inflammation and HF progression [51]. In a similar animal model, activated monocytes and macrophages increased in kidney as well as

peripheral blood, mRNA expression of inflammatory cytokines was augmented, and microvascular endothelial permeability and renal tubular cell apoptosis increased through the acute and subclinical phases [52]. Further, depletion of monocytes or macrophages led to alleviation of tubular cell apoptosis and renal fibrosis [52]. Meanwhile, pharmacologic therapy targeting interleukin-1 inhibition [53] or glucocorticoid therapy to promote uricosuria [54] have provided some proof-of-concept demonstrations regarding the inflammatory hypothesis of acute CRS but would require further validation.

Metabolic Contributions. Patients with HF had more permeable intestinal walls than healthy controls, and more pathogenic bacteria were cultured in stool from HF patients. These findings were prominent in patients with severe HF symptoms. Particularly higher serum inflammatory markers in HF patients alluded to bacterial translocation through intestinal walls, which, in turn, is attributable to increased intestinal permeability resulting from intra-abdominal venous congestion [55, 56]. When we incubated renal tubular cells in plasma obtained from CRS septic patients, they had higher levels of apoptosis and caspase-3,-8,-9 expression in plasma with higher endotoxin activity than in plasma with lower endotoxin activity. Plasma inflammatory cytokines were associated with high endotoxin activity and assumed to mediate both extrinsic and intrinsic apoptosis of renal tubular cells, suggesting the presence of detrimental humoral factors in cross-talk between distant organs [57, 58]. Therefore, it is possible that translocation of bacterial endotoxin through intestinal walls worsens renal function in HF patients [59]. Phagocytic systems can generate catecholamine when exposed to bacterial endotoxins, while the disconnection of phagocytes from the autonomic nervous systems leads to reduced inflammatory responses [60]. The autonomic nervous system can influence immunity such as toll-like receptor ligation. During the inflammatory reflex, cytokines locally released from immune cells can transmit signals to the central nervous system through activated vagal afferent nerves [61].

Uremic Toxins. Deterioration of renal function leads to accumulation of protein-bound uremic toxins, such as indoxyl sulfate and p-cresyl sulfate and a tryptophan metabolite produced by gut microbiota, which are excreted by the healthy kidney. Exposure to these uremic toxins can cause, in part, the loss of kidney function [62–64]. Uremic toxins originate mainly from protein metabolism, food intake, and can be produced by gut microbiota. In addition to the rise in production, there is an increase in intestinal permeability in CKD allowing a greater absorption of those uremic toxins. [65] The retention of these substances has been associated with an inflammatory state, progression of CKD, cardiovascular disease, and risk of death in CKD patients [66–68].

There have been reports that oxidative stress can induce cardiac injury, [69] and urinary indoxyl sulfate excretion was reported to have a positive linear relationship to oxidative stress markers in cardiac tissue [70]. Increased levels of indoxyl sulfate were also associated with chronic inflammation, through indoxyl sulfate-associated pro-inflammatory cytokines, such as TNF-α, IL-6, and IL-1β, leading to left ventricular hypertrophy and cardiac fibrosis [71]. Indoxyl sulfate caused cardiac fibrosis and cardiomyocyte hypertrophy in salt-sensitive hypertensive rats, accompanied by increased oxidative stress marker expression, and decreased anti-oxidative protein expression in cardiac tissue [72]. Reduction in serum indoxyl sulfate levels caused decreased myocardial fibrosis in subtotal-nephrectomized rats [73]. Indoxyl sulfate entered cardiac fibroblasts through OAT1/3, and significantly increased collagen synthesis via activating p38, p42/44 MAPK, and NFκB pathways [71, 74]. Elevated levels of indoxyl sulfate were associated with an increased risk of left ventricular diastolic dysfunction in humans [75]. Thus, emerging evidences from clinical and experimental studies reveal that indoxyl sulfate plays a role in the progression of cardiovascular disease in CKD patients. Although other protein-bound uremic toxins possibly also are involved in the pathogenesis of cardiovascular disease, investigation of the cardiovascular effects of the uremic toxins has been limited to a few toxins. Furthermore, a demonstration that treating indoxyl sulfate leads to improved cardiovascular outcomes is lacking.

7.4 Preventing Type 1 CRS: Identifying Sub-Clinical Cardio-Renal Injury

The key to managing acute (Type 1) CRS is to prevent cardio-renal injury by recognizing the underlying substrates at subclinical stages and preventing the development of cardiac and renal failure (Fig. 7.2). This concept, while logical, has not been fully embraced due to the lack of insights into these potential treatable targets.

Biomarkers to Detect Cardio-Renal Injury. The Acute Decompensated Heart Failure National Registry (ADHERE) reported the prevalence of renal insufficiency was about 30% but also likely underestimated [76]. With technological advances, more sensitive and specific novel biomarkers of early organ injuries have been proposed in order to help identify high-risk patients before progression to irreversible stages of CRS [77, 78]. It is therefore postulated that like cardiac troponins for acute coronary syndromes, early detection with AKI biomarker may identify the cohort of patients at higher risk of developing Type 1 CRS and then be triaged to appropriate interventions. Biomarkers of renal tubular damage, such as neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule 1 (KIM1), interleukin-18 (IL-18), liver-type fatty acid binding protein (L-FABP), and tissue inhibitor of metalloproteinase 2 plus insulin-like growth factor-binding protein 7 (TIMP2-IGFBP7), have all been investigated for this purpose [79]. However [80], circulating NGAL (a protein of the lipocalin superfamily) was not superior to creatinine for the prediction of worsening renal function (WRF) or adverse in-hospital outcomes [81, 82]. In contrast, few if any acute HF patients who experienced WRF had elevated urinary NGAL levels, and even if levels were high they did not track with poor outcomes despite having pre-existing renal insufficiency [83, 84]. Despite early optimism, few studies have demonstrated the ability of urinary kidney injury biomarkers to provide any prognostic insights or therapeutic directives [84–86].

Weight Loss. Obese individuals, even without frank diabetes mellitus, are at risk of CRS development. Obesity *per se* can induce long-standing glomerular hyperfiltration and obesity-related glomerulopathy, evidenced by focal segmental glomerular sclerosis, foot process effacement,

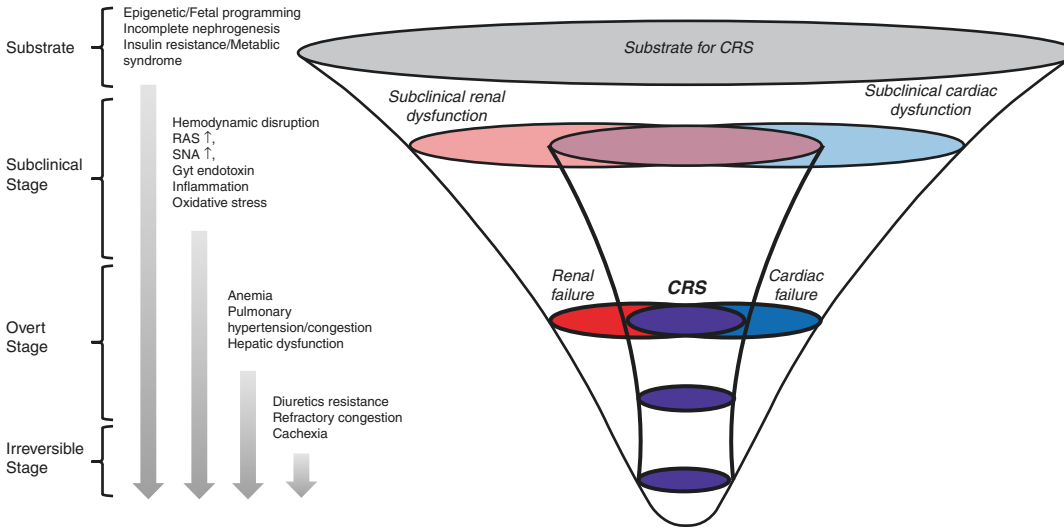

Fig. 7.2 Conceptual Framework of Acute (Type 1) Cardio-Renal Syndrome. Once overt cardio-renal syndrome ensues, it seems very difficult to reverse the natural course of disease. Therefore, early detection of patients at risk of cardio-renal syndrome may be a better therapeutic strategy. At the subclinical period of cardio-renal syndrome, there are substrates for renal dysfunction in, particularly, patients with heart failure. Medical resources may be concentrated on these patients to prevent further deterioration of renal function

and glomerulomegaly [87–90]. In an animal model of HFpEF and insulin resistance, glycosuria/proteinuria and microvascular fibrosis were highly analogous to the earliest change of the human cardio-renal syndrome, suggesting the presence of CRS substrate in humans as well [91]. Indeed, phenomapping of HFpEF subtypes has identified a "natriuretic peptide deficient" subtype that likely promotes fluid retention [92]. Intensive lifestyle intervention reduced the incidence of CKD after long-term follow-up, through reductions in bodyweight, HbA1c, and systolic blood pressure [93–95]. An enhanced metabolic profile via weight reduction in patients with obesity-associated cardio-renal disease draws attention for a novel therapeutic option [96, 97].

7.5 Managing Type 1 CRS

The latest consensus statement in diuretic use highlighted this goal-targeted strategy (Fig. 7.3), with the introduction of assessing urine output or urine sodium excretion following initial dosing of loop diuretics to assess diuretic efficacy [98]. This is based on observations that urine sodium excretion is diminished in acute HF requiring pharmacologic augmentation, and that insufficient natriuresis either due to abnormal drug delivery at the site of action and/or inadequate urine excretion due to renal sodium avidity may contribute to poor diuretic responses and adverse long-term outcomes [99, 100].

Loop Diuretics. Escalation of intravenous (IV) loop diuretic has been the mainstay of decongestion in HF, and often the key adjustment in Type 1 CRS since most patients remain diuretic responsive. The key determination remains whether loop diuretic dosing is insufficient or whether diuretic resistance is inevitable. Effective diuresis with good urine output despite a rise in serum creatinine or "worsening renal function" should not be classified as CRS. In fact, these patients actually have favorable long-term outcomes [101]. The Diuretic Optimal Strategy Evaluation in Acute Heart Failure (DOSE-AHF)

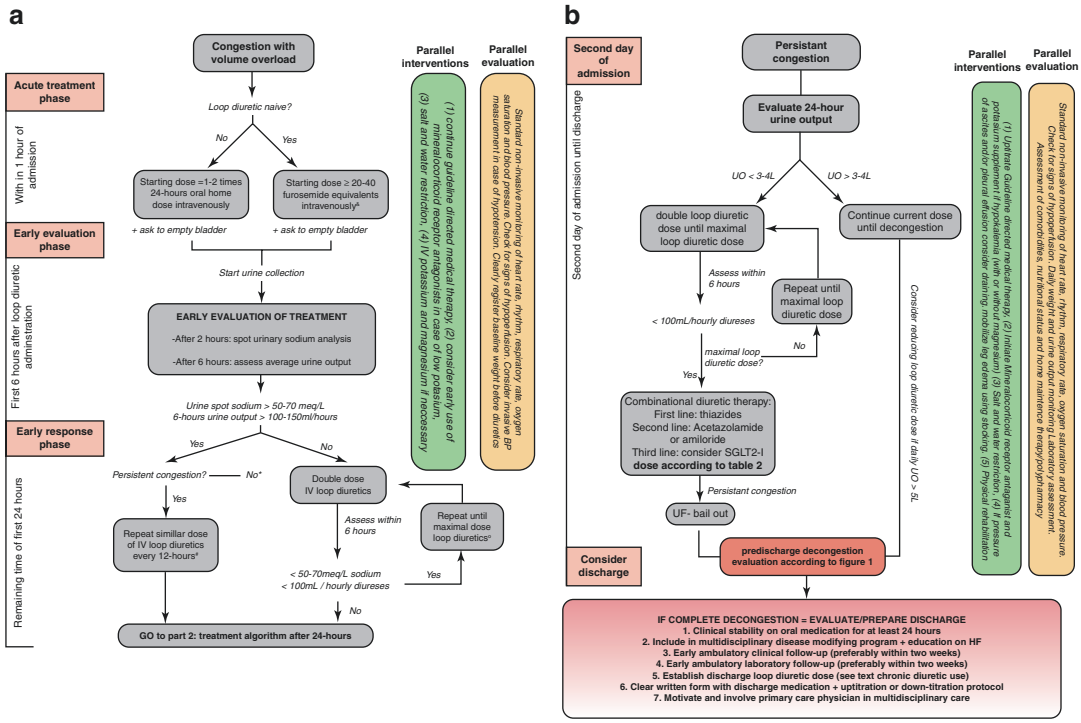

Fig. 7.3 European Society of Cardiology Heart Failure Association Recommendations of the Use of Diuretics in Acute Heart Failure and Cardio-Renal Syndrome. (**a**) Treatment algorithm for the first 24 hours of admission; (**b**) Treatment algorithm of second day of admission until discharge

study attempted to address the question of whether higher-dose or continuous administration is superior than standard-dose or bolus administration [102]. While the overall findings were largely neutral except for a statistically significant subjective assessment of well-being in the high-dose arm, a recent *post-hoc* analysis suggested that when adjusted for total amount of diuretic use, the high-dose strategy may have provided benefits [103].

Part of the challenge has been the inability of the kidneys to excrete loop diuretics to their sites of activity (luminal Na-K-Cl cotransporter at the ascending limb of the Loop of Henle). Indeed, diminished urine sodium per urine furosemide levels in patients with advanced HF receiving IV loop diuretics has been associated with impaired diuresis and natriuresis and poor long-term outcomes [100]. Hence, increasing loop diuretic dosing can be an effective strategy, although doses above the ceiling dose are only moderately effective (despite relatively predictable dose-response curves). Other strategies include increasing frequency of administration (including continuous dosing) or add other types of diuretics for synergistic effects to achieve maximal urinary sodium excretion.

Other Diuretic Drugs. In the stepped pharmacologic uptitration arm of the Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF) study [104], patients who experienced worsening renal function were treated with a goal-directed escalation of diuretic drugs including continuous loop diuretic infusion and addition of thiazide diuretics (sequential tubular blockade strategy) [105]. In the majority of cases, urine output goals of 3–5 L negative per day can be achieved.

While there was early enthusiasm on mineralocorticoid receptor antagonist to attenuate distal sodium reabsorption, such strategy was deemed not incremental to standard therapy in a prospective trial [106]. An ongoing multicenter study testing the role of acetazolamide to augment proximal sodium excretion by attenuating tubular renin release is ongoing [107, 108].

Inotropic and Vasoactive Drugs. The typical inotropes used in cardiac intensive care units include dobutamine and milrinone (or to a lesser extend oral digoxin loading), and they are effective in restoring hemodynamics in the "cold and wet" patients under hemodynamic guidance. However, prospective data supporting their use is limited [109, 110]. Vasodilators may improve hemodynamic derangements, although overzealous use can lead to hypotension and worsening renal function [111]. In the setting of vasoplegia, norepinephrine (and to a lesser degree dopamine) may be also be used as it has beta adrenergic activity. Less popular now, is the use of dopamine as an inotrope and pressor especially with no added benefit to the renal vasculature as previously thought [112].

Ultrafiltration/Aquapheresis. Ultrafiltration provides mechanical removal of isotonic fluid independent of the kidneys, thus providing effective and consistent salt and volume removal. Although early studies were promising, subsequent randomized controlled trials have more mixed results [104, 113, 114]. Interestingly, ultrafiltration may even exacerbate hyponatremia as the effluent is relatively more hypertonic [115]. This can exacerbate the cycle of renal vascular constriction and neurohormonal activation if the settings are too aggressive. Peritoneal dialysis has also been employed as an alternative treatment strategy [116].

Hypertonic Saline. Considerations of electrolyte depletion leading to renal sodium avidity has implied potential benefits of hypertonic saline (HSS) infusions during aggressive IV diuretics. This was suggested a decade ago in early Italian series, in which low-volume, intermittent, 1.4–4.6% sodium chloride (depending on serum sodium levels) coupled with high-dose loop diuretics can produce effective diuresis and prevent decline in renal function [117–119]. Recent reports using 1.7% salt supplementation (500 mg) with lower doses of IV diuretics also demonstrated improved diuretic efficiencies, especially in those with elevated urinary BUN/creatinine levels [120, 121]. Real-world experience have also supported such a potential strategy in selected patients [122]. However, nephroprotection was not observed in patients with baseline creatinine over >2.2 mg/dL [123]. This was confirmed by

preliminary results from a randomized, double-blind study of 50 patients with acute heart failure and renal insufficiency (creatinine >2 mg/dL, BUN >60 mg/dL) that demonstrated a non-significant increase in diuresis with HSS but also BUN elevation from baseline [124]. Hence, further investigations are warranted.

Mechanical Circulatory Assist Support. With the advent of temporary mechanical support such as the Impella® devices, a bridge-to-decision strategy can be instituted as demonstrated in animal models that improve renal blood flow [125]. After a test period to see if there is myocardial recovery, a durable left ventricular assist device (LVAD) may be considered [126]. Renal recovery following LVAD maybe transient [127], and renal function may deteriorate again after early improvement [11]. However if there is right ventricular dysfunction, orthotopic heart transplantation is the only durable solution. Implantable ventricular assist devices are rarely performed in patients reaching end-stage kidney diseases due to their high mortality rates and are not recommended by clinical guidelines [126, 128].

Temporary Renal Support Device Therapies. Recently, a handful of intriguing hemodynamic support devices have emerged targeting venous congestion and/or renal hemodynamics support. Examples include transcatheter intra-aortic pump [129], transcatheter renal venous decongestion system, innovative fluid/diuretic management systems (RenalGuard) [130]. Other examples of volume removal strategies include implantable pump or device designed to continuously remove excess abdominal fluid or direct sodium removal [131, 132], and catheter-based enhancement of lymphatic drainage [133]. The majority are in early clinical development.

7.6 Conclusions

Acute (Type 1) CRS is associated with an acute cardiogenic disturbance leading to acute worsening of renal function. However this cascade also forms a feedback loop further perpetuating cardiac dysfunction, hormonal dysregulation, and treatment resistance. Once ADHF is recognized, treatment must be initiated quickly to break the cycle but despite medical therapy, short term and long term aftereffects can make treatment a challenge. Ultimately changes in traditional renal biomarkers may not accurately reflect the state of the renal system while new insight into electrolyte metabolism may more accurately predict clinical outcomes.

While increases in serum creatinine have been closely tied to renal function, long term predictors of mortality and rehospitalization have not been closely linked. The response of the kidney in light of an acute cardiac insult should be largely viewed as appropriate and natural in the physiologic setting. However, the clinician should note that breaking the renal cycle will ultimately lead to a decongested patient with a chronic illness rather than an acute hospitalization.

Once developed, CRS becomes a serious medical and economic burden. Although hemodynamic derangement, an over-activated neurohormonal system, and systemic inflammation have been recognized as major players in CRS pathophysiology, there are also other cardio-renal mediators contributing to the development of CRS. The intricate network of these mediators makes their pathophysiologic hierarchy opaque. Investigators may need to divert their attention from overt cardio-renal connector in clinical CRS, to more fundamental substrates during a period of subclinical CRS as a part of an early detection and prevention strategy.

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Type 2 Cardiorenal Syndrome

8

Natalia Rocha and Peter A. McCullough

8.1 Introduction

The fundamental interplay between heart and kidney has been described for centuries [1, 2], yet its intricate interactions and clinical consequences have remained controversial despite valuable advances in the fields of cardiology and nephrology. The term Cardio renal syndrome has been vastly utilized to describe acute or chronic conditions of heart or kidney caused by a primary insult in either one of these two organs [2, 3]. In an effort to standardize the definition and promote advancement in the field, Ronco et al. [4] proposed a classification of cardiorenal syndromes into 5 distinct types as will be detailed in separate chapters of this book.

8.2 Description of CRS2

Cardiorenal syndrome type 2 (CRS2) is described as progressive chronic kidney impairment or injury provoked by a chronic cardiac dysfunction. Renal impairment is common in patients with cardiovascular disease, especially heart failure and it is a strong, fundamental predictor of morbidity and mortality [5, 6]. Whenever possible, it is important to attempt to separate this entity from intrinsic comorbid kidney dysfunction due to hypertension and diabetes, comorbidities that are prevalent in the congestive heart failure (HF) and coronary artery disease populations. It is also relevant to highlight that the coexistence of chronic kidney and heart disease is not sufficient to affirm a diagnosis of CRS2. Rather, the onset of heart disease should take place prior to kidney disease and the severity of kidney impairment should be reasonably explained by the degree of heart disease, known as pathophysiological plausibility [3, 7]. Unfortunately, is it often challenging to confirm this temporal association on large cohort studies and the discrimination between cardiorenal type 2 and cardiorenal type 4 (CRS4; chronic renal impairment leading to chronic heart dysfunction) may not always be possible. Similarly, a large proportion of individuals with chronic heart failure have some degree of chronic kidney disease and commonly present with episodes of acute heart failure and worsening renal function, characterizing cardiorenal syndrome type 1 (CRS1). This fluidity should be appreciated as part of the natural course of a complex chronic condition known to present with acute exacerbations. Recognizing the diverse pathophysiology of acute exacerbations and its impact on chronic disease trajectory is critical to guide prognosis and therapy.

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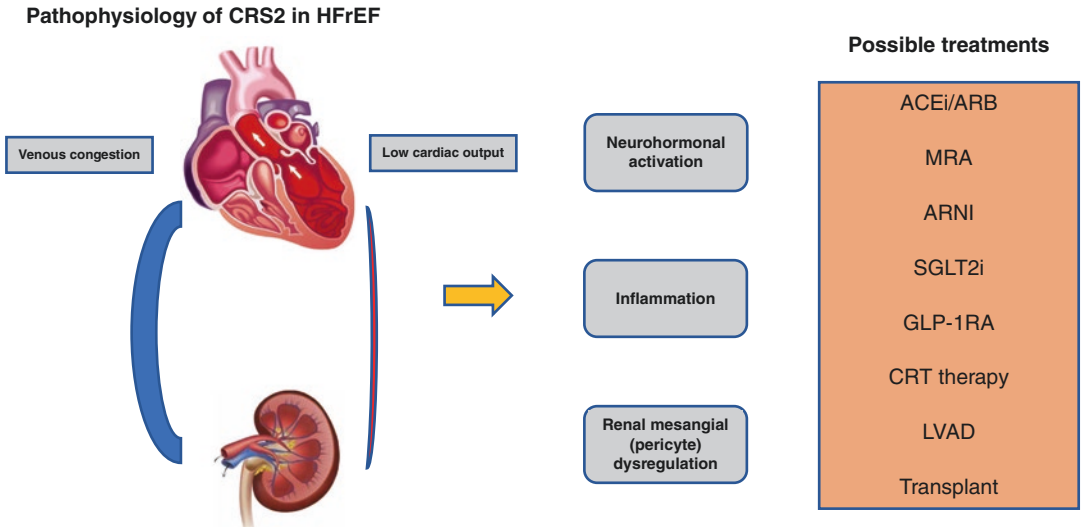
8.3 Pathophysiology

The majority of the pathophysiological concepts of cardiorenal syndromes have been obtained from experimental animal studies [8]. The main accepted mechanisms of CRS2 include decrease in renal plasma flow (RPF), increase in venous congestion, neurohormonal activation and chronic inflammatory state/oxidative stress (Fig. 8.1). The first two are inherently appealing due to being physiologically explained by reviewing the determinants of glomerular filtration rate (GFR). Simply put, GFR can be described by two formulas:

1. GFR = Kf × (PG – PB – πG + πB) in which Kf is the filtration constant, PG is the hydraulic pressure in the glomerular capillaries, PB is the hydrostatic pressure in the Bowman's capsule. Based on this, GFR is decreased when PG is low such as in low volume states, hypotension or use of renin-angiotensin system antagonists or when PB is high such as in venous congestion.
2. GFR = RPF × FF in which RPF is renal plasma flow and FF is filtration fraction. Filtration fraction is influenced by contraction and relaxation of the afferent and efferent arterioles. The reduction in mean arterial pressure (MAP) and consequent compensatory increase in vascular resistance may lead to a reduction in blood flow to the kidneys, inducing a drop in GFR [9]. Similarly, an increase in venous congestion causes a reduction is RPF leading to decrease in GFR. In addition, it impairs the ability of the afferent, efferent and intrinsic arteriolar vascular beds to regulate blood flow.

Thus, it is expected that chronic cardiac dysfunction such as in HF would lead to fluctuations is GFR as instances of hypotension, reduced cardiac output, venous congestion and renin-



ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; ARNI: Angiotensin Receptor-NeprilysinInhibitor; MRA: Mineralocorticoid receptor antagonist; SGLT2-i: sodium-glucose co-transporter 2 inhibitor; GLP-1RA: glucagon-like peptide-1 receptor agonist; CRT: cardiac resynchronization therapy; LVAD: Left ventricular assist devices.

Fig. 8.1 The main proposed mechanisms of CRS2 in HFrEF involve hemodynamic factors such as decrease in cardiac output and increase in venous congestion, neurohormonal activation and chronic inflammation. Possible mitigators are neurohormonal blockers such as ACEi, ARB, MRA and ARNI. For patients with T2DM who have prominent CV and renal disease, SGLT2i and GLP-1RA are additional options. Once symptoms become refractory to maximum tolerated medical therapy, cardiac devices such as CRT and LVAD may be offered. *ACEi* angiotensin converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *ARNI* angiotensin receptor-neprilysin inhibitor, *MRA* mineralocorticoid receptor antagonist, *SGLT2-i* sodium-glucose co-transporter 2 inhibitor, *GLP-1RA* glucagon-like peptide-1 receptor agonist, *CRT* cardiac resynchronization therapy, *LVAD* left ventricular assist devices

angiotensin antagonist use are common. Importantly, the consequences of alterations in eGFR may differ depending on the cause of the fluctuation, for instance, when eGFR changes due to the use of renin-angiotensin antagonists this does not seem to translate into worse cardiac or renal outcomes.

Evidence from elegant experiments have suggested that in the setting of HF there is a reduction in blood flow to the kidneys due to a decrease in cardiac output and increase in systemic vascular resistance [10, 11]. These experiments showed that in the earlier stages of HF, GFR remains stable due to a compensatory angiotensin II-mediated contraction of efferent artery and consequent increase in filtration fraction. Subsequently, as a response to a higher filtration fraction, sodium avidity and reabsorption peaks at the proximal nephron, decreasing the availability of sodium to the macula densa. This stimulus releases renin and starts the cascade of activation of the renin-angiotensin-aldosterone system, perpetuating the syndrome [12]. On the other hand, once the disease advances (i.e.; when cardiac output reaches <1.5 L/min/m^2), GFR becomes flow dependent and it decreases [9, 13]. In this situation, there is an overall increase in renal vascular resistance, suggesting more prominent constriction of the afferent artery rather than efferent.

Despite its persistent presence in the literature, the concept of decrease in cardiac output inducing kidney dysfunction in heart failure has been challenged by a growing body of evidence [14–16]. Large studies have shown that even in subjects with advanced HF, there is no linear relationship between cardiac output (CI) and GFR [17, 18]. In fact, certain studies have shown a paradoxical association between the two (meaning the higher the CI, the lower the GFR) [18]. Authors suggested that the well-developed mechanisms of auto-regulation in the kidney including myogenic and tubulo-glomerular feedback pathways are able to preserve a constant perfusion and GFR even when the aorta is sensing a markedly low cardiac output [18].

On the other hand, it has been demonstrated with greater certainty that the kidneys are highly sensitive to increase in central venous congestion and intra-abdominal pressure leading to reduction in renal blood flow and increase in vascular resistance. This finding is not only physiologically instinctual, but it has been depicted in epidemiologic studies [15, 16]. Furthermore, multicenter trials involving hemodynamic parameters have replicated the association between high central venous pressure and worse kidney outcomes [19]. Interestingly, a strong association was found between impaired kidney function and a disproportionately elevated right atrial pressure to pulmonary capillary wedge pressure (PCWP). It is thought that perhaps this represents an inability of the right heart to provide adequate left ventricular pre-load and it leads to worse left heart function and that this signature association may provide important insight to the appropriate therapies to patients that fit this profile [20–22]. Congestion, therefore, is decisively one of the major determinants of heart failure progression.

Although most studies evaluating hemodynamics and markers of kidney dysfunction were carried out during an acute exacerbation of heart failure, not with stable chronic heart failure to delineate the population with CRS2, it is known that even asymptomatic patients with HF commonly have sings of renal congestion, neurohormonal activation and a decrease in natriuresis in response to volume expansion leading to the perpetuation of congestion [23]. An interesting study with stable HF patients being treated in an outpatient setting showed that the presence of non-invasive markers of elevated CVP or pulmonary artery systolic pressure are independent determinants of future worsening renal function [24].

Heart failure is not purely a hemodynamic disease. The neurohormonal hypothesis has long been proposed to explain the almost inevitable progression of heart failure [25]. Both the decrease in renal blood flow and venous congestion translate to excess neurohormonal activation. Beyond actions in the heart itself, activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system can be seen as an adaptive response to maintain perfusion pressure to various organs, especially the

kidneys [26]. However, it can be maladaptive, precipitating systemic vasoconstriction and sodium and water retention, which can eventually contribute to atrial stretch and further activation of neurohormones [27].

The participation of specialized renal mesangial cells, also known as pericytes, in the development and progression of CRS2 has not been fully established. It is hypothesized that these cells respond to RAAS leading to an imbalance between endothelin 1 (ET 1) and nitric oxide (NO). The result is vasoconstriction and mesangial cell contraction and a steady loss of glomerular filtration [28, 29]. As will be demonstrated further in this chapter, neurohormonal blockage has been the cornerstone of chronic heart failure treatment.

The relevance of the renal tubules as opposed to the glomeruli as protagonist in vital cardiorenal interactions has been the focus of interesting contemporary research. Investigating diuretic resistance as the anchor, Testani et al. have shown evidence that, contrary to prior belief derived from the chronic kidney disease (CKD) literature, renal dysfunction (i.e. lower eGFR leading to defect in drug delivery) does not seem to be the main driver of diuretic resistance in acute heart failure. Rather, resistance at the level of the renal tubule explained the majority of the diuretic resistance. In fact, when compared to recruited patients without renal dysfunction, those with lower eGFR appeared to have a better overall diuretic response at the level of the renal tubule as assessed by the fraction of excretion of sodium (FeNa), implying that the role of renal dysfunction in affecting diuretic resistance is limited [30].

Further exploring the tubular mechanisms of diuretic resistance by utilizing the measure of fraction of excretion of lithium (FeLi) as surrogate for proximal renal tubule/loop of Henle sodium handling and FeNa as measure of overall tubular sodium handling, Testani et al. have demonstrated that in chronic HF patients, the administration of high doses of loop diuretics yields an appropriate response at the level of the proximal tubule/loop of Henle and that the culprit for the low sodium present in the urine in diuretic resistance is a heightened, compensatory distal tubule sodium reabsorption [31]. In addition to contributing to clarify the pathophysiological underpinnings of the cardiorenal interactions, this finding is of major clinical importance since it sheds light into better management strategies when dealing with patients responding poorly to diuretics.

8.4 Chronic Inflammatory State: Fibrosis as the Unifying Pathogenesis

An additional theory regarding etiology of CRS2 involves the systemic inflammatory response. Patients with severe HF have been found to have high levels of interleukins such as IL-6, IL-18 and tumor necrosis factor (TNF-α), suggesting a pro-inflammatory state [3, 32]. Evidence is emerging from animal experimental studies suggesting that pro-inflammatory cytokines produced by cardiac myocytes under stress can have a remote effect in the kidneys [33, 34]. A pro-inflammatory state can be mounted in the setting of intestinal ischemia, increased gut absorption of endotoxins, and gut bacteria translocation as a consequence of chronic venous congestion [8, 32].

It has recently been proposed that fibrosis, as a consequence of chronic inflammation and endothelial dysfunction caused by oxidative stress, may be considered the unifying pathway and bolster of the cardiorenal continuum triggered by hypertension, obesity, aging and diabetes. Fibrosis is a common pathologic finding in chronic heart disease and chronic kidney disease and aldosterone appears to trigger and perpetuate this process. This hypothesis is contemporarily being further explored with focus on biomarker phenotyping. Determining which patients in the cardiorenal spectrum appear to be in a profibrotic state and if this determination changes response to modulators of the RAAS system, MRAs and other antifibrotic agents under development may be an appropriate strategy in managing cardiorenal syndrome [35].

8.5 Cardiorenal Type 2 in Heart Failure with Preserved Ejection Fraction

While the majority of the science of the cardiorenal interplay has been based on heart failure with reduced ejection fraction (HFrEF), renal dysfunction is also widely prevalent in patient with heart failure with preserved ejection fraction (HFpEF) and it is known to be linked to worse morbidity and mortality in this population [36, 37]. There are fundamental differences in the pathophysiology of cardiac dysfunction that leads to HFrEF and HFpEF. In HFrEF, there is a disruption in cardiac contractile function due to cardiomyocyte death and abnormal calcium cycling. Conversely, it appears that the main driver of impaired cardiac function in HFpEF is largely based on the relationship between inflammation and endothelial function. Succinctly, the systemic inflammatory state promoted by prevalent comorbidities in HFpEF such as obesity, diabetes and hypertension leads to the production of reactive oxygen species (ROS), causing a reduction in nitric oxide (NO) bioavailability. This leads to a cascade of events that culminates in cardiac remodeling, stiffness and impaired relaxation [38, 39].

Since cardiac contractility is not affected in HFpEF, the main hemodynamic element of this syndrome is congestion [17, 40]. The consequences of elevated right and left sided filling pressures have been discussed previously in this chapter and are similar for HFrEF and HFpEF with consequent decrease in RBF and activation of RAAS and sympathetic nervous system. It is important to highlight that HFpEF is marked by high end-diastolic volumes and consequent high filling pressures [41]. This can lead to a reduction in stroke volume reserve due to decrease in systolic filling and eventually cause a decrease in cardiac output, especially in instances of high demand such as during exercise [42]. Patients with HFpEF are thought to be more pre-load dependent, with a drop in pre-load caused by vasodilators or diuretics possibly leading to renal dysfunction [43–45]. In addition, the ventricular and arterial stiffness caused by chronic inflammation and low NO availability may lead to a less compliant system in which small changes in pressure and load are translated into more dramatic consequences to the kidneys.

8.6 Diagnosis

8.6.1 Biomarkers and CRS2

8.6.1.1 Cardiac Biomarkers

The utility of cardiac and renal biomarkers in the diagnosis and prognosis of acute and chronic kidney disease and heart failure has been fairly well stablished. However, its usefulness in cardiorenal syndromes remains unclear. The dynamics of cardiac biomarkers such as troponin and BNP/NT-proBNP are altered by baseline kidney function. Troponin T (cTnT), Troponin I (cTnI), BNP and NT-proBNP levels are elevated in patients with CKD due to reduced excretion. However, despite this, their levels still predict both cardiovascular and all-cause mortality in CKD and ESRD [46–48]. Further studies are needed to determine the effect and usefulness of these and other biomarkers specifically in CRS.

8.6.1.2 Renal Biomarkers

GFR and Albuminuria

The two standard biomarkers of kidney function classically utilized to diagnose and prognosticate patients with kidney disease or at risk of kidney disease are the glomerular filtration rate (GFR) and urinary albumin to creatinine ratio (UACR). Although they are both used by the National Kidney Foundation Kidney Disease outcomes Quality Initiative to characterize renal dysfunction, these biomarkers are two different entities with distinct physiologic mechanisms and independent prognostic impact [49]. While GFR is a hemodynamic parameter, affected mainly by perfusion, albuminuria is known to be a marker of morphologic kidney damage related to inflammation and endothelial dysfunction, commonly associated with comorbid conditions such as diabetes and hypertension [38].

The prognostic value of GFR in stable, ambulatory HF patients is well defined and it outperforms measures of left ventricular ejection fraction (LVEF) and New York Association (NYHA) class [26, 50]. It is considered an adequate measure of kidney function as it is a marker of the filtration capacity of the kidneys. Direct quantitation of kidney function with assessment of GFR requires elaborated and time consuming tests such as inulin or ^{125}I-iothalamate clearance which are not practical for day to day assessments. The same is true for the use of creatinine clearance (CrCl) which requires a 24 h urine collection, thus, a variety of creatinine base formulas that add demographic information to correct for difference in muscle mass are often used to estimate GFR. The most commonly used formulas are the Cockcroft-Gault, the Modification of Diet in Renal Disease (MDRD) and simplified MDRD. In a cohort of patients with HF, all 3 creatinine-based formulas were validated against exact measurement of GFR with ^{125}I-iothalamate clearance. All formulas overestimated in the lower ranges and underestimated in the upper ranges of GFR. The MDRD formula was found to be the most precise and to have a good prognostic value [51].

Elevated UACR is known to be linked to cardiovascular (CV) morbidity and mortality [52, 53]. It is associated with incident HF with reduced and preserved ejection fraction in the general population [54] and in patients with established HF, higher levels of AUCR predicts outcomes such as overall CV mortality and hospitalizations for heart failure even after adjustment for classic CV risk factors [55–57].

Although albuminuria often coexists with abnormal GFR, a significant proportion of subjects in heart failure trials were found to have GFR >60 mL/min and would otherwise not be classified as having kidney dysfunction if albumin was not measured [56]. Its association with mortality has been shown to be independent of GFR and serum creatinine, further supporting its complementary and independent relationship to GFR [49].

The presence of albuminuria in the heart failure population seems to be more intricate than initially thought as can be exemplified by the CHARM and PARADIGM cohorts [56, 58]. The Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) Programme randomized 7599 patients with heart failure to receive either Candesartan or Placebo with a follow up of about 3 years. In a substudy of the CHARM trial involving 2310 patients, UACR was measured at baseline and during follow up. The authors found a prevalence of 30% of microalbuminuria and 11% of macroalbuminuria. Despite being more prevalent among patients with comorbid conditions such as hypertension and diabetes, a significant number of patients with abnormal UACR did not have any comorbidities known to cause albuminuria, raising the possibility of heart failure itself being the culprit. It is not yet fully established if the pathophysiology of proteinuria in heart failure without other comorbidities is similar to that of proteinuria due to diabetes, hypertension and CKD. This is a clinically relevant question as it brings to a debate whether therapies with the goal to reduce albuminuria would benefit patients with HF as is does with diabetes and CKD [59, 60].

A contemporary subanalysis of the PARADIGM-HF trial (Prospective Comparison of the ARNI [Angiotensin Receptor-Naprilysin Inhibitor] to Determine Impact on Global Mortality and Morbidity in Heart Failure) has shown an unexpected result, challenging our current understanding of the pathophysiology and prognosis of albuminuria [58]. The authors randomized 8399 patients with HFrEF to either sacubitril/valsartan or enalapril and data on UACR was available for 1872 patients. They found that, compared with enalapril, the use of sacubitril/valsartan was associated with a less steep decline in GFR, which was apparent as early as 4 months after randomization. However, it also resulted in a persistent rise in UACR over time. Interestingly, patients with higher levels of albuminuria at baseline were, as expected, more prone to developing the renal composite endpoint, but patients who developed worsening albuminuria during the study were only found to be at higher risk of developing the post hoc composite renal endpoint if undergoing enalapril use, not

sacubitril/valsartan. This finding raises the hypothesis that the rise in AUCR from sacubitril/valsartan use is due to a mechanism not associated with loss of glomerular function. Furthermore, in PARADIGM-HF the pattern of AUCR change is of immediate rise with initiation of therapy followed by normalization after discontinuation of therapy, implying that the mechanism of albuminuria is not related to irreversible podocyte injury. Rather, it is proposed that instead of affecting hyperfiltration, natriuretic peptides may modify the contractile state of mesangial cells by altering its hydraulic conductivity, leading to an increase in AUCR. Therapy with sacubitril/valsartan was associated with lower risk of hospitalizations for HF and cardiovascular mortality when compared to enalapril, despite a rise in AUCR, supporting the hypothesis that this rise has no impact on clinical outcomes [12].

8.6.2 Cystatin C

Cystatin C is a protein produced by all nucleated cells, freely filtered by the kidneys and reabsorbed by the proximal tubule. Unlike creatinine, cystatin C is not affected by muscle mass and diet and for this reason it is more accurate to estimate GFR in the extremes of body size. Although to a less extent when compared to creatinine, cystatin C is affected by age and sex. Importantly, it is also affected by thyroid function, smoking status and steroid use [46, 61]. In the population with HF, cystatin C is associated with progression of disease and higher risk of death, even when controlled for baseline eGFR [62]. When compared to direct measurements of GFR with iothalamate clearance as gold standard, cystatin C-based GFR estimation performed well with good precision, accuracy and the lowest bias when compared to other estimating equations when assessed in stable patients [63].

It is important to highlight that both creatinine based and cystatin C based eGFR are reliable in stable setting, but they have not been validated in the absence of steady state such as in acutely ill patients. Despite the above mentioned advantages, the usefulness of Cystatin C in diagnosing and differentiating the cardiorenal syndromes remains unestablished [61, 64].

8.6.3 Potential Therapies

There are several challenges involved in evaluating treatment strategies for cardiorenal syndrome. There are no trials designed to specifically assess treatment of cardiorenal syndrome type 2, however, several large heart failure trials have evaluated prevention of new-onset kidney dysfunction and attenuation of existing kidney disease. Unfortunately, most large randomized clinical trials in cardiology and in nephrology have so far utilized surrogate endpoint such as progression of albuminuria and decrease in eGFR, without assessment of FDA accepted hard clinical kidney outcomes such as time to doubling in serum creatinine, time to ESRD and renal death [65].

Knowing that the progression of heart dysfunction is the main risk factor for the development of kidney dysfunction in CRS2, maintaining an optimum management of the primary heart disease is mandatory (Fig. 8.2).

8.6.3.1 Angiotensin-Converting Enzyme (ACE) Inhibitor and an Angiotensin Receptor Blocker

Based on the neurohormonal hypothesis, activation of the renin-angiotensin system leads to detrimental effects on the heart and contribute to the progression of HF. Thus, it is reasonable that blocking this system would lead to better outcomes. The era of angiotensin inhibition was solidified by the result of remarkable trials starting with the CONSENSUS trial [66] in 1987 and SOLVD [67] in 1991 which demonstrated the beneficial effects of enalapril on lowering mortality in patients with heart failure and reduced EF. Subsequently, the V-HeFT II trial [68] in 1991 showed superiority of enalapril when compared to the combination of hydralazine and isosorbide dinitrate in chronic HF and the SOLVD-prevention trial [69] in 1992 proved that

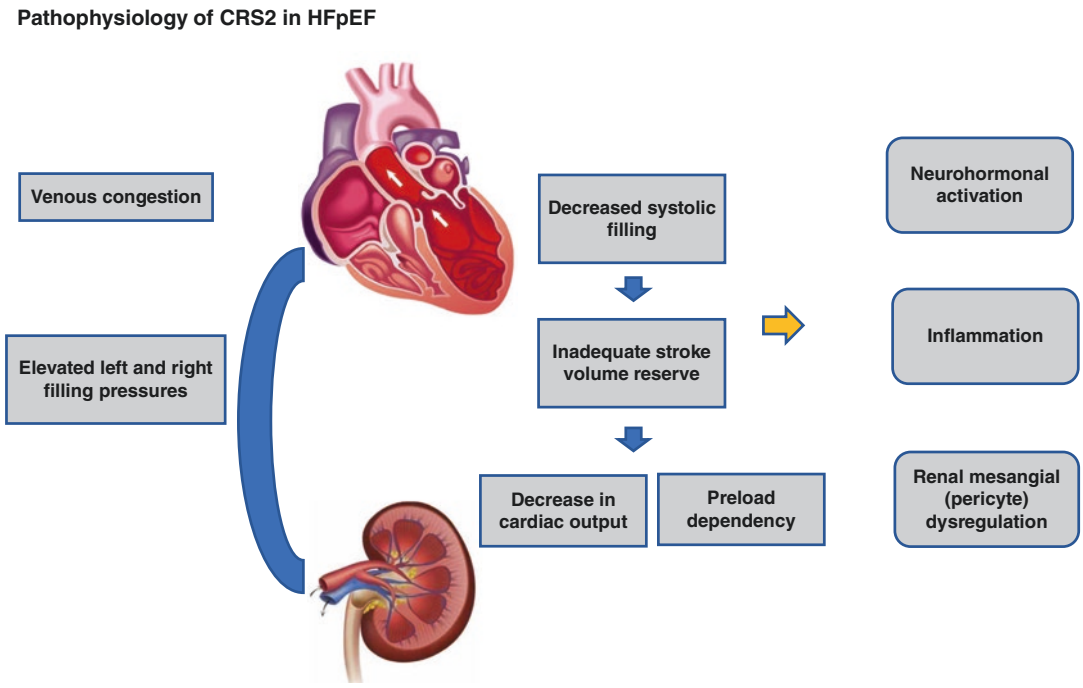


Fig. 8.2 The hallmark of CRS2 in HFpEF is venous congestion and an increase in right and left sided heart filling pressures. Cardiac filling is compromised and it leads to an inadequate stroke volume reserve. The consequences include increased pre-load dependency and in certain situations a decrease in cardiac output. As with HFrEF, inflammation and activation of RAAS will subsequently take place. Unlike HFrEF, data on the use of ACEi, ARB, MRA and ARNI in HFpEF is scarce and guidelines recommend treatment of congestion and comorbidities. *ACEi* angiotensin converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *ARNI* angiotensin receptor-neprilysin inhibitor, *MRA* mineralocorticoid receptor antagonist, *SGLT2-i* sodium-glucose co-transporter 2 inhibitor, *GLP-1RA* glucagon-like peptide-1 receptor agonist

the benefit in reducing heart failure admissions is also true for asymptomatic patients. Similarly, the Val-HeFT trial [70] published in 2001 gave support for the use of Valsartan in heart failure, without demonstrating its superiority against enalapril and for this reason its use is reserved for patients who are intolerant to ACEi. The evidence for ACEi use in patients post myocardial infarction is also robust both for patients with and without LV dysfunction [71–74] (Table 8.1).

As treatment for chronic hypertension, a regimen including an ACEi was found to mitigate the progression of nondiabetic kidney disease including reduction in the rates of serum creatinine doubling, death, transition to dialysis and transplantation when compared to a regimen without this class and this result was found to be independent of their blood pressure lowering effect [75]. On the other hand, the evidence for the use of ACEi in patients with T2DM with the goal to promote kidney protection is limited and based on surrogate outcomes only, such as reduction of proteinuria or improvement in kidney function assessed by either creatinine clearance or eGFR, without hard endpoint appraisal [76, 77]. Furthermore, ACEi have not been adequately compared with other antihypertensives regarding time to ESRD in renal outcome trials, making it difficult exclude the effect of better blood pressure control as the reason for an improvement in the measured surrogate markers. Nonetheless, although evidence for prevention of CRS2 and blunting of its progression with ACEi is lacking, data for mortality benefit in HF and

Table 8.1 Selected trials with ACEi, ARB, MRA, Sacubitril/Valsartan, SGLT2i and GLP-1RA with possible benefit for patients with CRS2

Drug class	Name of trial	Year of publication	Drug	Sample size	Intervention	Primary outcome measured	Baseline renal status	Hazard ratio (95%CI) and p value for primary composite endpoint
ACEi/ ARB	CONSENSUS [66]	1987	Enalapril	253	Enalapril vs. placebo	Mortality in 6 months	Excluded if Cr > 3.4 mg/dL	0.60 (95% CI not given), p < 0.02
	SOLVD [67]	1991	Enalapril	2569	Enalapril vs. placebo	Mortality in 48 months	Excluded if Cr > 2.0 mg/dL	0.84 (0.95–0.74), p < 0.0036
	SOLVD prevention [69]	1992	Enalapril	4228	Enalapril vs. placebo	Mortality by the end of the trial (average 37.4 months)	Excluded if Cr > 2.0 mg/dL	1.08 (0.92–1.21), p = 0.3
	V-HEFT II [68]	1991	Enalapril	804	Enalapril vs. hydralazine/ isosorbide	Mortality in 48 months	Not specified	0.72 (not provided), p = 0.016
	Val-HEFT [70]	2001	Valsartan	5010	Valsartan vs. placebo	1. All-cause mortality 2. All-cause mortality, cardiac arrest with resuscitation, HF hospitalization, IV inotropic agents, or IV vasodilator therapies	Excluded if Cr > 2.5 mg/dL	1. 1.02 (0.88–1.18), p = 0.80 2. 0.87 (0.77–0.97), p = 0.009
ARNI	PARADIGM-HF [95]	2014	Sacubitril-valsartan	8399	Sacubitril/ valsartan vs. enalapril	CV mortality or HF hospitalization	Excluded if eGFR <30 mL/ min/1.73 m^2	0.80 (0.73–0.87), P < 0.001
MRA	RALES [78]	1999	Spironolactone	1663	Spironolactone vs. placebo	All-cause mortality	Excluded if Cr > 2.5 mg/dL	0.70 (0.59–0.82), p < 0.001
	EMPHASIS-HF [79]	2011	Eplerenone	2737	Eplerenone vs. placebo	CV death or HF hospitalization	Excluded if eGFR <30 mL/ min/1.73 m^2	0.63 (0.54–0.74), p < 0.001
	EPHESUS [80]	2003	Eplerenone	6642	Eplerenone vs. placebo	1. All-cause mortality 2. CV mortality or hospitalization for CV events	Excluded if Cr > 2.5 mg/dL	1)0.85 (0.75–0.96), p = 0.008 2)0.87 (0.79–0.85), p = 0.002
SGLT-2i	EMPA-REG Outcome [99]	2015	Empagliflozin	7020	Empagliflozin vs. placebo	CV death, MI or stroke	Excluded if eGFR <30 mL/ min	0.86 (0.74–0.99), p = 0.04
	CANVAS [100] Program	2017	Canagliflozin	4330	Canagliflozin vs. placebo	CV death, MI, UA or stroke	Not specified	0.86 (0.75–0.97), p = 0.02 for superiority

(continued)

Table 8.1 (continued)

Drug class	Name of trial	Year of publication	Drug	Sample size	Intervention	Primary outcome measured	Baseline renal status	Hazard ratio (95%CI) and p value for primary composite endpoint
GLP-1RA	LEADER [107]	2015	Liraglutide	9340	Liraglutide vs. placebo	First occurrence of CV mortality, nonfatal MI, or non-fatal stroke	ESRD	0.87 (0.78–0.97), p = 0.01
	SUSTAIN-6	2016	Semaglutide	3297	Semaglutide vs. placebo	CV mortality, nonfatal MI, or nonfatal stroke	ESRD	0.74 (0.58–0.95), p < 0.001 for noninferiority and P = 0.02 for superiority

ACEi angiotensin converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *ARNI* angiotensin receptor-naprilysin inhibitor, *MRA* mineralocorticoid receptor antagonist, *SGLT2-i* sodium-glucose co-transporter 2 inhibitor, *GLP-1RA* glucagon-like peptide-1 receptor agonist

CAD as well as better renal outcomes in chronic nondiabetic hypertensive disease can reasonably be used to justify its use in this population.

8.6.3.2 Mineralocorticoid Receptor Antagonists

Aldosterone is a mineralocorticoid responsible for BP, sodium and water regulation in the body. It is part of the RAAS system and when present in excess leads to water and sodium retention and hypertension. Spironolactone and eplerenone are steroidal mineralocorticoid receptor antagonists (MRA) known to have beneficial effects in the diseased heart and possibly in the kidneys. The RALES trial [78] was the first to affirm the mortality benefits of spironolactone in severe HF. Subsequently the EMPHASIS-HF trial [79] with eplerenone gave strong evidence for this benefit to be a drug class effect and extended the benefits of MRAs to less-severe HF. Eplerenone was also shown in the EPHESUS trial [80] to reduce mortality in patients with LV dysfunction and heart failure after myocardial infarction (Table 8.1).

When it comes to possible kidney protection, although aldosterone is known to be associated with inflammation and fibrosis of the kidneys as well as renal vascular remodeling, the evidence for possible kidney protection with MRAs is based in short duration studies with small number of participants and assessed reduction in proteinuria, without appraisal of hard clinical outcomes [81–83]. Large clinical trials with steroidal MRAs have been limited partly due to concern for side effects in patients with impaired kidney function [84, 85].

Despite advances in guideline directed therapies for heart failure, interventions with high impact on morbidity and mortality such as ACE inhibitors, ARB and steroidal MRAs are greatly underprescribed in the population with CKD due to safety concerns, especially the risk worsening of kidney function and hyperkalemia. Finerenone is one of the non-steroid MRA currently in phase III studies in patients with heart failure and diabetic kidney disease. It is considered a third generation MRA due to its higher affinity and selectivity to the MR receptor [86]. Pre-clinical studies have shown a high potential for end-organ protection with lower risk of electrolyte abnormalities when compared to eplerenone and spironolactone. The ARTS (MinerAlocorticoid Receptor Antagonist Tolerability Study) study, a phase 2a trial with 392 patient with stable HFrEF and mild to moderate CKD, concluded that Finerenone is able to decrease NT-proBNP levels to the same degree as spironolactone but with a smaller increase in serum potassium and smaller decrease in GFR [87]. Subsequently, the phase 2b ARTS-HF aimed to examine safety, efficacy and target dose of finerenone when compared to eplerenone in patients with worsening chronic heart failure requiring hospitalization and concomitant CKD or T2DM [88]. Results showed a similar reduction in serum NT-proBNP when compared to eplerenone with a good safety profile. The phase 3 FINESSE-HF study in under way and plans on recruiting >3600 chronic HFrEF patient with T2DM and/or CKD across 35 different countries and it will have CV death or hospitalization for heart failure as primary endpoint [89].

Unlike HFrEF, the data on the use of ACEi, ARB and MRA in patients with HFpEF is less clear [90–93]. Current guidelines recommend management of volume status with diuretics as well as optimization of treatment of comorbidities. The use of MRAs is recommended as class IIa in patients with HFpEF with the goal to reduce HF hospitalizations [94].

8.6.3.3 Angiotensin Receptor Neprilysin Inhibitor

The evidence above highlights the hypothesis that neurohormonal axis inhibition with ACEi or ARB is the cornerstone of HF therapy. For the past several years, attempts were made to explore the counter-regulatory axis mainly promoted by natriuretic peptides, thought to have beneficial effects when activated in chronic HF. Neprilysin is an endopeptide that breaks down vasoactive peptides known to counter-act the maladaptive effects of neurohormonal activation. Initial attempts to combine a naprilysin inhibitor with an ACEi in clinical trials was associated with a prohibitive risk of angioedema due to the accu-

mulation of bradykinin. The interest in this combination returned in 2014 with the release of the PARADIGM-HF trial [95] results utilizing the compound LCZ696, a combination of the neprilysin inhibitor sacubitril and the ARB valsartan. In this trial, 8400 patients with ejection fraction ≤35%, NYHA functional class II to IV and elevated NT-proBNP, on guideline-directed medical therapy for HF were randomized to receive either sacubitril/valsartan or enalapril. The trial was stopped early after a median follow up of about 27 months by its data monitoring committee due to overwhelming benefit of sacubitril/valsartan. The authors found a 20% relative risk reduction in the primary composite outcome of death from cardiovascular causes or hospitalization for HF (HR 0.80; 95% CI 0.73 to 0.87; $p < 0.001$) as well as a 16% reduction in the risk of death from any cause (HR 0.84; 95% CI 0.76 to 0.93; $p < 0.001$) (Table 8.1).

For patients with HFpEF, the PARAMOUNT trial (**P**rospective comparison of **ARN**i with **A**RB on **M**anagement **O**f HF with preserved ejectio**N** fraction **T**rial) was a phase 2 trial that tested the efficacy and safety of sacubitril/valsartan to valsartan in reducing the level of NT-proBNP in patients with LVEF ≥45% [96]. The positive results and low incidence of overall adverse events were reassuring. Results of the large multicenter, double-blind, placebo-controlled PARAGON-HF are awaited in hopes to determine if sacubitril/valsartan is superior to ARB in patients with HFpEF [97].

Importantly, as mentioned in the biomarker session of this chapter, in a subanalysis of the PARADIGM-HF trial [58], the authors reported a lower risk for the post hoc composite renal endpoint of reaching end-stage renal disease or ≥ 50% reduction in eGFR from baseline. Pertinent to the population of patients with CRS2, the mean eGFR in this trial was 70 ± 20 mL/min/1.73 m^2 and only 30% of patients had CKD at baseline. The effect of kidney and CV protection was seen in patients with and without baseline kidney disease. Despite showing a consistent less steep decline in GFR which was apparent after 4 months of therapy, the use of sacubitril/valsartan was associated with rise in UACR and when evaluated along with the totality of their findings, does not seem to be linked to irreversible podocyte damage or progressive loss of kidney function [12].

8.7 Newer Options for Diabetics: Sodium–Glucose Cotransporter 2 Inhibitors and Glucagon-Like Peptide-1 Agonist

Patients with diabetes type 2 are prone to the development of diabetic kidney disease and are at high risk of both atherosclerotic cardiovascular disease and heart failure. The timing of development of renal disease and CV disease is variable and it is likely that a proportion of these patients will develop a degree of CRS2 when cardiac disease is the first to manifest. Fortunately, patients with the combination of diabetes and CV disease now have a wider range of therapy options with the goal to decrease cardiovascular morbidity and mortality with sodium–glucose cotransporter 2 inhibitors (SGLT2i) and glucagon-like peptide-1 agonist (GLP-1RA) (Table 8.1).

Empagliflozin and Canagliflozin are SGLT2i medications that act by blocking sodium and glucose reabsorption at the proximal tubule, leading to natriuresis and glucosuria. Additionally, since more sodium is available to reach the macula densa, this is translated into restoration of afferent vasoconstriction through activation of the tubule-glomerular feedback (TGF) leading to decrease in glomerular pressure and consequently a decrease in hyperfiltration which is the hallmark of diabetic kidney disease [98]. The EMPA REG outcome trial had unprecedented results in 2015 demonstrating superiority of empagliflozin when compared to placebo in reducing the risk for the composite outcomes of CV mortality, all-cause mortality and hospitalizations for heart failure [99]. The CANVAS Program followed a similar path, demonstrating superiority of canagliflozin in reducing the incidence of the primary outcome of incidence of CV death, MI or stroke among 10,000 patients with T2DM and high CV risk [100].

Since echocardiography data was not collected on EMPA REG, it is not known whether individuals experienced heart failure with reduced or preserved ejection fraction. However, it appears that CV outcomes in this trial were consistent among patient with and without diagnosed heart failure at baseline, suggesting that empagliflozin may decrease not only the rates of HF decompensations but also the incidence of HF [101].

Both empagliflozin and canagliflozin have also shown important kidney protective effects. In EMPA REG, kidney outcomes were assessed as part of a secondary prespecified analysis. Results included a lower incidence of worsening nephropathy (12.7% vs. 18.8%, HR 0.61, 95% CI 0.53–0.70; $p < 0.001$), and lower incidence of the composite kidney outcome of doubling of serum creatinine, initiation of renal replacement therapy or death due to kidney disease (HR 0.54, 95% CI 0.40–0.75; $p < 0.001$) [102]. In CANVAS, patients in the canagliflozin group had a 40% relative risk reduction in the composite kidney outcome (defined as 40% reduction in eGFR, need for renal replacement therapy or death from renal causes) when compared to placebo (5.5 vs. 9.0 participants per 1000 patient-years with the outcome, HR: 0.60; 95% CI: 0.47 to 0.77) [100].

The average eGFR was within normal limits among patients included in EMPA-REG OUTCOME (74 mL/min/1.73m^2) and CANVAS Program (76 mL/min/1.73m^2) and baseline albuminuria was present in about 30% of patients only. No difference in the protective effect was noted among patients with and without baseline kidney disease. Evaluating a population with mild kidney dysfunction and even normal kidneys is pertinent for the population at risk of CRS2 in which a CV insult may precede the kidney insult, making prevention a key factor. Although there are several proposed direct mechanisms for kidney protection with SGLT2i [98], the benefits to a failing heart including decrease in pre-load and afterload may also be part of the factors leading to a healthier kidney.

Given the prominent results in decreasing CV mortality, empagliflozin has been FDA approved for the indication of reducing risk of CV death in patients with diabetes and cardiovascular disease. Question remains whether this should be the preferred class of antidiabetic drug to be used in patients with diabetes and heart failure and even without diabetes with the goal to reduce HF admissions and protect the kidneys. Studies assessing the use of SGLT2i in HF with reduced and preserved ejection fraction with and without diabetes such as the EMPEROR REDUCED (NCT03057977) [103] and PRESERVED (NCT03057951) [104] are contemporarily in progress. Similarly, trials such as CREDENCE (canagliflozin, NCT02065791) [105] and DAPA-CKD (Dapagliflozin, NCT03036150) [106] have kidney primary composite outcomes and are being conducted with a papulation with more advanced stages of CKD in order to elucidate if SGLT2i should be used with the intent of kidney protection.

Liraglutide and semaglutide are glucagon-like peptide-1 receptor agonists (GLP1-RA) which have shown superiority against placebo in reducing CV events [107, 108]. Additionally, liraglutide had a 22% reduction in CV death and has received FDA approval for the indication of reducing major CV events and CV death in T2DM patients with established CV disease. GLP1-RA are compounds that mimic the actions of incretin hormones. They lead to insulin secretion from pancreatic beta cells in response to an oral glucose load, decrease glucagon release and slows gastric emptying [109]. In addition, both trials demonstrated a reduction in the prespecified kidney outcome which was driven primarily by lower rate of new onset macroalbuminuria which might be explained by the degree of improvement in glucose control [110]. It is unclear whether there are additional direct actions of this compound to the kidneys and if would confer benefit to patients with chronic CV disease with the goal to prevent of mitigate CRS2.

8.7.1 Cardiac Devices

Although the medications mentioned above are the foundation for cardiorenal syndrome primary and secondary prevention, evidence for the ben-

efit of cardiac devices such as cardiac resynchronization therapy (CRT) and left ventricular assist devices (LVADs) to a diseased kidney due to poor heart function is growing. Both CRT and LVADs have shown promising results in improving kidney function when used in adjunct to medical therapy for heart failure and it demonstrates the potential for reversibility of kidney impairment with improvement in cardiac output and reduction in congestion.

8.7.1.1 CRT

Patients with HFrEF (LVEF <35%) who have a baseline left bundle branch block (QRS complex >120 ms) on electrocardiogram and who remain significantly symptomatic despite maximum tolerated guideline directed medical therapy benefit from cardiac resynchronization therapy (CRT) in an attempt to coordinate the contraction of the ventricles and hopefully lead to remodeling and improvement in LV function [111]. CRT is known to improve symptoms and prolong survival when appropriately indicated [112, 113].

In theory, CRT may benefit patients with cardiorenal syndrome type 2 by raising cardiac output and decreasing congestion at the expense of a small, short-term risk of contrast induced nephropathy in order to define the coronary venous anatomy during implantation. CRT is also known to lead to a reduction in adrenergic tone and RAAS activity in patients who respond to this therapy with LV remodeling [114].

The impact of CRT on eGFR was assessed in a retrospective analysis of the MIRACLE Trial [115], a randomized, double-blind, placebo-controlled trial among patients with NYHA class III or IV, QRS duration ≥130 ms, LVEF ≤35%, and LV end-diastolic diameter ≥ 55 mm. The authors divided patients into 3 categories based on baseline eGFR (increased eGFR if ≥90 mL/min/1.73 m^2, mildly reduced eGFR if 60 ≤ eGFR <90 mL/min/1.73 m^2, and moderately reduced eGFR if 30 ≤ eGFR ≤60 mL/min/1.73 m^2). They found that with CRT, only the group with moderately reduced eGFR had a significant improvement in kidney function when compared to controls [116]. Similar results were observed in nonrandomized studies [117].

Small studies have suggested that improvement in kidney function is contingent on the response to CRT. It appears that only those who are classified as "responders", i.e. the ones with improvement in LVEF with this therapy, usually show mild recovery in kidney function. Additionally, this effect seems to be true mainly or patients with baseline renal impairment [118].

Although, once again, most studies assessed improvement in eGFR only, without assessment of hard kidney outcomes, even a mild improvement in eGFR may be enough for patients with moderate to severe kidney impairment to be offered more aggressive guideline directed medical therapy known to improve mortality in HF.

8.7.1.2 LVAD

Left ventricular assist devices are implantable mechanical circulatory support pumps that can be used in patients with advanced heart failure refractory to medical therapy both as destination therapy (when patient are not eligible for transplantation) or as a bridge to transplant with the goal to improve quality of life and survival [119]. Since LVADs ameliorate circulation and congestion, kidney function is expected to improve early after LVAD implantation if the cause of kidney impairment is CRS2. Furthermore, there is evidence to suggest that LVADs also mitigate RAAS activity and decrease sympathetic tone [120]. Whenever there is a high component of intrinsic renal disease due to other comorbidities, the likelihood of improvement in GFR post LVAD implantation is lower.

The majority of the improvement in GFR after LVAD placement takes place shortly after implantation and up to the first month and the lower the pre-implantation GFR the greater the improvement [120]. Data from the INTERMACS database with over 3000 LVAD patients has shown a median improvement in eGFR of almost 50%, with 22.3% of patients improving their pre-implantation eGFR by >100% within the first few weeks. Importantly, this initial improvement was consistently followed by a subsequent drop within the first year to a new baseline usually above pre-implantation levels [121].

This pattern of early improvement followed by subsequent decline in eGFR has been shown in diverse cohorts [120–122] and it is thought to be caused by consequences of chronic hemolysis, lack of pulsatile flow to the kidneys and worsening right heart failure. The repercussions of diminished pulsatility caused by continuous flow LVADs is the focus of extensive contemporary research. In the kidneys, animal models have found periarteritis and afferent arteriole smooth muscle proliferation which can lead to stimulation of the RAAS system [123, 124]. It will be interesting to follow long term kidney outcomes of patients implanted with the HeartMate III LVAD which is designed to have artificial pulsatility. Similarly, after LVAD implantation and improvement in LV output, an impaired right ventricle may suffer with the increase in pre-load, leading to worsening right heart failure and consequent late impairment in kidney function [120, 125, 126].

8.8 Conclusion

The consequences of chronic heart disease in the kidneys is known as CRS2. Renal impairment is common in CV disease and it is an important predictor of morbidity and mortality. Hemodynamic factors as well as neurohormonal activation and chronic inflammation are the main proposed mechanisms of CRS2. Evidence highlighting the renal tubules as opposed to the glomeruli as the mainstay of certain cardiorenal interactions, especially diuretic resistance is growing. Fibrosis is contemporarily being highlighted as the unifying pathogenesis of chronic heart and kidney interplay and advances in the field of biomarker phenotyping and targeted therapies should be expected. The utility of cardiac and renal biomarkers in cardiorenal syndrome remains unclear. Estimated GFR and AUCR are distinct markers of kidney impairment with independent prognostic impact in CV disease. Contemporary evidence derived from cohorts of patients exposed to neprilysin inhibitors has challenged the classic knowledge of albuminuria as a marker of irreversible podocyte injury.

Challenges involved in assessing treatment strategies for cardiorenal syndrome include lack of specific large trials with this population, exclusion of CKD patients from clinical trials and the use of surrogate endpoints instead of hard clinical kidney clinical outcomes such as time to HD and renal death.

Optimum management of the primary heart disease to avoid renal impairment seems to be the most appropriate, evidence-based approach. Neurohormonal blockage with ACEi, ARB, MRA and ARNI are well established tools known to change the natural history of heart failure with reduced ejection fraction. The evidence for direct kidney protection is less established. For the population with T2DM and cardiovascular disease, therapy with SGLT2i and GLP-1RA are additional options with the goal to decrease CV mortality and kidney impairment.

For patients who present with symptoms of HF refractory to maximal tolerated medical therapy, cardiac devices such as CRT and LVAD are adjunct options. Both have demonstrated the potential of reversibility of kidney impairment as a consequence of the improvement in heart function.

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Type 3 Cardiorenal Syndrome

9

Sandeep Soman and Lindsey Aurora

9.1 Introduction

One of the most common causes of death in patients with kidney disease is a cardiovascular event. Kidney and cardiac diseases are common, increasingly prevalent, and frequently co-exist. The failing kidney can initiate various complex metabolic and humoral pathways affecting distant organs, contributing to the high overall mortality rate. In recent years, there has been growing interest in organ–organ interaction, or so-called organ crosstalk, as a way of understanding the natural history of this complex disorder. A consensus definition and classification scheme proposed in 2008 by the Acute Dialysis Quality Initiative workgroup for CRS included specific subtypes. CRS type 3, or acute renocardiac syndrome, is characterized by acute worsening of kidney function, causing cardiac dysfunction. The general definition of CRS refers to any disorder of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other [1, 2]. Cardio-Renal syndrome (CRS) type 3 is a sub-classification of CRS whereby acute kidney injury (AKI) leads to acute cardiac dysfunction and/or injury (Fig. 9.1) [3–5]. The spectrum of CRS-3 comprises acute cardiac dysfunction including acute decompensated heart failure (ADHF), acute myocardial infarction (AMI), and cardiac arrhythmias in the setting of AKI defined by consensus-based Risk, Injury, Failure, Loss, End-stage kidney disease classification (RIFLE)/Acute Kidney injury Network (AKIN) or the Kidney Disease Improving Global Outcomes (KDIGO) criteria.

There is limited literature pertaining to the pathophysiology of this syndrome. Therefore, through improved understanding, it should be possible to develop management strategies including prevention, early detection, and effective therapy to improve outcomes [3].

9.2 Epidemiology of AKI

The impact of AKI on patient outcomes and health care systems is significant. It is estimated that AKI in high-income countries costs $1 billion USD, claims 300,000 lives, results in 170,000 end-stage kidney disease diagnoses, and contributes to the development of 300,000 advanced chronic kidney disease cases on an annual basis [6]. Several risk factors for acute kidney injury are consistent across different clinical settings, including the presence of advanced age, diabetes, male gender, African American race, and factors

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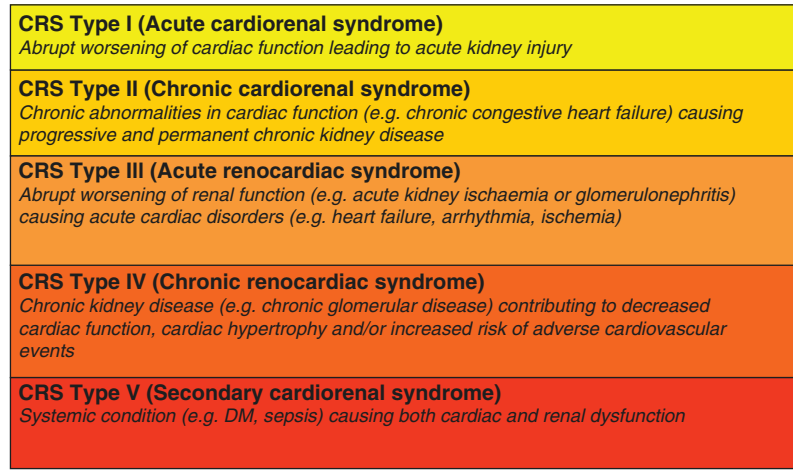

Fig. 9.1 Cardiorenal Syndrome and it's subtypes. (Adapted from Shah BN, Greaves K. The cardiorenal syndrome: a review. *Int J Nephrol.* 2010;2011:920195 [4])

related to the underlying procedure or illness. Among the most potent appears to be the presence of underlying kidney dysfunction as defined by creatinine clearance. Pannu et al. described a robust stepwise increase in the risk for severe AKI with an advancing CKD stage (adjusted Odds Ratio (OR) 18.3 (95% CI, 16.5–20.3)) relative to those with preserved eGFR in a population-based setting [7]. In a recent multinational cross-sectional study, the rate of AKI in the intensive care unit (ICU) was reported at 58% [8]. The incidence of AKI in the general ward has been reported at 6.4% (4.3% community, and 2.1% hospital-acquired) [9]. Multiple studies report that the rate of AKI among hospitalized patients has consistently increased over the past two decades. Hsu et al. found that the incidence rate of community-based AKI increased from 323 cases per 100,000 person-years in 1996 to 522 cases per 100,000 person-years in 2003 [10]. A similar percentage increase was observed among patients who required renal replacement therapy (RRT) following AKI. In the first decade of the twenty-first century, the incidence of dialysis-requiring AKI in hospitalized patients has risen [11]. This observation is attributed to several factors including an aging population with a growing number of comorbidities, increased utilization of invasive interventions in high-risk groups, greater use of potentially toxic medications, and sensitive criteria to better define AKI. To add to the complexity of the issue, the incidence of AKI also varies between different populations. Srisawat et al. reported that the incidence of AKI differed from 15% to 44% and RRT-requiring AKI from 5% to 12% among six different medical centers [7, 12]. However, a recent paper by Kashani et al. reported that the overall trend of sniffer-diagnosed (a validated AKI electronic sniffer to identify patients using the Acute Kidney Injury Network criteria with high reliability) AKI incidence in Olmsted County was flat in all categories (following adjustment for age and sex), except for an increase in AKI stage III incidence among the general ward patients and a decrease in AKI stage II among ICU patients. Factors leading to a slight increase in AKI in general ward patients was attributed to changing demographics, as well as a prevalence of higher risk surgery among hospitalized patients.

9.3 Epidemiology of Renocardiac Syndrome

Acute reno-cardiac syndrome, or CRS-3, indicates cardiac disorders that follow AKI. This entity can be attributed to metabolic derangements seen with AKI, fluid overload, or effects of activation of an inflammatory cascade on the myocardium [2].

Type 3 CRS is usually triggered by an episode of acute kidney injury (AKI); nephrons are particularly sensitive to ischemia and blood borne toxins (nephrotoxins). AKI is often superimposed

on chronic kidney disease and could be a necessary precursor of end-stage renal disease. Elucidation of mechanisms remains difficult due to the complex interplay between chronic and acute kidney disease phenotypes [13]. Acute worsening of kidney function can ultimately lead to cardiac dysfunction (i.e. acute decompensated heart failure, acute myocardial infarction and arrhythmias) [3]. The overall incidence of AKI in the general population appears to be increasing based on Risk, Injury, Failure, Loss, End-stage kidney disease classification (RIFLE)/Acute kidney injury network (AKIN) criteria [14, 15] that use change in serum creatinine and urinary output as primary markers of kidney dysfunction. CRS-3 or acute renocardiac CRS occurs when AKI contributes and/or precipitates development of acute cardiac injury. AKI may directly or indirectly produce an acute cardiac event. This can be associated with volume overload, metabolic acidosis, and electrolytes disorders (i.e., hyperkalemia and/or hypocalcemia); coronary artery disease, left ventricular dysfunction, and fibrosis have also been described in patients with AKI with direct deleterious effects on cardiac outcomes [16, 17].

Acute kidney injury (AKI) is common, increasing in incidence, and associated with excess morbidity and mortality in the critically ill patient [10, 18–20]. Based on the KDIGO (Kidney Disease: Improving Global Outcomes) definition, AKI complicates 18% of all hospitalized patients, with an associated in-hospital mortality of 11% [21, 22]. In the critically ill patient, the incidence of AKI increases to 57%, with 27% in-hospital mortality [23]. Despite widespread availability of renal replacement therapy, a hospitalized patient who develops AKI faces a mortality risk as high as 40–60% [9, 10, 24]. The mortality rate soars to 45–60% when AKI is complicated by other organ dysfunction, such as pneumonia, acute cardiac failure, or sepsis [25]. Much of this mortality risk is thought to stem from extrarenal complications or the distant organ effects of AKI.

Uremic toxin accumulation, metabolic acidosis, electrolyte imbalances, and fluid overload are the traditionally well-known consequences of AKI that contribute to the high mortality [26]. However, a significant proportion of the AKI-associated mortality cannot be explained simply by loss of kidney function or by complications occurring during AKI and it's treatment. Instead, AKI-induced multiorgan dysfunction is of importance in outcomes of critically ill patients with AKI. "AKI-induced distant organ crosstalk" describes the phenomenon when AKI leads to dysfunction of other organs, including lung, heart, brain, liver, and intestine, by aberrant organ-organ communication [22, 27, 28]. Accumulating evidence indicates that interruption of normal immunologic balance and generation of inflammatory mediators are important in AKI induced distant organ crosstalk [29]. Additional mechanisms include increased endothelial injury, cellular apoptosis, and oxidative stress [22, 30–32].

Organ crosstalk can happen following various types of AKI, but there are no clear data to date about whether the cause of AKI affects the extent of distant organ dysfunction. There is a higher chance of distant organ dysfunction with more severe AKI, but even patients with mild to moderate AKI that is not severe enough to require renal replacement therapy can also experience multiorgan dysfunction [33]. In this review, we aim to update clinical and experimental findings on distant organ effects of AKI and discuss potential molecular and therapeutic targets.

Defining incidence and prevalence of CRS-3 is difficult due to lack of epidemiologic data. In a northern Scotland population-based study, the incidence of AKI and acute-on-chronic renal failure were 1811 and 336 per million population, respectively [34]. Another prospective, multicenter, community-based study in 748 AKI patients reported the following common causes of death in AKI: infections (48%), hypovolemic shock (45.9%), respiratory distress (22.2%), heart disease (15%), disseminated intravascular coagulation (6.3%), gastrointestinal bleeding (4.5%), and stroke (2.7%) [24, 35]. In a more recent retrospective study of AKI following trauma, cardiac arrest was reported as cause of death in 20% of patients. Other causes of death included cerebrovascular accidents (46%), sepsis (17%), multiple organ dysfunction syndrome (7.3%), and respiratory insufficiency (3.2%) [36].

Pathophysiological interactions between kidney and heart during AKI has been referred to as "cardio-renal connectors" [37] or potentially "renocadiac connectors". This is thought to include the activation of immune (i.e. pro- and anti-inflammatory cytokines and chemokines release) and sympathetic nervous system, activation of the RAAS and coagulation cascades. Oliguria can lead to sodium and water retention with consequent fluid overload and development of edema, volume overload, hypertension, pulmonary edema, and myocardial injury. Electrolyte disturbances (primarily hyperkalemia) can contribute to risk of fatal arrhythmias and sudden death, while uremia-related metabolic acidosis can affect myocyte metabolism and produce pulmonary vasoconstriction, increased right ventricular afterload and negative inotropic effect (Fig. 9.2) [38, 39].

Wu et al., sheds some light on long term cardiovascular effects of AKI using insurance claims data. Among 10,000 patients with AKI requiring dialysis, the risk of developing a coronary event was higher in patients who did not attain independence from dialysis (HR, 1.67; 95% CI, 1.36–2.04) [40]. A recent robust systematic review of 25 studies revealed that AKI was associated with 86% increased risk of cardiovascular mortality and 38% increased risk of major cardiovascular events (composite of cardiovascular death, stroke, acute myocardial infarction, and CHF). Furthermore, AKI was associated with 58% (RR, 1.58; 95% CI, 1.46–1.72) increased heart failure, 40% increased risk of acute myocardial infarction (RR, 1.40; 95% CI, 1.23–1.59) and 15% increased for stroke (RR, 1.15; 95% CI, 1.03–1.28) [41]. This data by Odutayo et al., is clinical evidence that can be supportive of renal-cardiac 'cross-talk'.

A standardized definition of AKI has helped us better understand the prevalence of AKI in a hospitalized patient, nevertheless, it is highly variable depending on the population studied [23, 42]. Patients admitted to the intensive care unit with AKI have increased mortality and have associated cardiac failure up to 54% of the time [9]. The difficulty is to ascertain direct causality of cardiac disease due to AKI as multiple co-morbid conditions including underlying cardiovascular comorbidities can predispose to AKI. As such, the true prevalence and implications of CRS-3 is not well described, and extrapolation of existing data can bridge our understanding until studies specifically designed in this regard become available.

Data on short term cardiovascular sequelae of AKI is lacking. Correlates for increased cardiac morbidity can be made from data that evaluates complications of AKI. For instance, volume overload, a consequence of AKI, has been shown to independently increase mortality [43].

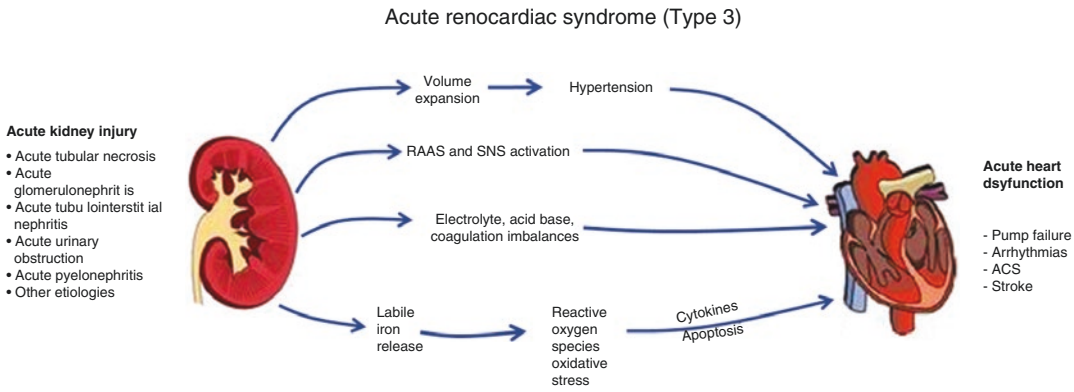

Fig. 9.2 Pathophysiological interactions between heart and kidney in type 3 cardiorenal syndrome (CRS) or "acute renocardiac syndrome" (acute kidney injury leading to abrupt worsening of cardiac function, e.g., acute cardiogenic shock or acute decompensation of chronic heart failure). (Adapted from: McCullough PA. Cardiorenal Syndromes: Pathophysiology to Prevention. *International Journal of Nephrology.* 2011;2011:762590 [38])

Similarly, the metabolic acidosis and hyperkalemia seen in AKI is likely proarrhythmogenic.

Recent findings document that detrimental bi-directional interaction between different renocardiac connectors influence vascular endothelium (renin–angiotensin–aldosterone system, sympathetic nervous system, activated inflammatory mediators, reactive oxygen species, endothelin and uremic toxins) and contribute to the progression of multi-organ failure [37, 44, 45]. Under normal circumstances, bi-directional communications between the heart and kidneys coordinate to modulate cardiac output, vascular tone, and volume status as well as excretion of metabolic waste products. Disruption of either of these pathways contributes to progressive cardiovascular or kidney dysfunction; indeed, failure of one organ system appears to accelerate structural damage and failure of another organ [37]. Vascular endothelial health may also be key to reducing the negative effects of cardiorenal syndrome; activation of the endothelium is important for innate immunity and inflammation, complement activation, coagulation, platelet function, and vasoconstriction [46]. Capillary loss, induced by endothelial injury, can also lead to ischemia and its attendant complications.

9.4 Diagnosis of AKI

Over the last century, the definition of AKI has evolved significantly. The diagnosis of AKI has changed from a clinical and biochemical level to a molecular level, with the most recent advances in tubular damage biomarkers increasing the accuracy of the diagnosis. The use of standard classifications to define and stratify AKI has helped to increase the recognition of this disease in clinical practice and epidemiological research, which has led to defining the incidence of AKI in different settings and assessing its association with adverse outcomes [47, 48]. The three common classification for AKI include: Risk, Injury, Failure, Loss of Kidney Function, End-Stage Kidney Disease (RIFLE) Classification; Acute Kidney Injury Network (AKIN) Classification and the Kidney Disease Improving Global Outcomes (KDIGO) Classification. The features of these classification are summarized in Fig. 9.3 [49, 50].

Ultrasound evaluation of the kidney and heart in patients with CRS-3 can be helpful. Without knowledge of prior baseline renal function, kidney size and echogenicity provide primary features to discern between acute and chronic kidney disease [51, 52]. A hyperechogenic renal cortex with low corticomedullary ratio is suggestive of chronic kidney disease [51, 52]. However, cortical hyperechogenicity can also be present in acute tubular necrosis or acute glomerulonephritis [51, 52]. The echocardiographic pattern is not diagnostic, showing an increase in atrial volumes, pleural or pericardial effusion, and is often associated with evidence of "lung comets" on thoracic ultrasound [53]. Ultrasound lung comets consist of multiple comet tails originating from water-thickened interlobular septa and fanning out from the lung surface. The technique requires ultrasound scanning of the anterior right and left chest, from the second to the fifth intercostal space [54].

Over the past 5–10 years, a number of potential biomarkers have been proposed for the diagnosis of CRS-3. Among AKI novel biomarkers (each with pros and cons), some seem to be particularly interesting, such as neutrophil gelatinase associated lipocalin (NGAL), KIM-1, interleukin-18 (IL-18), interleukin-6 (IL-6), Cystatin C (CysC), N-acetyl-β-d-glucosamide, liver-type fatty acid-binding protein (L-FABP), Netrin-1, Klotho and Midkine (neurite growth-promoting factor 2 (NEGF2)). Several cardiac biomarkers are routinely employed in clinical practice: biomarkers of myocardial necrosis, such as troponins T (cTnT) and I (cTnI) and markers of heart failure as B-type natruretic peptide (BNP) and its inactive N-terminal fragment (NT-proBNP) [3, 55] (Fig. 9.4).

9.5 Pathophysiology of Renocardiac Syndrome

There are numerous complex mechanisms that have been identified as having a role in the development of cardiorenal syndrome. Specifically,

Criteria	Diagnostic criteria	Staging
RIFLE criteria	Increase in Scr to ≥1.5 times baseline within 7 days; GFR decrease >25%; or urine volume <0.5 ml/kg/h for 6 h	*Risk*. Scr increase of 1.5–1.9 times baseline; GFR decrease of 25–50%; or urine output < 0.5 ml/kg/h for 6 h *Injury*. Scr increase of 2.0–2.9 times baseline; GFR decrease of 50–75%; or urine output < 0.5 ml/kg/h for 12 h *Failure*. Scr increase ≥3.0 times baseline; GFR decrease of 50–75%; Scr increase ≥4.0 mg/dl (353.6 μmol/L) with an acute increase of at least 0.5 mg/dl (44 μmol/L); urine output < 0.3 ml/kg/h for ≥24 h; or anuria for ≥12 h
AKIN criteria	Increase in Scr by ≥0.3 mg/dl (26.5 μmol/L) within 48 h; increase in Scr ≥ 1.5 times baseline within 48 h; or urine volume < 0.5 ml/kg/h for 6 h	*Stage 1*. Scr increase of 1.5–1.9 times baseline; Scr increase ≥0.3 mg/dl (26.5 μmol/L); or urine output <0.5 ml/kg/h for 6 h *Stage 2*. Scr increase of 2.0–2.9 times baseline or urine output <0.5 ml/kg/h for 12 h *Stage 3*. Scr increase of 3.0 times baseline; Scr increase ≥4.0 mg/dl (353.6 μmol/L) with an acute increase of at least 0.5 mg/dl (44 μmol/L); urine output <0.3 ml/kg/h for ≥24 h; or anuria for ≥12 h
KDIGO criteria	Increase in Scr by 0.3 mg/dl (26.5 μmol/L) within 48 h; increase in Scr to ≥1.5 times baseline that is known or presumed to have occurred within the previous 7 days; or urine volume < 0.5 ml/kg/h for 6 h	*Stage 1*. Scr increase of 1.5–1.9 times baseline; Scr increase ≥0.3 mg/dl (26.5 μmol/L); or urine output <0.5 ml/kg/h for 6–12 h *Stage 2*. Scr increase of 2.0–2.9 times baseline or urine output < 0.5 ml/kg/h for ≥12 h *Stage 3*. Scr increase of 3.0 times baseline; Scr increase to ≥4.0 mg/dl (353.6 μmol/L); initiation of renal replacement therapy; urine output < 0.3 ml/kg/h for ≥24 h; or anuria for ≥12 h

Fig. 9.3 Risk, Injury, Failure, Loss of Kidney Function, End-Stage Kidney Disease (RIFLE) Classification; Acute Kidney Injury Network (AKIN) Classification and the Kidney Disease Improving Global Outcomes (KDIGO) Classification. (Lei L, Li L, Zhang H. Advances in the Diagnosis and Treatment of Acute Kidney Injury in Cirrhosis Patients. Biomed Res Int. 2017;2017:8523649 [49])

Type 3 CRS is characterized by abrupt cardiac dysfunction as a result of acute primary renal impairment. Potential mechanisms for Type 3 and 4 CRS can be categorized on the basis of hemodynamic or non-hemodynamic criteria [56]. In addition, renal ischemia fundamentally affects the function and structure of the tubular epithelium. Nevertheless, two further events take place and are highly important for the dynamics of post-ischemic kidney regeneration: interstitial inflammation and microvasculopathy [57].

9.5.1 Hemodynamic Factors

Cardiac function is responsible for ensuring that blood is circulated within the body, while the kidneys are responsible for filtering the circulating blood and managing electrolyte and acid base balance. Cardiac and renal functions are strongly dependent on each other to maintain homeostasis [58]. Cardio-renal interactions are generally explained using extracellular fluid volume homeostasis and blood pressure control criteria [59].

Progressive kidney dysfunction without pharmacologic/non-pharmacologic treatment ultimately results in multiple organ failure. Acid–base and electrolyte imbalance, fluid overload, atrial distension, hematologic dysfunction and diminished capacity to eliminate drugs all contribute. Pathophysiologic mechanisms responsible for communications between kidney injury and cardiac dysfunction remain to be established. However, reduced cardiac performance ultimately

Biomarker	Mechanism of release	Key trials
NGAL	Proximal and distal tubular epithelial cells in response to injury. Also systemically from other organs under stress (i.e., sepsis)	Haase et al. meta-analysis of 2358 patients: NGAL an AUC of 0.815 across all settings to detect AKI [14]
Cystatin C	Synthesized and released into plasma by all nucleated cells at a constant rate	Ahlstrom et al.'s ICU study with 202 patients found an AUC of 0.901 for early detection of AKI [60]
IL-18	Cleaved to mature fom1 in prox imal tubular cells after ischemia-reperfusion injury but also general inflammatory states	Parikh et al. showed elevated levels in 52 patients with AKI versus 86 nomml individuals [34]
KIM-1	Upregulated in proximal tubular epithelial cells in response to injuries such as ischemia-reperfusion and nephrotoxins	Han et al. shows favorable AUC of 0.90 for the diagnosis of established AKI in 44 patients versus 30 controls [24]
BNP	Ventricular myocytes in response to hemodynamic stress	Breathing Not Properly trial of 1586 patients found that the diagnostic accuracy of BNP at 100 pg/ml was 83.4%, with a negative-predictive value of 96% at a cutoff of 50 pg/ml [62]
SDF-1	Constitutively expressed by most organs but upregulated after injury or DNA damage	Togel et al. showed in mice that SDF-1 is a mediator for the migration of CXCR4 (its receptor)-expressing cells to the kidney with possible renoprotective effects as well as renal repair [4 1]
Urinary exosomes	All segments of the nephron as a part of normal signaling; upregulated in response to stress	Zhou et al. found exosomes containing ATF3 in four patients with AKI compared with eight controls [44]
Osteopontin	Loop of Henle and distal nephrons in normal kidneys; upregulated in all tubular and glomerular segments fo llowing kidney damage	Lorenzen et a/. showed it osteopontin be a predictor of mortality with a AUC of 0.82, sensitivity of l 00% and specificity of 61% for a cutoff value of 577 ng/ml in 109 critically ill patients [39]
NAG	Lysosomal enzyme leaked into renal tubules from damaged proximal tubular cells	Han et al. showed NAG had an AUC of 0.97 in distinguishing established AKI in 44 patients versus 30 controls [25]

AKI: Acute kidney injury; ATF3: Activating transcription factor 3; AUC: Area under the curve; BNP: B-type natriuretic peptide; ICU: Intensive care unit; KIM-1 : Kidney injury molecule- 1; NAG: N-acetyl-β-D-glucosaminidase; NGAL: Neutrophil gelatinase-associated lipocalin; SDF-1: Stromal cell-derived factor-1.

Fig. 9.4 Biomarkers for acute kidney injury. (Adapted from Taub PR, Borden KC, Fard A, Maisel A. Role of biomarkers in the diagnosis and prognosis of acute kidney injury in patients with cardiorenal syndrome. Expert Rev Cardiovasc Ther. 2012;10(5):657–667 [55])

limits blood perfusion of all organs including the kidneys and thereby contributes to renal injury in patients with heart failure. Similarly, volume overload in patients with renal impairment predisposes to onset and progression of congestive heart failure. AKI affects the heart either directly or by limiting remote organ function which then indirectly influences cardiac function.

Consequences of heart failure including reduced cardiac output and blood pressure stimulate both the sympathetic nervous and renin angiotensin systems which results in volume expansion [60, 61]; the latter allowing for some restoration of renal perfusion. Data for kidney hemodynamics and segmental sodium handling are limited for patients with combined heart and renal failure. However, bi-directional coupling between dysfunctional heart and kidneys induces sodium and water retention that ultimately exacerbates heart failure by affecting arterial pressure (lower) and renal venous pressure (higher).

Recent studies have also suggested that central venous pressure (CVP) is an important hemodynamic determinant of CRS. Congestive heart failure is marked by increased CVP resulting in a reduced perfusion gradient across the glomerular capillary bed and decline in renal function. The resulting right ventricular dysfunction also causes dysfunction in left ventricular filling and disturbances in forward flow. Studies by Mullens et al. showed that a higher CVP is indicative of CRS progression during hospitalization and Uthoff et al. reported that high CVP was significantly associated with lower eGFR in patients with low systolic blood pressure [62]. On the other hand, CVP appeared to have no effects on eGFR in normal to high systolic blood pressure.

9.5.2 Non-hemodynamic Factors

In addition to the proposed hemodynamic factors, various cardiorenal connectors may activate

endogenous systems after AKI and contribute to progression of symptoms. These include, but are not limited to, the sympathetic nervous, renin-angiotensin aldosterone and coagulation systems, inflammation, oxidative stress and nitric oxide equilibrium [37].

For type 3 CRS, AKI produces rapid and significant functional changes in the heart characterized by LV dilatation and alterations of various functional parameters including LV relaxation time, fractional shortening and end-systolic and end-diastolic fractional shortening. Cardiomyocyte apoptosis has been suggested to play a role in promoting these changes along with stimulation of inflammatory mediators. Ischemia initiates a cascade of inflammation that is crucial to organ repair and if unchecked, eventual deterioration of organ function. There are prominent morphologic features of ischemic AKI which include effacement and loss of proximal tubule brush border, patchy loss of tubule cells, focal areas of proximal tubular dilation and distal tubular casts, and areas of cellular regeneration [64]. In rodent models of acute and chronic kidney disease, the role of inflammation is predominant as evidenced by greater secretion of pro-inflammatory cytokines and infiltration of inflammatory cell types [64, 65]. This can lead to oliguria with resultant sodium and water retention and subsequent development of hypertension, pulmonary edema, and myocardial injury. Concomitant electrolyte disturbances can contribute to fatal arrhythmias and sudden death due to hyperkalemia and pulmonary vasoconstriction ensues with increased right ventricular afterload and negative inotropic effect due to uremia related metabolic acidosis [66].

The neuroendocrine system also plays an important role in physiopathology of type 3 CRS; complex pathways are activated after onset of AKI resulting in activation of the systemic nervous and renin-angiotensin systems. Chronic activation of the these neurohormonal system can have deleterious effects on the cardiac and renal systems [58]. Initial activation of the systemic nervous system protects cardiac output but it also appears to stimulate apoptosis [67], neointimal formation and affects immune system function [3]. In addition, activation of the renin angiotensin system stimulates renin secretion by the kidneys; it also leads to dysregulation of extracellular fluid volume and vasoconstriction which can exacerbate the effects of ischemia by limiting adequate oxygen delivery cardiac and kidney failure. Unique risks are also associated with dialysis procedures particularly in patients with end-stage renal disease, including intra-dialytic hypotension, electrolyte fluxes, activation of inflammatory markers [5]. Ventricular remodeling is another downstream neurohormonal effect secondary to RAAS activation and increase in oxidative stress [58]. With impairment in forward flow, chronic SNS over-activation has been shown to reduce cardiac beta-adrenoceptor density and sensitivity, and cause cardiomyocyte hypertrophy [58].

A recent review by House provides an exclusive summary of potential mechanisms in CRS [68]. The role of the uremic milieu in development of multi-organ dysfunction still needs to be clarified; specific uremic toxins (guanidines, phenols, parathyroid hormone, proinflammatory cytokines, etc.), or combinations thereof, could directly cause metabolic and physiologic derangements and contribute to progression of the disease phenotype. In patients with progressive renal insufficiency and congestive heart failure, pressure and volume overload result in augmented cardiac work and compensatory hypertrophy (in part due to cardiac and renal fibrosis), further increasing the risk of adverse coronary events due to impaired oxygen delivery. Similarly, using a two-stage subtotal nephrectomy uremia model (AKI by permanent occlusion of renal artery branches that produces type 3 CRS) Kingma et al. have been able to provide evidence for significant perfusion abnormalities across the ventricular wall in relation to severity of kidney dysfunction (assessed by serum creatinine) [69]. In normal animals, myocardial blood flow increases in a dose-dependent fashion during dobutamine challenge (i.e. increased cardiac work); however, in uremic dogs even low-dose dobutamine maximally increased myocardial blood flow and oxygen transport. On the basis of these findings, there is

suggestion of an increased risk of adverse coronary events due to the loss of transmural autoregulation and potential for maldistribution of myocardial perfusion [69].

Renal autoregulation has also been shown to be significantly impaired during CKD; this would exacerbate injury due to limited perfusion of blood [70]. The hypothesis that coronary blood flow regulation and distribution of ventricular blood flow could be compromised during acute renal failure (ARF) was tested by Kingma et al. In two separate groups (n = 14 each) of dogs with ARF, (1) coronary autoregulation (pressure-flow relations), vascular reserve (reactive hyperemia), and myocardial blood flow distribution (microspheres) along with (2) coronary vessel responses to intracoronary infusion of select endothelium-dependent and -independent vasodilators were evaluated. In addition, coronary pressure-flow relations and vascular reserve after inhibition of nitric oxide and prostaglandin release were evaluated. Under resting conditions, myocardial oxygen consumption increased in dogs with ARF compared with no renal failure (NRF; 11.8 ± 9.2 versus 5.0 ± 1.5 ml O(2)/min per 100 g; P = 0.01), and the autoregulatory break point of the coronary pressure-flow relation was shifted to higher diastolic coronary pressures (60 ± 17 versus 52 ± 8 mmHg in NRF; P = 0.003); the latter was shifted further rightward after inhibition of both nitric oxide and prostaglandin release. The endocardial/epicardial blood flow ratio was comparable for both groups, suggesting preserved ventricular distribution of blood flow. Severe AKI results in a significant rightward shift of the coronary perfusion pressure-blood flow relation and markedly blunted vessel reactivity to endothelium dependent/independent agonists. These pre-clinical findings support the hypothesis that increased levels of uremic toxins can directly influence vasoregulation and endothelial function and thereby organ perfusion [16]. The incidence of mortality is markedly higher in dogs with elevated serum creatinine and blood urea nitrogen. The relevance of these findings to organ dysfunction merits further investigation as endothelial dysfunction, vascular calcification, and accelerated systemic inflammation all contribute to increased vascular stiffness and alteration of arterial pulse pressure and myocardial perfusion in patients with end-stage renal disease [16, 71, 72].

Continued investigation to determine the physiopathological mechanisms involved in development of renal disease after AKI will require a multifaceted and bidirectional approach. Identification of risk factors involved in early kidney injury might be the most logical approach to prevent and delay adverse outcomes; as vascular remodeling in the presence of uremic toxins increases oxidative stress, inflammation and lipid metabolism that exacerbates endothelial dysfunction. Thus, prevention of early microvascular dysfunction may be fundamental to limiting adverse effects of progressive kidney and heart disorders.

9.6 Endothelial Dysfunction

The relevance of post-ischemic microvasculopathy has been proven for the first time in the early 1970s. Mannitol treatment of animals abrogated post-ischemic endothelial cell swelling in the kidney, subsequently promoting faster reperfusion and tissue regeneration [73]. Comparable observations were made by Prof. M. Goligorsky from the New York Medical College [74, 75]. Nude rats subjected to renal ischemia displayed endothelial cell swelling in intrarenal capillaries, associated with slower post-ischemic reperfusion. Such no-reflow phenomenon was partly reversible if the animals were injected with mature endothelial cells of human origin. Thus, cells of the endothelial lineage provided renoprotection by modulating the vascular structure/function. Since then, further studies expanded this therapeutic approach. During the last 7 years, so-called Endothelial Progenitor Cells (EPCs) were successfully administered in murine AKI [76–78]. Another aspect of post-ischemic microvasculopathy is related to the risk for developing chronic kidney disease in the long-term. Morphological analyses of kidneys from animals with AKI reveal a decrease in peritubular vascular density with increased accumulation of connective tissue in the interstitial space [79, 80].

Interstitial fibrosis indicates a higher risk for chronic tissue damage and current investigations focus on the role of vascular rarefication as risk factor for chronic kidney disease per se.

Terms such as "endothelial dysfunction (ED)," "endothelial cell activation," and "endothelial damage/injury" are currently used interchangeably in the medical literature [81–87]. Although widely used, ED still does not have a well-accepted definition [85]. In terms of arterial stiffness, linking cardiac and renal disease, several authors have referred to ED as a maladapted endothelial phenotype characterized by reduced nitric oxide (NO) bioavailability, increased oxidative stress, elevated expression of proinflammatory and prothrombotic factors, and reduced endothelium-derived vasodilation [11, 81]. On the other hand, in terms of de novo protein synthesis or gene transcription, ED can be defined as a series of cellular alterations of the endothelium [83, 86]. The sequence of events leading to ED may be described as:

1. Type I endothelial activation, in which the surface of the activated endothelium is capable of shedding prestored proteins such as endothelial adhesion and antithrombotic molecules (P-selectin, thrombin, heparin, von Willebrand factor, antithrombin III, and thrombomodulin), thereby requiring no de novo protein synthesis. In addition, a set of protective genes [NF-κB inhibitor-α, A20, and BcL-2] are constitutively expressed within the endothelial cell; NF-κB inhibitor-α is a specific inhibitor of NF-κB, and A20 and BcL-2 are antiapoptotic genes; these genes downregulate the expression of the transcription factor NF-κB, thereby requiring no gene transcription;
2. Type II endothelial activation, in which de novo protein synthesis and gene transcription are required; activation of NF-κB triggers endothelial cell activation and provides the endothelium with new capacities and new functions. As a result, activated endothelial cells release new proteins (E-selectin, intercellular adhesion molecule-1, vascular cell adhesion molecule-1, tissue factor, monocyte chemoattractant protein-1, etc.);
3. Endothelial apoptosis; and
4. Endothelial necrosis [86].

9.7 Management: Cardiac Related

Although management of congestive heart failure and acute kidney injury have separate established guidelines, there is no defined consensus on the treatment of CRS as an entity or for its specific subtypes. Treatment strategies have been empiric with no conclusive clinical trial data and largely focused on treating the underlying cause, whether it be predominant cardiac or renal etiology [88]. The overall goal is to manage congestion in patients with congestive heart failure and minimize renal insult with use of agents such as diuretics, vasodilators, and via extracorporeal means, namely dialysis and ultrafiltration.

9.7.1 Diuretics

Loop diuretics represent the primary class of diuretics in congestive heart failure, named for their site of action in the loop of Henle of the nephron. They have been the mainstay of therapy in patients with acute decompensated heart failure (ADHF), more so than thiazide diuretics due to limited efficacy in reduced kidney function [89]. The Diuretic Optimization Strategies Evaluation (DOSE) trial was designed to compare bolus versus continuous infusion of furosemide and high-dose versus low-dose therapy [62]. This study was a prospective, randomized controlled trial in which 308 subjects were randomized to receive intravenous furosemide either by continuous infusion or bolus infusion every 12 h. Primary end points included global assessment of symptoms and change in serum creatinine from baseline to 72 h. No statistically significant difference was noted in either of the primary end points. Therefore, continuous or bolus administration of loop diuretics demonstrated equivalent safety and efficacy. Although symptoms are markedly improved with these agents, they can cause electrolyte and acid base

disturbances along with neurohormonal activation, worsening renal function, and resultant diuretic resistance defined as inadequate urine output despite increases in diuretic doses.

9.7.2 Vasodilators

As mentioned earlier, high CVP, in comparison to pulmonary capillary wedge pressure or cardiac index, is associated with a decline in kidney function in patients presenting with ADHF [90]. In the setting of a rise in CVP, the net filtration pressure across the glomerulus drops as a result of a reduced pressure gradient between afferent and efferent vessels [88]. This brings forth a treatment strategy with vasodilator therapy in order to improve perfusion within the kidneys while decreasing CVP. Agents such as Nitroprusside and Nitroglycerin have been shown to offer symptomatic relief, with their ideal vasodilating or venodilating properties, respectively, especially when combined with diuretic therapy in ADHF but their efficacy in CRS has yet to be established [91].

9.7.3 Natriuretic Peptides

Natriuretic peptides, synthesized as preprohormones, are classified as a family of structurally related hormones factors which are responsible for regulating blood volume, blood pressure, ventricular hypertrophy, fat metabolism, and long bone growth. Three peptides occur in mammals including atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), and C-type natriuretic peptide (CNP) with BNP found most commonly in cardiac ventricles during times of cardiac stress such as congestive heart failure or myocardial infarction [92]. Nesiritide, an analogue of B-type natriuretic peptide, use in patients with left ventricular dysfunction undergoing cardiovascular surgery has been associated with improved postoperative renal function in comparison without Nesiritide therapy, demonstrating nephroprotective properties [93]. Initial safety concerns about this drug came forth through a meta-analysis of 1269 patients pooled from five trials which demonstrated a risk of worsening kidney function associated with the use of Nesiritide [24, 88]. Concerns were dispelled through Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF), a trial conducted from May 2007 through August 2010 at 398 centers throughout the world. This randomized, double-blind, and placebo-controlled study comprised 7141 patients who were hospitalized with ADHF to receive either Nesiritide or placebo in addition to standard care [94]. Coprimary end points were comprised of change in dyspnea along with composite end point of rehospitalization for heart failure or death within 30 days. There was no conclusive benefit seen with Nesiritide with regards to death or rehospitalization. Furthermore, this drug was not associated with worsening renal function. Ultimately, similar to vasodilator therapy, the role of Nesiritide has yet to be deciphered in management of CRS in patients with ADHF.

9.7.4 Mechanical Ultrafiltration and Dialysis

It is important to keep in mind that use of diuretics in patients with ADHF may lead to deterioration of renal function. Challenge exists in maintaining a volume overload state to maintain cardiac index and preserve renal function [95]. At times, pharmacologic treatments have reached its limits and patients develop oligo-anuric renal failure at which point renal replacement therapy is a difficult yet required solution, with any delay in critical illness associated with increased mortality and re-hospitalizations [96]. The mode of renal support in critically ill patients with AKI remains a matter of debate, with continuous therapies generally preferred in the sickest patients who are hypotensive or in circulatory shock that requires vasoactive agents. Lower ultrafiltration (UF) rates characteristic of continuous modes are associated with improved hemodynamic stability, but this apparent physiologic benefit fails to translate into better clinical outcomes, with similar mortality and mor-

bidity rates between intermittent and continuous modes of renal support. Fluid removal by ultrafiltration, defined as extracorporeal removal of plasma water has been increasingly used in patients with ADHF and renal dysfunction. This means of fluid removal offers benefits over diuresis including removal of isotonic plasma, increased sodium removal, decreased hypokalemia, and decreased neurohormonal activation [97]. Randomized trials including Ultrafiltration versus Intravenous Diuretics for Patients Hospitalised for Acute Decompensated Congestive Heart Failure (UNLOAD), Relief for Acutely Fluid-Overloaded Patients With Decompensated Congestive Heart Failure (RAPIDCHF), Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARESS-HF) have compared diuretic therapy and ultrafiltration in patients with acute decompensated HF [98–100]. In UNLOAD and RAPIDCHF, ultrafiltration was associated with greater fluid loss than diuretic therapy with no observed differences in serum creatinine. CARESS-HF specifically studied the use of ultrafiltration to treat ADHF in the setting of worsening kidney function. However, the trial ended early due to higher adverse events observed in the ultrafiltration group with comparison to pharmacologic therapy, driven by increases in serum creatinine, even though weight loss was similar to other trials. Further smaller trials proceeded to evaluate the role of ultrafiltration in treatment of ADHF including Continuous Ultrafiltration for Congestive Heart Failure (CUORE) trial [101] and Aquapheresis vs. Intravenous Diuretics and Hospitalizations for Heart Failure (AVOID-HF) [102]. These studies were largely underpowered to show the utility of ultrafiltration over diuretic therapy but did show marked trends towards improvement with ultrafiltration. Despite ideal benefits of fluid removal via ultrafiltration over loop diuretics, further prospective studies are needed to establish the clear role and advantages of ultrafiltration with respect to ideal candidates, timing and concurrent use of medical therapy along with effect on hospitalizations in patients with ADHF.

CRS management largely focuses on the major classes of drugs including diuretics, vasodilators, renal replacement therapy and via fluid removal through ultrafiltration. Treatment of ADHF and CRS remains a challenge due to the complex nature and pathophysiology of CRS and its subtypes. Current literature offers comprehensive clinical data with effective therapies that need to be applied in the correct clinical context.

9.8 Prevention of CRS-3

Because AKI treatment is not simple, prevention is always critical. Patients at high risk for AKI development (for example, kidney injury provoked by the use of potential nephrotoxins) should be identified early, monitored and prevention should be employed. Preventive actions to avoid AKI are critical for clinical practice because once AKI sets in, supportive treatment is the mainstay of therapy with few clinically applicable therapeutic options.

The importance of avoiding various nephrotoxic drugs and their combinations is receiving more attention. Two large pragmatic studies have compared 0.9% saline to crystalloids with more physiological chloride concentrations for intravenous fluid therapy. Together, these studies included nearly 30,000 patients, and both studies found reduced rates of major adverse kidney events (death, dialysis, or persistent kidney dysfunction) when alternatives to saline, such as lactated Ringer solution or PlasmaLyte, were used (ARR $\approx$ 1% in both studies) [103, 104]. Importantly, these are all patient-centered outcomes, and because virtually all patients admitted to hospitals receive intravenous fluids, the effect on public health is substantial. In addition, when patients develop severe AKI, they may receive dialysis. Although the time to initiate dialysis remains controversial, strong evidence indicates that receiving dialysis at an earlier stage of AKI is associated with better outcomes compared with initiation at a more advanced stage.

Early diagnosis of AKI is critical. The serum Creatinine (sCr) concentration is the parameter to assess renal function decay and AKI. However, sCr concentration may not change until approximately 50% of kidney function has been lost

[105]. Moreover, the return of sCr to basal levels—reflecting a recovery in renal function—does not necessarily demonstrate a complete structural recovery and renal integrity. Long term, the impairment of kidney structure may imply a loss of renal function and progression to chronic kidney disease due to a maladaptive repair. In this context, it is important to evaluate functional and structural markers in a noninvasive way for diagnosing, monitoring, and quantifying kidney damage. The emerging novel biomarkers specific for kidney damage are likely to play more important role in the diagnosis of early AKI. Altogether, biomarker development is a long-term investment to be included in the existing consensus definition of AKI (RIFLE, AKIN or KDIGO) but it should be embraced as critical for successful AKI therapy.

Careful assessment of volume status and hemodynamics should be undertaken in addition to appropriate treatment with intravenous fluids, diuretics, or other means of hemodynamic support as indicated. The eventual use of renal replacement therapy (RRT) is required in most of cases [106].

Treatment strategies for the heart in type 3 CRS pose a particular challenge. Prevention of LV volume overload is fundamental to limit the potential for worsening cardiac and renal function. Use of diuretics to improve clinical symptoms in heart failure patients is the status quo; however, evidence of a mortality benefit in patients with AKI remains controversial. Indeed, use of diuretics for AKI is contraindicated except for management of volume overload. Appropriate timing and choice of renal replacement therapy is critical. Clinical outcomes may also be improved using ultrafiltration and hemofiltration to reduce volume overload in patients that are refractory to diuretics, but not requring renal replacement therapy for solute control.

The last few years have produced a substantial amount of research that will directly influence the likelihood of developing AKI, and it will influence the treatment for patients who develop AKI. Despite substantial progress, the number of clinical trials for prevention and treatment of AKI remains inadequate. To continue progress for treating AKI, research agencies, foundations, and industry will need to increase funding for clinical research. In particular, greater use of AKI biomarkers and automated computer alerting are needed to identify patients at risk for AKI so that interventions, including care bundles, can be implemented promptly. Clinical trials should focus on new and existing interventions for specific etiologies of AKI (e.g. sepsis, cardiac surgery) rather than grouping multiple causes. Progress over the last numerous years has demonstrated that AKI can be successfully addressed and ameliorate it's sequalae; the need now is to expand and accelerate this work [107].

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Type-5 Cardiorenal Syndrome

10

Luca Di Lullo and Claudio Ronco

10.1 Introduction

The cardiorenal syndromes (CRS) are recently systematically defined as disorders of heart or kidney whereby one organ dysfunction leads to dysfunction of another. Five types of CRS are defined [1]. First four types describe acute or chronic cardiorenal or renocardiac syndromes. Type 5 CRS refers to secondary cardiorenal syndrome or cardiorenal involvement in systemic conditions. It is a clinical and pathophysiological entity to describe the concomitant presence of renal and cardiovascular dysfunction. Type 5 CRS can be acute or chronic (Table 10.1) and it does not strictly satisfy the definition of CRS. However, it encompasses many conditions where combined heart and kidney dysfunction is observed. As this entity is recently described there is limited information about the epidemiology, clinical course and treatment of this condition. All vital organs of the body share biological information also termed as organ crosstalk. The normal physiological functions of the body depend on this normal network. One organ dysfunction can result in dysfunction of another. The interaction between the heart and the kidney is fairly common. Heart and kidney dysfunction can be observed in many hospitalized patients, especially in the intensive care unit. Over the last decade, many intensivists, cardiologists, and nephrologists have shown keen interest in pathophysiology of this organ crosstalk between heart and kidney. Many terms for this organ crosstalk have been suggested, such as cardiorenal anemia syndrome, cardio-renal syndrome, reno-cardiac syndrome. Ronco et al. have proposed the definition and subdivision of CRS into five subtypes. Irrespective of the first insult (heart failure causing kidney injury or renal failure causing heart disease), CRS portends increased mortality and morbidity. Type-5 CRS is a recently defined clinical syndrome and complete epidemiological data on this entity are still incomplete.

10.2 Pathogenesis of CRS 5

10.2.1 CRS-5 and Sepsis

Inflammation and microvasculature alterations form basis to the pathogenesis for involvement of both the kidneys and cardiovascular system during sepsis, leading to cell ultrastructural alterations and organ dysfunction [2, 3]. Cardiovascular system is frequently involved in sepsis and always

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affected by septic shock. Cardiovascular dysfunction in sepsis is associated with a significantly increased mortality rate of 70–90% compared with 20% in patients without cardiovascular impairment [4]. Myocardial dysfunction in sepsis has been the focus of intense research. Many mediators and pathways (Fig. 10.1) have been implicated in pathogenesis of septic myocardial depression, however, the precise etiopathogenesis is unclear [5]. Calvin and his colleagues were the first to demonstrate myocardial dysfunction in adequately volume-resuscitated septic patients with decreased ejection fraction and increased end-diastolic volume index [4]. Echocardiographic studies have demonstrated impaired left ventricular systolic and diastolic function in septic patients [6, 7]. Many other studies have confirmed decreased contractility and impaired myocardial compliance in sepsis [8–11].

Table 10.1 Conditions causing acute and chronic type 5 cardiorenal syndrome

Acute CRS-5	Chronic CRS-5
SEPSIS	DIABETES MELLITUS
INFECTIONS (Malaria, Leptospira, HIV, Parvovirus B19, Cytomegalovirus, Coxsackie virus, Toxoplasmosis)	HYPERTENSION
CONNECTIVE TISSUE DISORDERS	TUBERCULOSIS
ELECTRIC SHOCK	SARCOIDOSIS
DRUGS (Cocaine, heroin, calcium-channel blockers, cisplatin, methotrexate, mitomycin)	FABRY'S DISEASE
THROMBOTIC MICRO-ANGIOPATHY	SLE (Systemic Lupus Erythematosus)
TOXINS (Arsenic, snake bite, scorpion bite)	CHRONIC LIVER DISEASE
WEGENER'S GRANULOMATOSIS	SICKLE CELL DISEASE
PHEOCHROMOCYTOMA	MULTIPLE MYELOMA
BURKITT'S LYMPHOMA	AMYLOIDOSIS

Septic cardiac dysfunction is multifactorial. Like septic AKI, ischemia and inflammatory mediators are the chief culprits. Global myocardial ischemia was postulated initially as a the main mechanism of cardiac dysfunction but later septic patients have been shown to have high coronary blood flow and diminished coronary artery–coronary sinus oxygen difference [12]. Further experiments suggested a possibility of myocardial hypoxia due to alterations in coronary blood flow and myocardial metabolism as a possible mechanism of cardiac dysfunction [13]. In patients with underlying coronary artery disease, myocardial ischemia is aggravated [14].

Inflammatory mediators also play a key role in the pathogenesis of cardiac dysfunction. TNF and Interleukin-1 (IL-1) are the principal culprits [15, 16]. Elevated levels of prostanoids such as thromboxane and prostacyclin, which may alter coronary autoregulation and endothelial function have also been demonstrated in septic patients [17]. One of these cytokines may also act as a myocardial depressant factor.

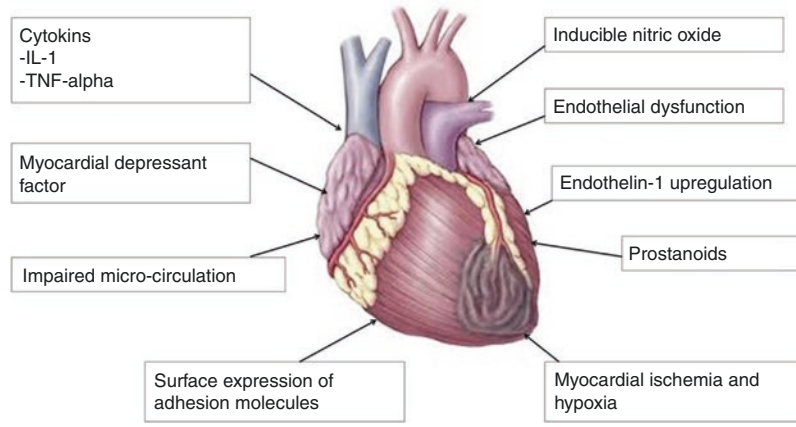

Fig. 10.1 Pathogenesis of cardiac dysfunction in sepsis

Nitric oxide (NO) has important biological role in cardiovascular system. Higher dose of NO has been demonstrated to induce myocardial dysfunction by depressing energy generation [18]. Sepsis leads to the expression of inducible NOS (iNOS) in the myocardium, which in turn importantly lead to myocardial dysfunction [19, 20].

Acute kidney injury (AKI) is common complication of patients with sepsis and carries poor prognosis. AKI occurs in 20% of critically ill patients and in 51% of patients with septic shock and with positive blood cultures [21].The mortality rate of sepsis induced Acute kidney injury is high, at approximately 70% whereas the mortality of AKI alone is 40–45% [22, 23]. Although presence of multiple organ dysfunction and other co-morbidities contributes to high mortality, AKI independently increases morbidity and mortality [24]. Sepsis is characterized by a generalized inflammatory response and by activation of coagulation and fibrinolytic system resulting in endothelial injury [25, 26]. Current opinion suggests that pathogenesis of septic AKI relies on hemodynamic factors and inflammatory mediators (Fig. 10.2). AKI in sepsis was earlier considered to be secondary to renal ischemia due to septic shock. Experimental studies of septic AKI have reported conflicting results [27]. On one hand some studies showed that global RBF declines after induction of sepsis or endotoxemia, leading to acute tubular necrosis, reduction in glomerular filtration and severe AKI [28, 29]. On the other hand, Ravikant demonstrated renal vasodilation with increased RBF [30]. A meta-analysis of 160 experimental sepsis studies found preserved or increased RBF in about 30% those studies [31]. Changes in intrarenal hemodynamics also play a role in the pathogenesis of septic AKI. The RBF may be preferentially redistributed to the cortex, causing a relative hypoxia of medulla [32].

Non hemodynamic kidney injury is mediated by various inflammatory mediators like cytokines, arachidonate metabolites, vasoactive and thrombogenic agents. These various mediators and are involved in the pathogenesis of organ dysfunction in sepsis [33]. Among variety of mediators of tumor necrosis factor (TNF) seems to have the predominant role in septic AKI [34]. Apoptosis seems to be an important pathway of cell dysfunction in sepsis than necrosis. All in all, there is a recent paradigm shift in understanding about the pathogenesis of septic AKI from ischemia and vasoconstriction to hyperemia and vasodilation and from acute tubular necrosis to acute tubular apoptosis.

Sepsis also affects central structures or pathways, including the autonomic nervous system (ANS), the renin-angiotensin-aldosterone system (RAAS) and the hypothalamus-pituitary gland-adrenal gland axis (HPA), impacting cardiac and/or renal function. Sepsis causes ANS dysfunction [35], as pointed up by changing in heart rate variability (HRV) associated with the release of inflammatory mediators, e.g. IL-6, IL-10 and CRP. Data with respect to kidney-related changes in ANS during sepsis is limited to animal studies. Here, sepsis-induced changes in renal sympathetic nerve activity did not seem to affect renal blood flow [36].

Sepsis activates the RAAS, reflecting the body's attempt to restore and maintain a sufficient blood pressure. Recent limited clinical data suggest that blockade of the RAAS might be beneficial, as RAAS activation has also been implicated in endothelial dysfunction [37]. Experimental studies also suggest deleterious effects of RAAS activation on renal function during sepsis [38]. The administration of ACE inhibitors improves creatinine clearance and urine output during experimental bacteremia; the application of selective angiotensin II type 1 receptor antagonist improves renal blood flow and oxygenation during experimental endotoxemia [38].

Finally, sepsis causes complex alterations of HPA and glucocorticoid signaling, leading to severe adrenal insufficiency in some patients. As consequence an increased production of pro-inflammatory cytokines, free radicals and prostaglandins as well as inhibition of chemotaxis and expression of adhesion molecules occurs. Administration of moderate-dose glucocorticoids for 7 days can exert positive effects reducing the need for vasopressors and intensive care unit (ICU) assistance [39].

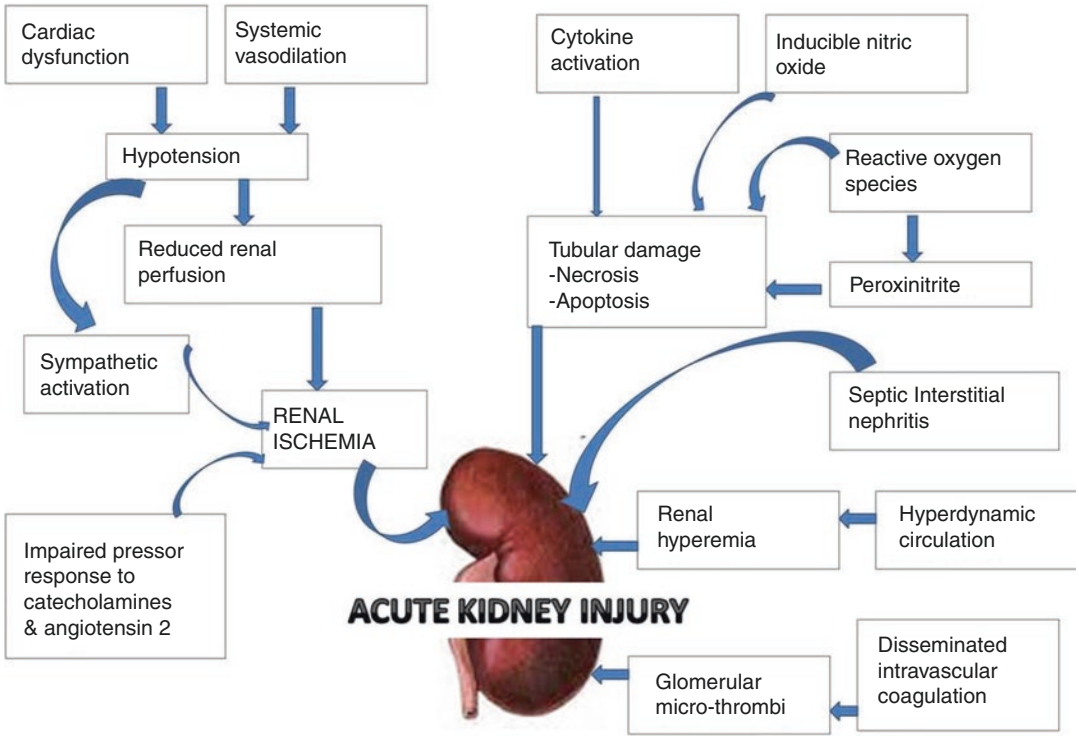

Fig. 10.2 Pathogenesis of acute kidney injury in sepsis

10.2.2 CRS-5 and Amyloidosis

The systemic amyloidosis are an uncommon group of disorders characterized by the extracellular deposition of amyloid in one or more organs. Cardiac and renal deposition leading to restrictive cardiomyopathy and proteinuric renal disease is a common feature of amyloidosis. Importantly, presence and severity of CRS drives the prognosis of systemic amyloidosis.

Among many types of amyloidosis, AL (Primary) and AA (Secondary) amyloidosis are the most frequently encountered types in clinical practice. AL amyloidosis, in which amyloid is derived from monoclonal light chains, is associated with clinical cardiac involvement in about 50% of all cases [40]. Subclinical cardiac involvement at autopsy or on endomyocardial biopsy may be detected in almost all patients. Renal involvement occurs in 30–40% of all AL cases [41]. On contrary, AA type is characterised by predominant renal involvement in 60–100% of all cases [42–45]. Cardiac involvement is less frequent and varies from 0% to 39.5% [42–45].

In amyloidosis, the heart demonstrates thickening of all four chambers, with biatrial dilation, mildly dilation of right ventricle with normal or small left ventricular cavity. Myocardial cells are separated by amyloid deposits with infiltration of intramyocardial vessels. Occasionally epicardial coronary vessels are also involved leading to myocardial ischemia [46]. Conduction system is frequently involved. The predominant manifestation of amyloid heart disease is congestive heart failure. In patients with small vessel involvement and minimal or no myocardial infiltration, the presenting complaint may be angina. In addition, atrial arrhythmias are frequently seen [40].

Renal amyloid is characterized by deposits in the glomerular basement membrane, the subendothelial area and the extracellular mesangial system. Occasionally tubular deposits are seen. The majority of patients with renal amyloidosis present with proteinuria, which can vary from

minimal asymptomatic proteinuria to nephrotic syndrome. Hematuria is present in about one-third of patients. Chronic renal insufficiency with little proteinuria can also be seen in patients with extensive vascular deposits [47]. In patients with tubular deposits, tubular dysfunction can be seen.

10.2.3 CRS-5 and Systemic Lupus Erythematosus (SLE)

Heart is very commonly involved in SLE. Any cardiac structure, including pericardium, myocardium, endocardium, conduction tissue and even coronary arteries are involved in SLE.

The spectrum of cardiac complications in SLE is as shown in Fig. 10.3. Pericarditis is the most frequent cardiac manifestation of SLE and pericardial involvement is seen in 11–54% of patients on echocardiographic studies [48]. Pericarditis is also included in the ARA/ACR classification criteria of SLE [49]. Direct immunofluroscence shows the granular deposition of immunoglobulin and C3. It indicates the role of immune complexes in the pathogenesis. Acute or chronic inflammatory changes are seen in pericardium. Acute Pericarditis can be fibrinous or serofibrinous and chronic pericarditis can be fibrous or fibrofibrinous. Pericarditis generally manifests at the start of the disease or during relapses and rarely leads to cardiac tamponade, constrictive Pericarditis or purulent Pericarditis.

Myocardial involvement in was seen in 40% of SLE cases in postmortem examination [50] and in 20% of cases on echocardiography [51]. But over myocardial involvement is seen in only 7–10% of patients [52]. Immunecomplex and complement deposition is seen on direct immunofluroscence whereas association with anti-Ro/SSA antibodies is also proposed [53]. Patient may present with acute illness or have a chronic course with development of cardiomyopathy but left ventricular failure is rarely seen [54]. Myocardial dysfunction in SLE may also be due to renal failure and hypertension, coronary artery disease (CAD), vulvular affection or toxic effects of medications used for treatment of SLE.

Libman-Sacks endocarditis also known as atypical verrucous endcarditis is the most typical presentation of endocardial involvement in SLE

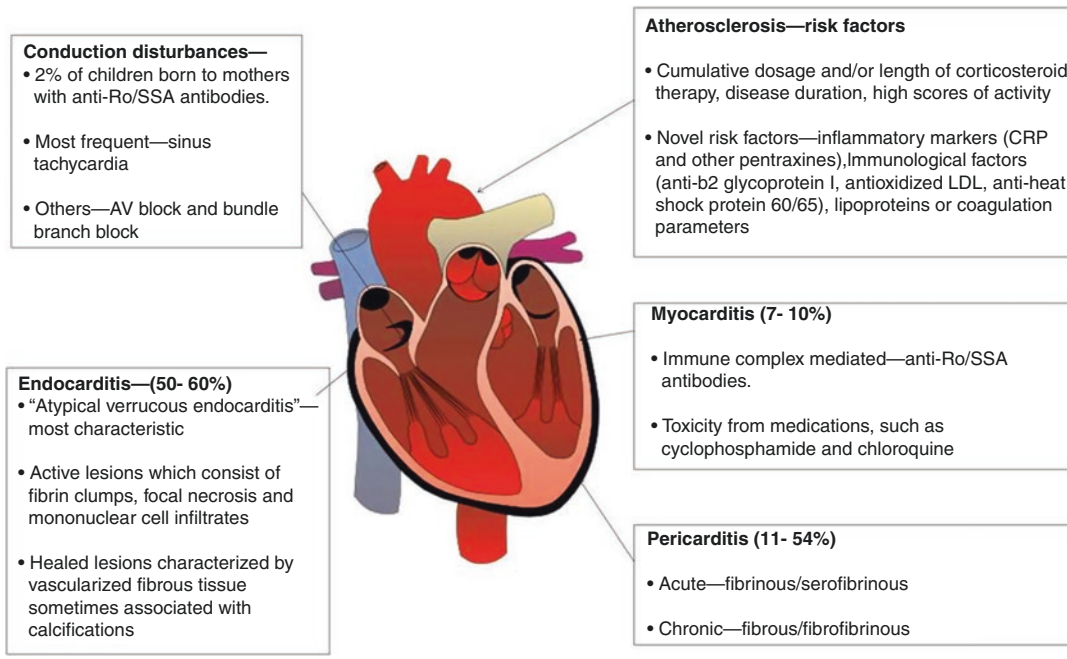

Fig. 10.3 Pathogenesis and manifestation of cardiac dysfunction in systemic lupus erythematosus

(libamann). These vulvular abnormalities are detected in 40–50% of cases with transthoracic echocardiography (TTE) and 50–60% with transesophageal echocardiography (TEE). Antiphospholipid (aPL) antibodies bind to endothelial cells and activate them. This leads to platelet aggregation and thrombus formation [55]. Immune-complex and complement deposition also has been reported to have association with vulvular involvement.

Libman-Sacks endocarditis is clinically silent in majority of patients and rarely leads to development of cardiac murmur. Verrucae develop near the edge of the valve and even if they become large they do not deform the closing line of the valves [56]. Endocardial involvement may lead to vulvular insufficiencies, most commonly of the mitral or aortic valves. Although complications are rare, embolic events do occur and stroke, peripheral embolism has been reported in 13% of cases. Infectious endocarditis has been reported in 7% of cases and risk of endocarditis is increased by dental treatments. Antibiotic therapy should be considered for patients with vulvular abnormalities as SLE patients may receive immunosuppressant therapy for their primary disease.

As patients with SLE live longer due to improved therapies and preventive measures, death and disability from cardiovascular events are increasing. SLE patients are 4–8 times more likely to suffer from CAD than non-SLE patients and it is seen in 6–10% of SLE patients [57]. Women are at risk of CAD 50 times more [58]. Atherosclerosis, hypertension, arteritis, thrombotic event, embolism due to endocarditis or vasospasm are the risk factors for development of CAD [59].

Hypertension, sedentary lifestyle, hyperlipidemia and hyperhomocysteinemia may lead to atherosclerosis in SLE patients [60]. Steroid therapy in these patients increases the lipoprotein and homocysteine levels [61]. Inflammation plays an important role in development of atherosclerotic plaque. Atherosclerotic lesions begin with the recruitment of inflammatory cells such as monocytes and T cells to the endothelial wall. Recently CRP and pentraxins are considered to be inflammatory markers in patients with SLE [62]. Autoantibodies and immunecomplexes also play a major role for atherosclerosis. Circulating antibodies to OxLDL (anti-OxLDL) have been described, though their relationship to the development and progression of atherosclerosis is unclear. Svenungsson et al. has demonstrated that autoantibodies to OxLDL are more common in SLE patients who have a history of cardiovascular disease than in SLE controls or normal subjects [63].

Sinus tachycardia is the most frequent rhythm disturbance observed in SLE patients. Atrioventricular block, bundle branch block are seen in children of mothers with anti-Ro/SSA antibodies and rarely in adults [64]. These patients are mostly asymptomatic or may lead to fatigue and palpitations. Syncope is seen in very rare cases [65]. Sinus tachycardia in SLE patients may be due to pericarditis, myocarditis or chloroquine use [49].

Renal involvement remains a major cause of morbidity in patients with SLE. Abnormalities of immune regulation lead to auto-antibody production in SLE. Antibodies directed against nuclear antigens (ANA) and specifically against the DNA (Anti-dsDNA) are considered diagnostic of SLE. Among these anti-Sm antibodies have significant association with Lupus Nephritis (LN). Initiating event may be the local binding of nuclear or other antigens to glomerular sites followed by in situ immune complex deposition. Immune complexes made up of DNA-anti-DNA along with some other aggregates (nucleosomes, ribosomes, chromatin, C1q, laminin, Sm, La (SS-B), Ro (SS-A), and ubiquitin) cause glomerular injury. Previously T cells were considered only as helping factor for B cells to produce auto-antibodies. But recent studies support the significant role of T cells for progression of renal disease in SLE. Additionally deposition of immune complex leads to release of chemokines like MCP 1 and RANTES in glomeruli. These chemokines causes proliferation of mesangium which results into acute glomerular nephritis characterized by mesangial expansion and cellular infiltration. With the progress of disease, acute glomerulonephritis turns into chronic glo-

merulonephritis characterized by glomerulosclerosis, interstitial fibrosis and tubular atrophy. Recent studies have been done on toll like receptors (TLR) and TLR expression on renal cells causes activation of end organ response and renal injury.

Females are more commonly affected by SLE but clinical manifestations are similar in both the genders, adults and children. SLE is a multisystem disease and any organ system can be involved in SLE. Kidneys are affected from the start of SLE or at any stage and follow a protracted course of remissions and exacerbations. Clinical renal involvement correlates well with degree of glomerular involvement [66]. Clinical features of renal involvement may be correlated with histologic findings seen on renal biopsy and classified by International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 (Table 10.2) [67].

Patients of class I having only mesangial involvement often have no or at the most, mild evidence of clinical renal disease. Patients of class II have proteinuria of less than 1 g/day. But these patients have high anti-DNA antibody titer and low serum complement. Hypertension is infrequently seen and serum creatinine, GFR in the normal ranges.

In class III patients, proteinuria is often more than 1 g/day and many patients present with nephrotic range proteinuria. Most of the patients suffer from hypertension and have elevated creatinine at the presentation. Serologic tests usually indicate active lupus disease at this stage.

Table 10.2 International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification of lupus nephritis

Class 1	Minimal Mesangial Lupus Nephritis
Class 2	Mesangial proliferative lupus nephritis
Class 3	Focal lupus nephritis[a]
Class 4	Diffuse segmental (IV-S) or global (IV-G) lupus Nephritis[b]
Class 5	Membranous lupus nephritis[c]
Class 6	Advanced sclerosing lupus nephritis

[a]Indicate the proportion of glomeruli with active and with sclerotic lesions
[b]Indicate the proportion of glomeruli with fibrinoid necrosis and cellular crescents
[c]Class V may occur in combination with class III or IV in which case both will be diagnosed

Patients of diffuse lupus nephritis (Class IV) present with extensive clinical features. Almost all patients have proteinuria and half of these patients fall in nephritic range. Hypertension is very common and renal dysfunction is typical. These patients have very high titers of anti-DNA antibody and low complement levels.

Patients with membranous lupus nephritis (class V) usually present with proteinuria, edema and other typical nephrotic syndrome features. Out of these 40% of patients will have less than 3 g/day proteinuria and upto 60% of patients will have elevated anti-DNA antibody titers and low serum complement levels. Usually these patients present with hypertension and renal dysfunction. Patients of this class are likely to develop thrombotic complication as seen in idiopathic membranous nephropathy.

Patients end up in class VI after long periods of flares alternating with periods of inactivity. Patients will have inactive sclerotic and fibrotic lesions. Almost all patients have hypertension and renal dysfunction. But anti-DNA antibody titers and serum complement levels may be normalized by the time patients reaches this stage [67].

10.2.4 CRS-5 and Fabry's Disease

Fabry's Disease is responsible of a CRS-5 with insidious onset where the kidney and cardiac dysfunction may develop slowly until a 'point of decompensation'. It can also be chronic, acute or acute-on-chronic CRS-5. Mechanisms in acute and chronic CRS-5 are different: the nature, severity and duration of organ dysfunction are also influenced by the management interventions. In most cases of CRS-5 there is usually a precipitating event that brings the condition to attention e.g. Fabry's crises, precipitated by fever, exercise, fatigue, stress, and rapid changes in temperature [68, 69].

Being a systemic disease, FD starts with an specific effect(s) involving kidney and/or heart, contributing for the bilateral organ crosstalk for the development of CRS 5.

10.2.4.1 Pathology of Renal Involvement

The natural course of Fabry nephropathy in children or adolescent patients is still largely not understood. Like most aspects of the disease, renal pathology increases in severity with age. In classically affected Fabry patients, renal lesions result from Gb3 deposition in the glomerular endothelial, mesangial, interstitial cells and in podocytes, which are terminally-differentiated epithelial cells that accumulate numerous myelin-like inclusions in their lysosomes. Podocyte foot process effacement has been described and it represents histological counterpart of proteinuria. Glycosphingolipid storage also occur in the epithelium of the loop of Henle and the distal tubules, and in the endothelial and smooth muscle cells of the renal arterioles [69, 70]. Histologic, potentially irreversible changes to glomeruli, interstitial tubules and vascular structures before the first appearance of signs can be observed in renal biopsy specimens from children [71] (Fig. 10.4). The glomerular podocytes are swollen and finely vacuolated in light microscopy examination such as epithelial cells of distal tubules (Fig. 10.5); lamellated lipid inclusions (zebra bodies) in podocytes' cytoplasma can be also seen on electron microscopy.

10.2.4.2 Clinical Renal Involvement

Signs indicative of early, insidiously progressing renal damage include microalbuminuria and proteinuria developing as early as in the second decade of life which, like in diabetic nephropathy, are believed to directly contribute to the progression of the Fabry's nephropathy. With advancing age, proteinuria worsens [72]. Isosthenuria accompanied by alterations in tubu-

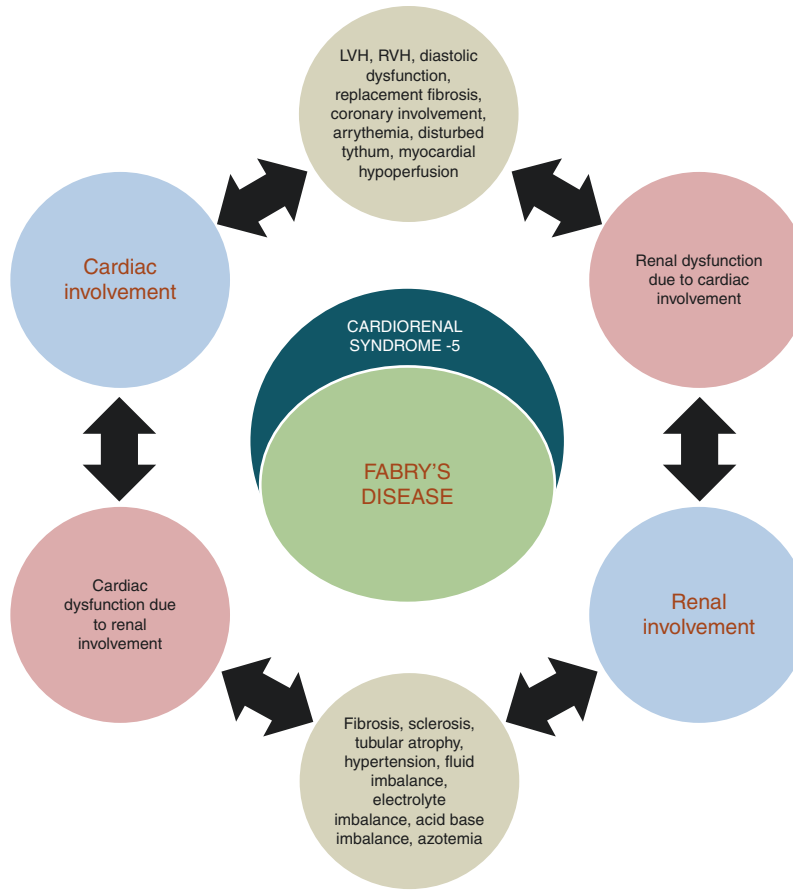

Fig. 10.4 Fabry's disease pathophysiology

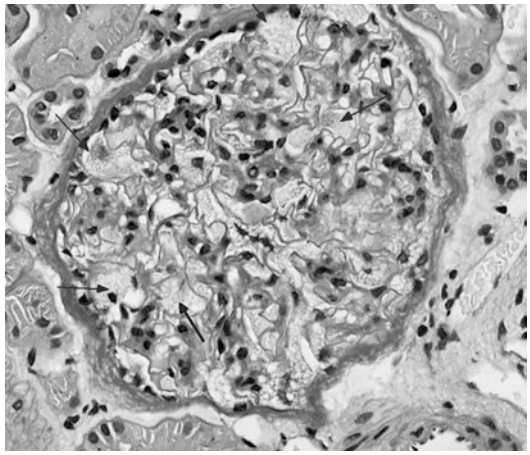

Fig. 10.5 Light Microscopy: The glomerular podocytes are swollen and finely vacuolated (arrows) in a patient with Fabry nephropathy disease

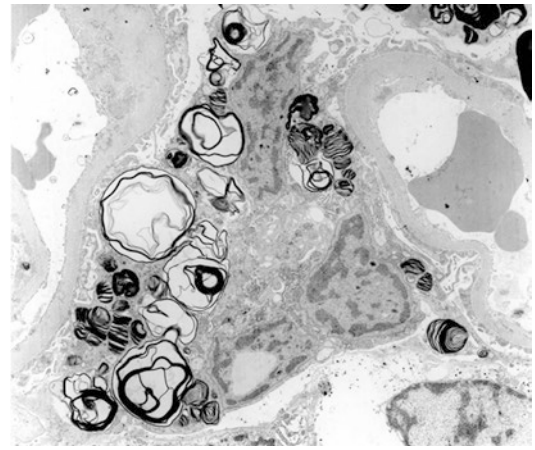

Fig. 10.6 Electron microscopy. Lamellated lipid inclusions (zebra bodies) in a podocyte cytoplasma

lar reabsorption, secretion and excretion develop. Initially, glomerular compensation (hyperfiltration) may mask impairment of renal function but, once a critical number of nephrons have been damaged, renal function will progressively decline. Gradual deterioration of renal function and development of azotemia usually occur in the third to fifth decades of life [73]. At this stage, fibrosis, sclerosis, and tubular atrophy dominate the disease activity portending end-stage renal disease that generally occurs in males in the fourth to fifth decade of life. The nephrological aspects of FD are major contributors to the morbidity and mortality associated with the disorder. Progression to end-stage renal failure is the primary cause of death in male patients with untreated FD and death most often results from uremia, unless chronic hemodialysis or renal transplantation is undertake (Fig. 10.4).

10.2.4.3 Pathology of Cardiac Involvement

Storage of globotriaosylceramide (Gb3) is found in various cells of the heart, including cardiomyocytes, conduction system cells, valvular fibroblasts, endothelial cells within all types of vessels, and vascular smooth muscle cells [74]. Gb3 storage by itself, however, is unable to explain the observed level of cardiac manifestations. Autopsy of an individual with Fabry's disease who had an extremely hypertrophied heart revealed a relatively limited contribution (1–2%) of the stored material to the enormous increase in cardiac mass. It appears that storage induces progressive lysosomal and cellular malfunctioning that, in turn, activates common signalling pathways. Energy depletion was recently proposed as the common denominator in multiple metabolic and even sarcomeric hypertrophic cardiomyopathies [75] (Fig. 10.6). Energy depletion may also occur in Fabry's disease, as suggested by the impairment in energy handling seen in skin fibroblasts. This might be further supported by the observation of a decreased ratio of ATP to inorganic orthophosphate, as has been shown by magnetic resonance imaging (MRI) studies in patients with sarcomeric hypertrophic cardiomyopathies [76] (Fig. 10.4).

10.2.4.4 Clinical Cardiac Involvement

Cardiac symptoms including left ventricular hypertrophy, arrhythmia, angina and dyspnea are reported in approximately 40–60% of patients with FD [77]. Arrhythmias and impaired heart rate variability arise from involvement of the sinus node, conduction system and imbalance between sympathetic and parasympathetic tone. Diastolic dysfunction and concentric left ventricular hypertrophy, which is typically non-obstructive, are important features, with men generally more severely affected than women.

Myocardial ischemia and infarction may result from compromised function of the coronary vascular bed [78]. With age, progressive myocardial fibrosis develops with both interstitial and replacement fibrosis [79]. Replacement fibrosis almost always starts in the posterior-lateral wall and in the mid-myocardium. In end-stage patients, transmural replacement fibrosis gradually reduces cardiac function to the stage of congestive heart failure [80]. Malignant arrhythmias are responsible for a number of cardiac deaths in patients affected with FD [80]. The cardiomyopathy of FD is characterized by reduced myocardial contraction and relaxation tissue Doppler velocities sometimes detectable even before development of left ventricular hypertrophy (LVH). Right ventricular hypertrophy (RVH) with normal chamber size and preserved systolic but impaired diastolic function represents the typical right ventricular (RV) structural change in FD. The myocardial perfusion reserve was found to be significantly reduced in patients affected with FD [81]. Patients with FD have abnormal coronary microvascular function. FD is associated to an increased risk of developing aortic root dilatation in male patients [82]. Aortic root dilation was detected in 24% of 71 hemizygous male patients and was statistically associated with the presence of a dolicho-ectatic basilar artery ($p = 0.008$) (Germain DP, unpublished data) [82].

10.3 Diagnosis of CRS-5

For whom to concern diagnostic approach to sepsis, prototype of type-5 CRS, initial emphasis has to be on setting of severe sepsis and septic shock, then on heart and kidney assessment and risk evaluation to start an appropriate treatment.

Systemic inflammation, like sepsis, has to be suspected when body temperature is less than 36 °C (96.8 °F) or greater 38 °C (100.4 °F), heart rate is greater than 90 beats/min and tachypnea is already present (more than 20 breaths/min). White blood cells count can be less than 4 × 100 cells/L or greater than 12 × 100 cells/L.

Recent review has pointed out some characteristic biomarkers whose elevation is typical during septic process: lipopolysaccharide binding protein, pro-calcitonin, C-reactive protein, pro-inflammatory cytokines (IL-6, TGF-β) [83].

Assessment of cardiac function in type-5 CRS is quite similar to other clinical situation in which myocardial dysfunction is present. Natriuretic peptides and troponins levels assays provide informations about cardiac chambers (especially left cardiac chambers) and myocardial cells damage. Leukocytosis and C-reactive protein are not specific for myocardial injury diagnosis and imaging devices are preferred by clinicians.

Sepsis cardiomyopathy present complex clinical picture and its pathophysiology is not well understood at all. In early stages of septic process there is a low output myocardial involvement. After starting fluid therapy clinical pictures shifts to typical distributive shock characterized by increased cardiac output and systemic vasodilatation [84]. Echocardiographic assay confirm high output cardiomyopathy with abnormalities in left ventricular regional contractility together with dilation of left heart chambers [85].

Diagnosis of kidney involvement in sepsis related type 5 CRS is overlapping to other forms of AKI with acute changes in serum creatinine levels according to RIFLE, AKIN and KDIGO criteria [86].

At present time, several other biomarkers are proposed such as Cystatin C (only new biomarker approved in the USA), KIM-1, NGAL, NAG but RIFLE, KDIGO and AKIN criteria still recommend serum creatinine levels and urine output for diagnosis and monitoring of AKI in type 5 CRS.

10.4 Management of CRS-5

Once diagnosis of type 5-CRS is made, every organ and tissue involved must be investigated to pay attention at risk prediction and protect from further and irreversible alterations in organ function.

Preliminary data (not published at present time) seem to indicate that biomarkers of cell cycle regulation may be predict patients will develop severe AKI in few days.

Regarding cardiac risk, patients who survive to septic shock showed to have lower ejection

fractions and higher left ventricular end-diastolic volumes to suggest myocardial depression protective role [4].

Treatment of type-5 CRS is mainly based on underlying disease management and on kidney and heart complications.

First of all, maintaining hemodynamic stability and guarantee tissue perfusion are key points to prevent type-5 CRS in hyperacute phase of sepsis together with fluid control and correct antibiotic treatment. Fluid therapy must be carefully managed to avoid fluid overload and other iatrogenic complications [87].

Since inflammation and immune-disorders play an important role in the pathogenesis of sepsis, removal of cytokines and immunomodulation are two approaches based on extracorporeal techniques utilizing convection, high volume hemofiltration and high permeability membranes [88]. Best results were obtained with high permeability membranes and absorption [88].

Therapeutic alternative is provided by hit cellular elements accountable for apoptosis and neutrophil activation and remove them by polymyxin filters or citrate anticoagulan based selective cytopheretic device [89, 90].

To manage heart complications, especially in hyperacute stage, multi-pronged approach is required to maintain filling pressures with fluid therapy together with vasopressors, vasodilators and inotropes; vasopressors should be carefully employed because of depressive effects on cardiac output (increased afterload) especially with concomitant hypovolemia. Vasodilators increase cardiac output, especially in ischemic patients, while phosphodiesterase inhibitors have inotropic and vasodilatatory effects but they provide less increase of myocardial oxygen requirements.

Vasopressin increases arterial pressure but it has negative effects on cardiac output; more recently levosimendan has to be proven to provide benefits in decompensated heart failure to increase ejection fraction and diuresis; levosimendan efficacy is still to be proven in prevention of type-5 CRS [91].

Renal support include removal of any nephrotoxic drug and media, maintenance of adequate perfusion pressure and, if indicated, early intervention with dialysis therapy [91, 92].

There is no role for dopamine for improving renal hemodynamics [93] and there limited studies with fenoldopam [94]. Norepinephrine decreases renal perfusion in normal conditions but increases systemic blood pressure in septic patients [88], while vasopressin increases diuresis and GFR in septic patients [95].

Diuretics have limited role in managing heart and kidney involvement in septic patients [96] and renal replacement therapy with CRRT (continuous renal replacement therapy) should be promptly started [93]; early ultrafiltration seems to improve renal outcomes in septic shock patients but these data have to be confirmed in further clinical trials.

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Post Contrast Acute Kidney Injury

11

Richard Solomon

11.1 Introduction

The first case of acute kidney injury following the administration of intravenous iodinated contrast media was reported in 1954 [1]. Since that initial report, more than 1700 publications on the (1) pathogenesis, (2) associated adverse events, and (3) preventative strategies have been published. Despite this large body of 'evidence', controversies remain in each of these three key areas. In this chapter, I plan to highlight what is known in each of these three areas and what remains unknown and/or controversial.

11.2 Name

Contrast induced nephropathy or CIN has long been the descriptor of the reduction in kidney function that follows closely the administration of contrast media. As knowledge of pathogenesis increased, it was natural to adopt a name that implied that contrast was the cause of the nephropathy. Most guidelines and text books do make the point that other causes of acute kidney injury need to be excluded before applying the CIN monikers. Since this is not always done, many began using the less specific term, contrast associated acute kidney injury (CA-AKI). Finally, with increasing appreciation for the adverse effects of manipulating catheters in the aorta above the renal arteries and the difficulty in diagnosing atheroembolic renal disease, the term post contrast acute kidney injury (PC-AKI) has begun to find its way into the literature [2]. Regardless of what term is used, it remains critical to exclude other etiologies of acute kidney injury. There is no specific biomarker of contrast induced kidney injury. Therefore, exclusion of other etiologies—hemodynamic factors, atheroemboli, normal variation in serum creatinine—take on increased importance.

11.3 Definition

Standard definitions of CIN all involve changes in kidney function as reflected in relative or absolute changes in serum creatinine over a fixed time period (usually 48–72 h). These definitions will result in vastly different incidences of CIN, particularly when looking at patients with baseline renal insufficiency. For example, in one study, the incidence of CIN was 5% using a 44.2 μmol/l (0.5 mg/dl) absolute rise, 11% using a 25% relative increase, and 25% when using an absolute 26.5 μmol/l (0.3 mg/dl) rise in creatinine (the KDIGO definition of AKI) [3]. As noted above, attributing these changes in serum creatinine to the nephrotoxic effects of contrast requires that

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all other etiologies of acute kidney injury are excluded.

Injury biomarkers have been looked at in patients undergoing contrast exposure. With intravenous contrast, urinary NGAL didn't change following a contrast enhanced CT in patients with chronic kidney disease [4]. In patients undergoing coronary angiography, some reports have found urinary NGAL to increase in patients diagnosed with CIN while others found no significant changes (see review [5]). At the current time, no specific injury biomarker has demonstrated sufficient sensitivity and specificity to warrant use, even in high risk patients.

11.4 Pathophysiology

11.4.1 In Vitro

When three different renal tubule cells are grown in culture and each exposed to either iso-osmolar (IOCM) or low osmolality contrast media (LOCM), the cells begin to die within 15 min and continue to lose viability over the next 60 min. Markers of oxidative stress are increased and apoptosis, not necrosis, results [6]. With higher concentrations of contrast, the cells die more quickly. This is convincing data that all contrast media are directly nephrotoxic. In addition, incubation with similar concentrations of inorganic iodine do not result apoptosis indicating that it is the organic compound, not the iodine that is directly toxic.

In a similar type of experiment, vasa recti, the small vessels that carry blood to the medullary portion of the kidney, are isolated and perfused with physiologic solutions. When contrast media (IOCM and LOCM) is added to the perfusate, the vessels immediately constrict, sufficient to potentially interfere with passage of red blood cells. Contrast media also enhance the vasoconstriction induced by angiotensin. The constriction is associated with a decrease in NO concentration in the wall of the vessels and an increase in reactive oxygen species (ROS). Preventing the rise in ROS with a superoxide dismutase mimetic prevents the vasoconstriction [7, 8]. These experiments highlight another effect of contrast media, i.e. vasoconstriction of the vessels supplying oxygen to the medullary portion of the kidney. This is a key pathophysiologic mechanism. The medulla of the kidney is uniquely sensitive to ischemia. It has a high metabolic requirement for sodium reabsorption in the thick ascending limb of Henle. However, it receives only 4% of total renal blood flow. Furthermore, the vasa recti follow next to the loop of Henle and oxygen diffuses out of the descending (oxygen rich) vasa recti into the ascending (oxygen poor) vasa recti resulting in a very low ambient tissue level of oxygen in this part of the kidney. Tissue oxygen in the medulla is approximately 50% of that in the cortex (20 mmHg vs. 40 mmHg) [9]. This makes the medulla of the kidney (containing the S3 segment of the proximal tubule and the descending and ascending loop of Henle) vulnerable to any perturbations that upset the balance between oxygen delivery and consumption. Thus ischemia is a second mechanism of injury following exposure to contrast [10].

11.4.2 In Vivo

Confirmation that similar mechanisms play a role in vivo come from a number of sources. The role of ischemia has been highlighted using BOLD-MRI in animals. BOLD-MRI is a technique for estimating tissue oxygen levels. Following the administration of contrast, the oxygen levels fall in the medulla but not the cortex, as might be expected from the in vitro vasa recti studies [11, 12]. Direct measurement of tissue oxygen in vivo has also been performed using microelectrodes and similar observations have been made [13]. These changes in medullary oxygen level are accompanied by histologic changes of ischemia [13] and elevations in injury biomarkers [12].

11.4.3 Man

Studies in man are much more difficult to perform. It is known that global renal blood flow is

diminished within minutes following intracoronary injections of contrast [14]. Direct measurements of tissue oxygen have not been performed. However, many studies find increases in urinary biomarkers of proximal tubule injury. However, they lack sensitivity and specificity for clinically meaningful changes in kidney function. Finally, histologic studies in patients who received contrast reveal vacuolization in the proximal tubule cells. Again, there is no data on sensitivity and specificity of these findings.

Table 11.1 Risk factors for contrast associated acute kidney injury

Patient-related	Procedure-related
Age	Intervention vs. diagnostic
Gender	Amount of contrast administered
Baseline GFR	Hemodynamic stability (use of IABP)
Diabetes	Urgent vs. elective
Congestive heart failure	
Anemia	
Volume depletion (prior use of diuretic)	
On ACEi or ARB therapy	

11.5 Epidemiology and Risk

Retrospective mining of large databases from cardiology laboratories provide estimates of the incidence of defined increases in serum creatinine following administration of contrast media. For most of the literature, increases in creatinine of ≥0.5 mg/dl or ≥25% over the baseline creatinine within 72 h of contrast exposure have been considered indicative of kidney injury. Not all patients have measurements of creatinine daily for the first 3 days following exposure. Because of the generally transient nature of the rise in creatinine, some patients with an elevation will be missed if daily creatinine is not done, leading to an underestimate of incidence. On the other hand, databases don't have enough granularity to exclude other causes of AKI in these patients, leading to potential overestimation of incidence.

Databases often have enough additional characteristics of the patient or procedure to generate a list of risk factors associated with CIN. These risk factors have become most important in determining which patients should receive special prophylactic therapy to prevent CIN. Table 11.1 provides a list of risk factors. A number of scoring systems have been developed using these risk factors to group patients into low, medium, high, and very high-risk categories [15, 16]. The most widely used is the Mehran score for patients undergoing PCI [17]. This scoring system uses patient characteristics and procedure elements to predict AKI, the need for dialysis, and in-hospital mortality. The elements of the scoring system are depicted in Fig. 11.1. Guidelines from Cardiology national societies all start with stratifying patients based upon risk for PC-AKI [18, 19].

It is generally acknowledged that the incidence of CIN is less with intravenous compared to intraarterial injections of contrast [2, 20] although there is inherent indication bias as well as confounding by comorbidities in the two groups. Notwithstanding these concerns, there are a number of potential explanations for a lower incidence with intravenous contrast. First, the concentration of contrast that reaches the kidney is much higher with intraarterial contrast [21]. Second, the amount of contrast administered intraarterially when an intervention is performed (PCI, angioplasty) is frequently much greater than with intravenous contrast (CT). Finally, intraarterial administration of contrast may be accompanied by atheroembolic injury to the kidney. PCI and TAVR both involve potential trauma to the aorta as stents or valve are manipulated into place. Evidence from the recent TAVR literature suggests that the degree of atherosclerotic disease in the aorta before TAVR is a strong risk factor for subsequent AKI [22]. Lastly, the patients who undergo intravenous contrast are likely different from those undergoing intraarterial contrast in terms of age, comorbid conditions, baseline kidney function, and hemodynamic stability at the time of contrast exposure.

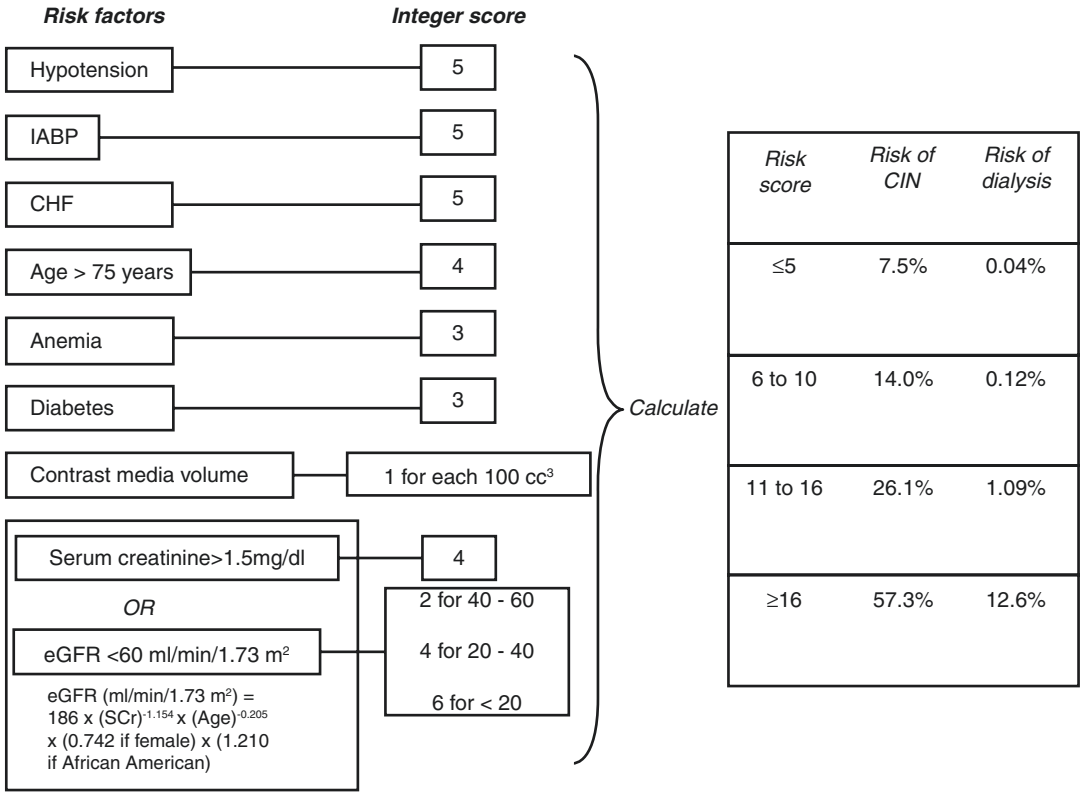

Fig. 11.1 Scoring system for predicting PC-AKI and need for dialysis post cardiac angiography [17]

11.6 Complications

CIN is usually associated with a transient increase in serum creatinine with the creatinine returning to near baseline within 7–10 days. Achievement of baseline creatinine is more likely in those with relatively normal kidney function at baseline. However, an increase in adverse events is seen even in those who have creatinine values that return to baseline levels [23]. The duration of the elevated creatinine has been identified as a risk factor for future adverse events [23]. Patients with chronic kidney disease may be left with a significant reduction in function and it these patients who are most at risk of needing dialysis as a result of the injury. This difference likely reflects how much 'renal reserve' the patient has at baseline. Renal reserve is generally lost before there is a reduction in baseline kidney function [24].

In addition to the acute changes in kidney function, CIN is associated with an increase in-hospital mortality (both for intraarterial and intravenous administration). This cause of death is primarily cardiovascular including heart failure, arrhythmia and bleeding [25].

Long term, CIN is associated with progression to more severe kidney disease, admission for heart failure, and decreased survival [26, 27]. There seems to be a correlation between the declining kidney function following an episode of PC-AKI and the increased cardiovascular events [28]. In randomized trials of different prophylaxis, a reduction in the incidence of CIN with a particular intervention was associated with a reduction in long term adverse events again suggesting that these are related [29].

11.7 Prevention

The most logical approach to avoiding CIN is to not give contrast or to use a minimum of contrast by employing other imaging techniques. This has been demonstrated in intraarterial injections in a

proof of concept study using IVUS [30] and devices that minimize the use of contrast, either by using automated injectors [31] or pressure sensitive manifolds that prevent excess contrast administration [32]. While these approaches reduce the use of contrast it is unclear that they reduce the incidence of CIN. Current guidelines from cardiology recommend setting an upper limit to the amount of contrast administered based upon renal function, decreasing "puff" injections, and ad hoc interventions, and using biplane imaging when available [33].

Another approach is to remove contrast before it gets into the kidney. This has been attempted using coronary sinus suction catheters which attempt to remove contrast as it passes through the myocardium [34]. A more distal approach is to remove contrast using dialysis, initiated as quickly as possible after contrast exposure [35]. These approaches have limited success. First, only contrast injected into the left coronary can be reliably recovered through the coronary sinus. Dialysis on the other hand is technically capable of removing contrast but the time course is too delayed to prevent a significant exposure to the kidney.

Finally, differences in the physical characteristics of specific contrast media may make them less nephrotoxic. This was clearly demonstrated in the 1990s when low-osmolar contrast media replaced high-osmolar contrast media [36]. Since that time, iso-osmolar contrast media have been introduced. While these agents have a significantly lower osmolality compared to the low-osmolar agents (290 mosm/kg vs. 700–800 mosm/kg), they are also more viscous. A number of randomized trials including patients with chronic kidney disease and in both intra-arterial and intravenous administrations have been performed. Most of the meta-analyses of these trials failed to find superiority of one type of agent over the other [37–39].

A central and consistent component of guideline recommendations is to provide "adequate hydration" before and after exposure to contrast [g]. Early studies observed that the more fluid administered, the lower the frequency of CIN [40]. Correcting volume depletion could be protective because it enhances anti-oxidant pathways in the kidney [41]. Producing a high urine output was also noted to be protective [42]. Which of these effects is key is still debated and many randomized trials exploring different amounts and types of fluids administered together with pharmacologic agents such as mannitol and furosemide to increase urine output have been published. What are the key observations?

11.7.1 More Fluid Rather than Less Is Beneficial [43–46]

Randomized trials that directly compared the amount of fluid given consistently found a lower incidence of CIN in the group that got more fluid. The one exception is a recent trial—AMACING—which compared a fluid strategy with giving no fluids intravenously and found no difference in the incidence of CIN [47]. This trial was probably underpowered, did not account for oral intake of fluids [48] and had an unusual statistical approach [49]. Even when fluid administration is guided by hemodynamic monitoring [50, 51] or bioimpedence measurements [52], the group getting more fluid did better.

11.7.2 Oral Fluid Intake May Be Very Important

While giving intravenous fluid is considered the standard of care, there is increasing evidence that oral fluids may be equally efficacious [53, 54]. This may reflect the fact that urine output increases more rapidly with water than with salt intake regardless of the route of administration.

11.7.3 Increasing Urine Output May Be the Key to a Successful Prophylactic Strategy

This may explain the observations that more fluid is better than less. Recent studies with the RenalGuard® device suggest that it is urine output not volume repletion per se that is important. The RenalGuard® device matches intravenous fluid with urine output in real time

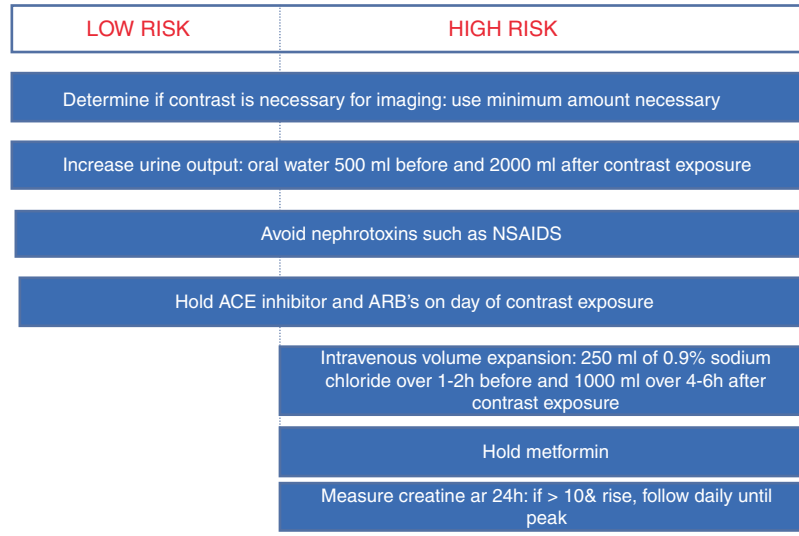

Fig. 11.2 Recommendations for preventing PC-AKI

using a sensitive digital scale holding a urine collection bag that drives an intravenous fluid pump. After an initial bolus of 250 ml of saline and a small dose of diuretic (0.25 mg/kg of furosemide), the device is activated and within an hour urine output exceeds 300 ml/h and continues to climb to 600 ml/h for 3–4 h before tapering back to 300 ml/h. Use of this device has been particularly successful in subjects undergoing cardiac interventions, including TAVR, reducing the incidence of CIN by 70% [55]. In those few patients who don't respond with an increased urine output, the incidence of CIN is unaffected [56].

Oxidative stress is a central mechanism of kidney injury including that following contrast exposure [10]. Attempts to mitigate this stress with N-acetylcysteine or vitamin C enjoyed support after the initial positive trials [57]. However, with larger trials the enthusiasm started to wane [58]. Finally, in 2017, the PRESERVE trial put the final 'nail in the coffin' and found that the addition of N-acetylcysteine to fluid management did not convey an extra benefit [59].

A variety of other strategies have been studied, generally in small trials. These have included vasodilator therapy using fenoldapam [60], atrial natriuretic peptide [61], prostaglandin [62], theophylline [63] and other agents. To date none of these strategies have gained acceptance.

Importantly, any consistent strategy to identify and manage high-risk patients is better than no strategy. Survey data of interventional cardiologists suggest that only 50% of cardiac laboratories have such protocols [64]. Adherence to published guidelines from the major cardiology societies is also poor [65]. In an observational study, Brown found that institutions that had a protocols had a lower incidence of PC-AKI compared to those that did not have a protocol even though the protocols differed compared to each other [66]. Figure 11.2, lists recommendations for prevention of contrast associated acute kidney injury based upon published guidelines and the author's opinion.

11.8 Controversies

As noted above, PC-AKI is defined as an increase in serum creatinine occurring within 72 h of contrast exposure in the absence of another etiology. Databases don't lend themselves to search for alternative causes of a rise in creatinine since the individual events surrounding an episode of AKI are rarely captured. Furthermore, there are no true controlled studies that looked at the incidence of AKI in patients who did and did not receive contrast. This lack of adjudication and controlled studies has led many, particularly in

the radiology community to question whether we have overestimated the true incidence of AKI and even whether PC-AKI actually exists.

Recently, a number of approaches have attempted to address this conundrum. Caspi and colleagues compared STEMI patients who underwent urgent revascularization either by PCI or fibrinolysis [67]. Contrast was administered only to the PCI patients. Although not a randomized trial, patient characteristics were similar, particularly with regard to such risk factors as age, baseline kidney function, prevalence of diabetes and congestive heart failure. AKI occurred in a similar proportion of PCI and thrombolysis patients suggesting that contrast administration played a minor role. In a similar approach, Hinson et al. compared the incidence of AKI in Emergency Department patients who received a CT exam with or without contrast and found no difference in rates [68].

In the Radiology literature, five retrospective database reviews involving over 15,000 patients used propensity matching techniques to compare patients who underwent CT scans with and without contrast. Patients were stratified by baseline GFR and further analyses looked at particular high-risk subgroups (elderly, diabetes, heart failure). The incidence of PC-AKI increased as GFR fell, but there was no difference between those who received contrast and those who didn't [69]. In a review of the National Inpatient Sample from 2009, the incidence of AKI, based upon ICD-9 codes, was not different in those who received contrast (most intravenous) and those who didn't. The data is limited by the use of ICD-9 codes rather than creatinine definitions and the lack of temporal association between AKI and administration of contrast [70]. However, the overall incidence of AKI was similar to other reports (5.5%).

11.9 Conclusion

Post contrast acute kidney injury (PC-AKI) remains a significant concern in the interventional cardiology domain. Its occurrence can be minimized by careful selection of patients and appropriate strategies to reduce the contrast load and facilitate contrast elimination by the kidney. There exist on-line tools for risk stratification and published guidelines for fluid administration and pharmacotherapy. Establishing a cardiac lab specific protocol will help to mitigate these concerns.

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12 Distinct Cardiorenal Syndromes: Cardiac Surgery Associated Acute Kidney Injury

Andrew A. House and Andrea C. J. Cowan

12.1 Introduction and Epidemiology

Acute kidney injury (AKI) is a common complication of cardiac surgery and is associated with significant increase in morbidity and mortality. As in other settings, description of the epidemiology of cardiac surgery associated AKI (CSA-AKI) was limited due to a lack of a consensus definition until the RIFLE and AKIN criteria were established [1, 2]. While the incidence of CSA-AKI varies depending on a number of factors including the definition used, the inclusion of urine output criteria, and the population studied, estimates range from 1–3% for those requiring renal replacement therapy post operatively, to 18–45% when considering all stages of AKI, with a meta-analysis of over 300,000 patients found the overall rate of AKI was 22.3% (Fig. 12.1) [3–13]. The majority of patients have relatively mild AKI, with 13% in AKIN 1 or RIFLE-R, 3.8% in AKIN 2 or RIFLE-I, 2.7% in AKIN 3 or RIFLE-L and 2.3% requiring renal replacement therapy [13].

As with AKI in other critically ill patient populations, CSA-AKI is independently associated with significantly increased short-term mortality which is proportional to the severity of AKI. While in-hospital mortality for those without AKI is between 1% and 2%, this increases to 5% for those with AKIN stage 1 or RIFLE-R [10, 12, 13]. Patients with AKIN 2 or RIFLE-I have a mortality of approximately 15%, which increases to 32–36% in AKIN 3, RIFLE-F, including those that require dialysis [10, 12, 13]. When comparing the RIFLE and AKIN classifications, both show similar discrimination in predicting mortality [5, 6, 12]. Interestingly CSA-AKI appears to have a larger effect on mortality than AKI in other critically ill patients, emphasizing the prognostic importance of AKI in this population [14].

This increased mortality persists over a longer time frame, with studies showing significantly increased mortality up to 10 years post surgery in those patients with AKI when compared to those without AKI [3, 4, 8, 15]. Although renal recovery improves likelihood of survival, even those with complete normalization of their creatinine continue to have increased mortality at 10 years over those without AKI [3, 4, 15].

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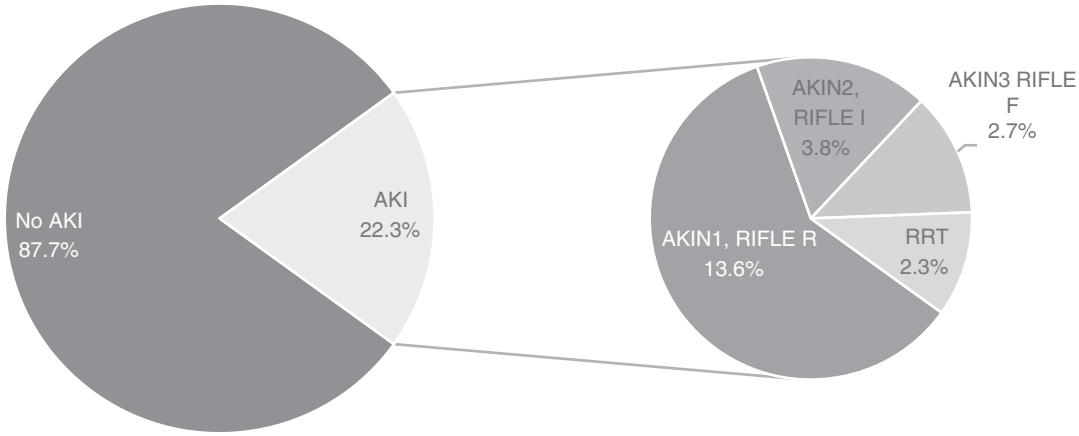

Fig. 12.1 The incidence of CSA-AKI

12.2 Risk Factors for CSA-AKI

Given the frequency of AKI after cardiac surgery, and the poor long term prognosis associated with even small deteriorations in renal function, there is considerable interest in identifying risk factors associated with AKI and dialysis requirement after cardiac surgery (Table 12.1).

Table 12.1 Risk factors for CSA-AKI

Patient specific	Preoperative	Intraoperative
GFR <60	IABP	Valvular surgeries
Increasing age	Contrast use (possible)	Prior cardiac surgery
Diabetes	Nephrotoxin use	CBP use
Peripheral vascular disease		CBP time
NHYA IV CHF symptoms		Anemia
Reduced LVEF		Red cell transfusion

12.2.1 Patient Specific Factors

A number of patient specific factors have been identified as being associated with increased risk of CSA-AKI. Patients with an elevated preoperative creatinine have a higher likelihood of AKI post operatively and incidence of AKI rises linearly with progressive decrease in preoperative estimated glomerular filtration rate (eGFR) [11, 16–20]. While age has been identified as an independent risk factor for CSA-AKI [15, 16, 18, 21–23] the evidence around the effect of gender is less consistent. While one large study identified male gender as a risk factor [15], a number of other analyses, including a well validated scoring system have found higher risk of CSA-AKI in female patients [19, 22]. Increasing burden of non-cardiac comorbidities, particularly both insulin and non-insulin dependent diabetes mellitus, peripheral vascular disease and obstructive lung disease have also been shown to increase post operative risk [15, 17–20, 22–24]. This is supported by the finding that the EuroScore, a scoring system for predicting mortality after cardiac surgery which also emphasizes comorbid status, has also been found to independently predict the risk of CSA-AKI [25].

Pre-operative cardiac disease is also associated with increased CSA-AKI, however definitions varied depending on study. Preoperative intra-aortic balloon pump requirement has been shown to be strongly associated with a three- to fourfold increase in both post operative AKI and dialysis requirement, presumably reflecting the unfavourable hemodynamics and urgency of intervention in this patient population [9, 16, 19–22]. To a lesser degree, a poor renal prognosis has been associated with both NYHA class IV heart failure symptoms and a reduced left ventricular

ejection fraction [15, 16, 18–20, 22, 25]. The study of preoperative myocardial infarction (MI) as a potential risk factor for CSA-AKI has been made more difficult by the urgency of surgical intervention acting as a strong potential confounder. While some studies identify it as an independent risk factor [16, 18] others have found this not to be significant in multivariate analysis [9, 17, 25].

The timing of preoperative angiography has been examined as a potential risk factor as there is concern about a double hit from a contrast dose immediately preceding cardiac surgery. Angiography within 1 day of cardiac surgery has been identified as a risk factor for CSA-AKI in observational studies but is also complicated by urgency of cases [26–28], however some studies have shown that in low risk, carefully selected patients, same day angiography is not associated with a higher risk [29–31].

12.2.2 Surgical Factors

There are a number of surgical factors which have been consistently shown to increase the risk of AKI after cardiac surgery. Valvular surgery carries with it a significantly higher risk of CSA-AKI as compared to CABG alone, and combined CABG and valvular surgery has the highest risk [11, 19, 20, 25]. Prior cardiac surgery has also been identified as a significant risk factor for CSA-AKI and has been included as a variable in the three most widely used risk scoring systems [17–22]. Finally, cardiopulmonary bypass (CPB) has been suggested as a risk factor for poor renal prognosis given the inflammatory effect and loss of pulsatile flow, however the evidence is mixed. While some observational studies have shown an increased risk of CSA-AKI with longer CPB time [9, 11, 15, 16, 21], a large randomized controlled trial comparing on-pump to off-pump procedures showed no benefit with regards to renal function after 1 year although there was a decrease in AKI [32] and a meta-analysis of 22 RCTs showed an improvement in rates of AKI but no statistically significant effect on dialysis requirement post operatively [33]. While there does appear to be some risk reduction with off pump cardiac surgery, the clinical magnitude of this benefit remains to be seen.

Both anemia and intraoperative red blood cell transfusion have been identified as increasing the risk of CSA-AKI [9, 23, 27, 34], however their interconnected nature make it difficult to discern if they are both independently related. Based on observational data, anemia is associated with an increased AKI risk regardless of transfusion status and the AKI risk conferred by red cell transfusion was increased in those with more severe anemia [34].

12.2.3 Risk Scores

Several risk scores have been designed in order to identify those at highest risk of the development of CSA-AKI, however widespread preoperative clinical use has been limited by cumbersome scoring systems and the inclusion of intraoperative variables.

There are three risk scores predicting dialysis after cardiac surgery which are the most robustly externally validated [18–20]. While the three employ different variables (Table 12.2), they commonly include: diabetes, preoperative GFR, previous cardiac surgery and the type of operation [18–20]. All scores performed reasonably well on their initial validation with an AUC of the ROC curves of greater than 0.8. When compared to one another, the Cleveland score [19] performs slightly better than either the Mehta score [18] or the Simplified Renal Index [7, 20, 35, 36], and external validation in European and North American populations have supported the discriminatory power of the scores [7, 35–37]. However, all three scores did not perform as well when applied to a Chinese population, raising questions about their validity in a non-Caucasian background [7]. While there have been some risk scores published for the prediction of non-dialysis requiring AKI, they are limited by the inclusion of intraoperative variables [11, 16] and all lack robust external validation [11, 16, 38].

Table 12.2 A comparison of the three most common risk scores

Mehta score [18]	Cleveland clinical score [19]	Simplified renal index [20]
Preoperative creatinine	Preoperative creatinine	Preoperative eGFR
Prior cardiac surgery	Prior cardiac surgery	Prior cardiac surgery
Surgery type	Surgery type	Surgery type
Diabetes requiring any medication	Diabetes requiring insulin	Diabetes requiring any medication
Cardiogenic shock	Preoperative use of IABP	Preoperative use of IABP
NYHA IV symptoms	LVEF <35%	LVEF <40%
Recent MI	Emergency surgery	Emergency surgery
Age	CHF	
Chronic lung disease	Chronic obstructive pulmonary disease	
Race	Female gender	

12.3 The Role of Novel Biomarkers in the Diagnosis of CSA-AKI

The diagnosis of AKI has traditionally been made by serum creatinine, which is limited as a diagnostic test by significant variability by age, sex and body mass as well as a late peak after a renal insult, requiring 2–3 days to reach its maximal level. This impairs the early diagnosis and treatment of AKI and may be one of the reasons why many tested interventions for AKI are unsuccessful [39]. As a result, there is considerable interest in finding an alternate biomarker with a more rapid peak and less inter-patient variability to aid in the early diagnosis of AKI. In patients at risk for CSA-AKI, the timing of the renal insult is well defined which makes it ideal for studying the kinetics of potential novel biomarkers and their utility in the diagnosis of AKI.

12.3.1 Neutrophil Gelatinase-Associated Lipocalin

Neutrophil gelatinase-associated lipocalin (NGAL) is the most extensively studied novel biomarker. It is expressed in a number of different tissues, including renal epithelium, and is rapidly upregulated in response to renal ischemia [40]. Its small size and protease resistance mean it is freely excreted in the urine as well as being detectable in the serum after renal injury [41]. NGAL was first examined in the pediatric population, as it is a more homogenous group, lacking many of the comorbidities such as type 2 diabetes mellitus and coronary artery disease which add heterogeneity to adult cohorts. In children, urine NGAL peaks within 6 h of cardiac surgery and rapidly falls thereafter, while serum peaks at a similar time but has a slower decline [42, 43]. Initial pediatric studies showed very promising results with an area under ROC of 0.998 for urine NGAL and 0.906 for serum NGAL 2 h after surgery [42]. However, this study involved a single centre and excluded any children with possible non-ischemic causes of AKI, limiting its broader applicability [42]. A later, multicentre trial showed a modest predictive value of urinary NGAL in children with an AUC of 0.71, but did not find that serum NGAL was a useful predictor [43].

In adults, the use of both serum and urine NGAL is more difficult, owing to the heterogeneous nature of AKI. While some single centre trials have shown some utility of serum NGAL [44, 45] and urine NGAL [46, 47] over conventional biomarkers, a large meta-analysis showed a modest predictive power with an AUC of serum NGAL of 0.71 and urine NGAL of 0.72 [39]. These mixed results are likely due to the pathophysiology of NGAL creation. While its transcription is upregulated in response to renal ischemia, it also serves as a marker of systemic inflammation that is produced in extrarenal tissues, which decreases its specificity for renal injury. As a result, NGAL has not been implemented for the diagnosis of CSA-AKI on a broader scale.

12.3.2 Cystatin C

Cystatin C is a low molecular weight protein which is freely filtered by the kidneys. Unlike creatinine, it is not affected by age, sex or body weight and has a shorter half life which makes both the serum and urinary levels an appealing

biomarker in the early detection of AKI [48]. It has also been shown as a relatively good predictor in mixed AKI with a sensitivity and specificity in prediction of 0.82 [49].

As with NGAL, plasma cystatin C performed well in pediatric populations for the prediction of postoperative AKI with an AUC of 0.89 [50], however, results in adults have been more mixed. While studies comparing serum cystatin C and NGAL have shown that the two are fairly similar in their predictive power [44, 45], the studies have found performance of cystatin C to be variable with an AUC ranging from 0.63 to 0.83 and a recent meta-analysis found it to be a poor predictor with an AUC of 0.69 [39, 44, 45, 51]. Although urine Cystatin C may be more promising in the prediction of AKI than serum values, it currently lacks the evidence to support its routine use [47, 51].

12.3.3 IL-18

IL-18 is an inflammatory molecule which is upregulated and activated in response to renal ischemia [52]. As a result, it is disproportionately elevated in patients with acute tubular necrosis (ATN) as compared to those with pre-renal azotemia or chronic kidney disease (CKD) [53]. Urinary IL-18 has been extensively studied as an early marker for the detection of AKI with mixed results, with AUC ranging from 0.5 to 0.92, and was found to be specific in the prediction of development of AKI but not sensitive [43, 53–55]. In the adult cardiac surgery population, a recent meta-analysis found an AUC for the prediction of AKI of 0.66, which is significantly poorer than established risk models, however individual studies have found that the addition of urinary IL-18 to risk model can improve its predictive performance [17, 19, 20, 39, 54]. In children, the performance of urinary IL-18 in the prediction of CSA-AKI is slightly better, likely owing to the more homogenous population and lower incidence of non-ischemic causes of AKI. The AUC for urinary IL-18 in children is modest, ranging from 0.72 to 0.75. Overall, IL-18's high specificity but low sensitivity limit its utility as a predictive biomarker, particularly in more heterogeneous patient populations such as adult cardiac surgery.

12.3.4 Kidney Injury Molecule-1

Kidney injury molecule 1 (KIM-1) is upregulated on renal epithelial cells in response to ischemic injury [56]. As a result, it is very specific for ischemic ATN, similar to IL-18 [57]. Urinary KIM-1 has been shown to significantly increase after cardiac surgery compared to preoperative levels but only has a modest predictive value for the prediction of AKI with AUC ranging from 0.68 to 0.73 [39, 46, 47]. Interestingly, it performs significantly less well in patients with pre-existing CKD (GFR <60 ml/min), perhaps due to the specificity of KIM-1 for ischemic processes [51].

A number of other biomarkers, both urinary and serum have been studied in the post cardiac surgery setting. A combination of insulin-like growth factor-binding protein 7 (IGFBP7) and tissue inhibitor of metalloproteinases-2 (TIMP-2) has recently been used successfully in a study to identify individuals at high risk of CSA-AKI and include them in treatment trials [58, 59]. Urinary liver-type fatty acid binding protein (L-FABP) has been shown to have modest predictive value [39], while serum BNP has shown relatively disappointing results [60, 61].

A recent study looked at the role of novel urinary biomarkers in the long-term prognosis of CSA-AKI. It found that in patients who developed CSA-AKI, those within the highest tertile of urinary NGAL, KIM-1, IL-18, L-FABP and albumin had a two- to threefold increased risk of mortality at 3 years [62]. Even in those patients who did not develop AKI by serum creatinine or urine output criteria, there was an increased risk of mortality in patients with elevations of IL-18 and KIM-1 into the highest tertile (HR 1.23 and 1.83 respectively) when compared to the lowest tertile [62].

Although biomarkers hold promise as a method of early detection of CSA-AKI, they have universally been limited by rather modest predictive power as well as variability and expense of assays. The emerging role of novel biomarkers likely lies in the refinement of predictive scores in

order to identify those individuals who are at highest risk of development of AKI who may benefit from more aggressive intervention or inclusion in research trials as well as potentially identifying those patients with "subacute AKI" and helping to define their prognosis.

12.4 Pathophysiology of CSA-AKI

Determining the pathophysiology of CSA-AKI is challenging due to heterogeneous patient populations and operative procedures, as well as a lack of animal models or high quality randomized controlled trials. As a result there is no clear causal evidence for the mechanism of CSA-AKI, however it is postulated that the risk is multifactorial, with contributions of ischemia reperfusion injury (IRI), inflammation and embolic phenomena around the time of surgery (Fig. 12.2) [63, 64].

12.4.1 Inflammatory Response

Cardiac surgery is associated with increased post operative levels of inflammatory markers including IL-6 and IL-10 [66–68]. Although the mechanism behind the inflammation is not completely clear, it includes surgical trauma, IRI and, in cases using CPB, exposure to an extracorporeal membrane [68, 69]. Although on-pump cardiac surgery has traditionally been thought to be associated with more inflammation due to circuit exposure, post operative inflammatory markers

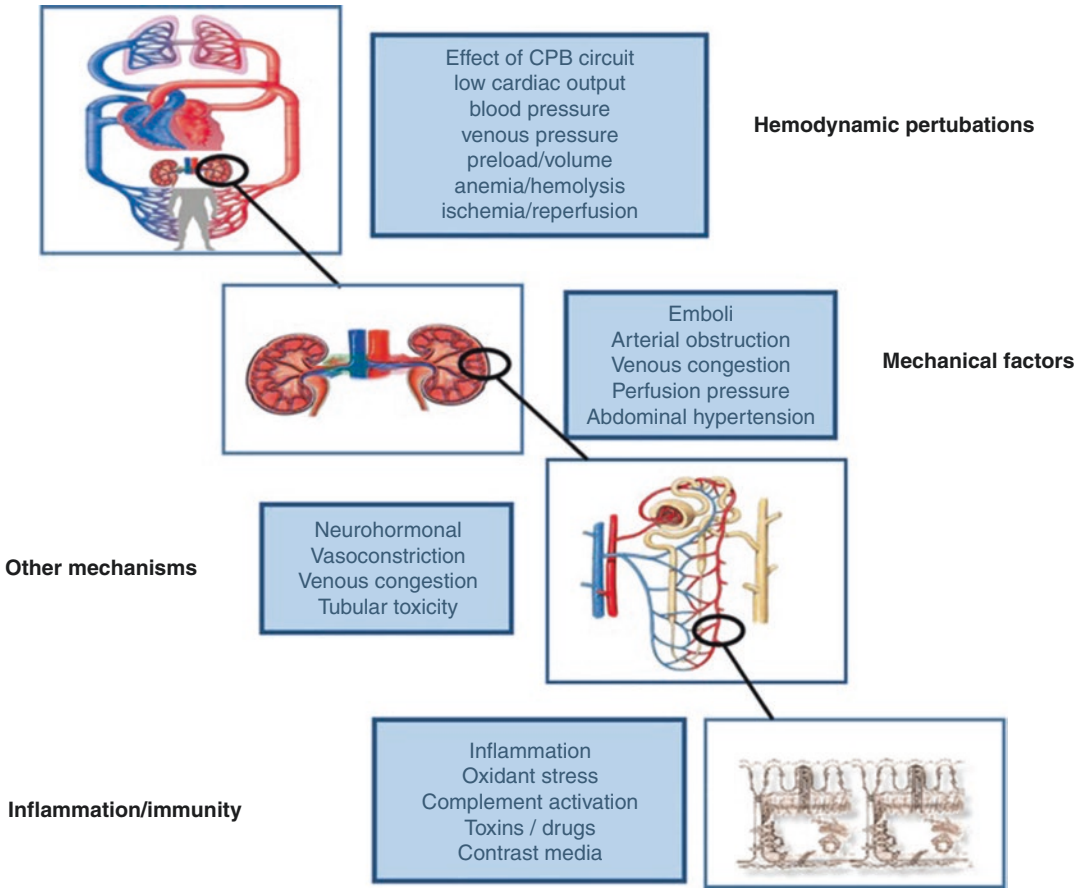

Fig. 12.2 The pathophysiology of CSA-AKI [65]. (With permission from Wiley Publishing Copyright © 2018 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley)

and markers of endothelial injury are similar between the two types of surgery [69]. However, off-pump cardiac surgery does have lower of and complement activation indicating a potential mechanism for the lower rates of CSA-AKI observed in these patients [69]. Operative inflammation contributes to AKI through the production of reactive oxygen species as well as triggering endothelial dysfunction and renal fibrosis [70]. The role of inflammation as a cause of AKI is also supported by a large study showing that increased levels of IL-6 postoperatively were associated with an increased risk of AKI, while higher levels of IL-10, an anti-inflammatory cytokine, was predictive of improved long term mortality [67].

12.4.2 Renal Ischemia

The renal medulla is relatively hypoxic to other tissues as a result of its blood supply, which is designed to preserve the solute concentration gradients in the vasa recta [71]. As a result, it is particularly sensitive to hypoperfusion around the time of surgery, which can be precipitated by perioperative hypotension and anemia.

In off pump cardiac surgeries, hypotension caused by cardiogenic shock, particularly in those with significant enough hemodynamic compromise to require intra-aortic balloon pump is associated with increased risk of AKI [17–22, 72]. However, with only observational data it is difficult to ascertain if this is truly causative or just a surrogate for sicker patients over all.

In surgeries using CPB, there are more hemodynamic variables. Given that oxygen delivery while on cardiopulmonary bypass is governed by hematocrit and pump speed, it has been hypothesized that higher pump speed or intraoperative mean arterial pressure (MAP) may reduce this risk of AKI. However, this has not been borne out in the literature [73–75]. Although there was a trend towards increased urine output in those with a higher intraoperative MAP, there is no clear evidence that it improves renal outcomes [73–75]. The exception may be those with a higher baseline MAP, as one study showed that the change in MAP rather than the absolute pressure was predictive of renal dysfunction postoperatively [76].

In addition to hemodynamic parameters, hematocrit and hemodilution play an important role in governing oxygen delivery. CPB employs hemodilution to reduce viscosity and increase microcirculation, however if the hematocrit drops too much it will impair oxygen delivery [77, 78]. One study identified a U-shaped relationship between hematocrit and AKI risk, with the optimal hematocrit ranging from 21% to 25% [78], while another found a linear relationship between lower hematocrit (between values of 10% and 30%) and increased creatinine postoperatively [77]. Furthermore, intraoperative bleeding also exacerbates the effects of anemia even in off pump surgeries that do not require hemodilution. This is also supported by observational evidence that patients with lower hemoglobin have increased risk of AKI, regardless of transfusion status, although transfusion alone also increases risk of AKI [74].

12.4.3 Nephrotoxic Medications

The most commonly studied perioperative nephrotoxin in CSA-AKI is radiocontrast, however the evidence is mixed as to whether or not preoperative contrast exposure increases the risk of AKI, as it is confounded by increased urgency in those cases with preoperative coronary catheterization [26, 28, 31]. More commonly, many cardiac patients also receive ACE inhibitors perioperatively which can contribute to AKI in susceptible individuals [79]. For those patients requiring antibiotic therapy for infective endocarditis, the use of nephrotoxic antibiotics, including aminoglycosides and vancomycin has also been associated with increased rates of AKI after surgery as well [80].

12.4.4 Factors Unique to Cardiopulmonary Bypass

A large randomized controlled trial and recent meta-analysis have both shown a correlation

between the use of CPB and an increased risk of AKI [32, 33], suggesting there may be a number of CPB specific factors which can contribute to CSA-AKI.

12.4.4.1 Hemolysis

Contact with the extracorporeal membrane during CPB causes hemolysis resulting in increased levels of free hemoglobin [81–83] which is worsened by the use of occlusive roller pumps and cardiotomy suction as well as autotransfusion [83]. This hemolysis is believed to cause AKI by direct injury to the tubules as well as increased systemic vascular resistance resulting from nitrous oxide depletion causing an increase in systemic vascular resistance [83, 84]. The deleterious effect of free plasma hemoglobin is also supported by evidence that the administration of haptoglobin decreases free hemoglobin concentrations and may improve renal outcomes, although further study is needed to confirm the clinical benefit for routine use [85, 86].

12.4.4.2 Embolism

Both cannulation and cross clamping during CPB can give rise to atheroemboli which affect multiple organs including the kidneys. On autopsy, almost 50% of those patients with embolic phenomena after cardiac surgery have renal involvement [87]. Although determining the renal significance of these emboli identified post mortem is difficult there is a correlation between increasing aortic atherosclerosis and worsening post operative renal function [88], and a correlation between increased number of cerebral emboli and likelihood of postoperative AKI [89]. This raises the idea of using aortic filters to minimize embolic phenomena however these have not been proven effective in the reduction of CSA-AKI [90].

12.4.4.3 Temperature Control

Hypothermia is employed during cardiopulmonary bypass to decrease end organ damage secondary to ischemia, and animal models show that moderate hypothermia during renal ischemia and reperfusion decreases rates of AKI [91], however there is less high quality evidence in clinical practice. A number of studies have suggested that early rewarming contributes to higher rates of AKI and that higher body temperature on admission to ICU imparts a poorer renal prognosis [92–94]. However, defining an ideal temperature target for cooling has been challenging due to differences in both methods of core body temperature measurement and hypothermic targets. While most studies have found a benefit to moderate intraoperative hypothermia (e.g. 34 °C) there is a potential increased risk of AKI when arterial CPB temperatures dropped below 27 °C [92, 93, 95].

12.5 Treatment and Prevention

12.5.1 Risk Factor Modification

While many risk factors for the development of CSA-AKI are unmodifiable, such as age and pre-existing renal function (Table 12.1), there are some operative factors which may be modifiable to reduce risk.

The avoidance of CPB, if possible, can help to mitigate some of the inflammatory cascade, hemolysis and hypothermia which have been shown to contribute to CSA-AKI [32]. A recent randomized controlled trial showed that off pump cardiac bypass was associated with lower rates of AKI, although there was no difference in renal function at 1 year between the groups [32]. In all patients, efforts to minimize renal ischemia are recommended. This includes avoidance of over-aggressive hemodilution, targeting a hematocrit >24%, minimizing intraoperative bleeding in order to prevent anemia and requirement of blood transfusion [9, 65, 78]. At the current time, there is no clear blood pressure target both intraoperatively and postoperatively, however there may be some evidence for targeting a higher MAP in those patients who have baseline hypertension [76, 96].

Fluid management can be challenging in post cardiac surgery patients particularly those with cardiac dysfunction and subsequent AKI. Guidelines suggest the avoidance of hypo-

volemia to maintain renal perfusion while being cautious of the effects of hypervolemia and interstitial edema on renal perfusion, and the PrevAKI trial discussed below provides some evidence to support this [58, 96]. With regard to resuscitative fluid choice, studies support the use of balanced crystalloids over colloids given the increased risk of metabolic derangements with saline and potential bleeding and AKI complications with older generation starch solutions [97, 98]. Careful temperature control, particularly the avoidance of hyperthermia and rapid warming, has also been shown to improve renal outcomes and is recommended in the 2018 ADQI guidelines [65, 92, 93].

Avoidance of nephrotoxic medications is also a cornerstone of treatment. Although the evidence surrounding the risk of contrast administration is mixed [26–29, 31], guidelines suggest avoiding its administration within 72 h if possible [65]. Although the evidence for the cessation of RAAS blockade in the perioperative period is primarily observational, there is some evidence that this may decrease the risk of AKI. Patients with cardiac disease are often on RAAS blockade, and a recent cohort study showed increased risk of CSA-AKI in those patients who were continued in the perioperative setting [99, 100].

Many of these preventative measures are combined into the Kidney Disease: Improving Global Outcomes (KDIGO) care bundle which is combination of recommendations including close monitoring of fluid status and hemodynamics, avoidance of nephrotoxic drugs and avoidance of hyperglycemia [101]. The recent PrevAKI randomized trial identified high risk individuals post cardiac surgery using urinary biomarkers and randomized this population to standard care or the KDIGO bundle which involved discontinuation of ACE/ARB for the first 48 h post operatively, hemodynamic monitoring using a pulse contour cardiac output (PICCO) catheter and treatment based on a pre-specified algorithm, tight glucose control for the first 72 h and close monitoring of serum creatinine and urine output [58]. Implementation of this combination had an absolute risk reduction of 16% for post operative AKI, but did not show an improvement in mortality or rates of renal replacement therapy (RRT). Despite this limited evidence recent guidelines recommend the implementation of the KDIGO care bundle for high risk patients [65, 96].

12.5.2 Pharmacologic Interventions

Determining pharmacologic targets for the treatment and prevention on CSA-AKI is hampered by our limited understanding of the pathophysiology as well as the heterogeneous patient population affected. As a result, a number of treatments have been extensively studied but none have shown the reproducibility required for translation into broad clinical practice (Table 12.3).

12.5.2.1 Natriuretic Peptides

Atrial and brain natriuretic peptides are produced in response to atrial stretch and increases in ventricular pressure respectively. They increase GFR through renal arterial vasodilation as well as suppressing the renin-angiotensin-aldosterone system and promoting natriuresis [102]. Although

Table 12.3 Pharmacologic treatment of AKI

Treatment	ADQI recommendation [65]	KDIGO recommendation [101]	OR for the occurrence of AKI [103]
Natriuretic peptides	More research needed	Against (2C)	0.24 [95% CI 0.16–0.34]
Fenoldepam	More research needed	Against (2C)	0.33 (95% CI 0.14–0.70)
Dexmetodomidine	For (2C)	n/a	0.54 (95% CI 0.31–0.84)
Levosimendan	Against (1A)	n/a	0.63 (95% CI 0.43–0.88)
N-Acetylcysteine	Against (1A)	Against (1A)	0.85 (95% CI 0.64–1.14)
Sodium bicarbonate	Against (1A)	n/a	0.96 (95% CI 0.69–1.29)
Statins	Against (1A)	n/a	1.05 (95% CI 0.70–1.41)

endogenous levels of these hormones rise after cardiac surgery, these characteristics make it an appealing therapeutic target for the amelioration of the hormonal and volume status changes that occur after cardiac surgery. A recent meta-analysis showed that natriuretic peptides were the most effective of all of the medications studied in the prevention of CSA-AKI with an odds ratio of 0.24 [103]. RCTs studying atrial natriuretic peptide (ANP) specifically have shown that it is effective in decreasing rates of CSA-AKI but show mixed results with regards to reduction of RRT and do not show any mortality benefit [102, 104–106]. The protective effect of ANP appears more pronounced in post cardiac surgery patients compared to all-comers at risk of AKI [104]. Evidence for the use of brain natriuretic peptide (BNP) is similar, with some evidence that it decreases AKI but little evidence in the reduction of renal replacement therapy or mortality [102, 107]. Although this evidence is promising, drawing a firm conclusion is hampered by small sample size and variability in study protocols and further investigation is needed before widespread use.

12.5.2.2 Fenoldepam

Fenoldepam is a selective dopamine (D1) agonist which acts on receptors in the kidneys to decrease renal vascular resistance and increase renal blood flow and GFR [108]. Unlike dopamine, it does not bind to any D2, alpha or beta receptors and has the theoretical advantage of causing fewer adverse effects including hypotension or tachyarrhythmias [108]. Initial studies examining prophylactic use in post cardiac surgery and other critically ill populations were promising and showed a reduction in rates of AKI and perhaps a decrease in rates of RRT [109–111]. Unfortunately, this did not translate to any change in clinically important outcomes including hospital length of stay or mortality [109–111]. While one promising meta-analysis did show a decrease in mortality it included a number of smaller, non-randomized studies [112]. In those patients who have already developed CSA-AKI there is also no evidence that its use will decrease the need for RRT [113]. Given the lack of conclusive evidence supporting the benefit of fenoldepam, further research is needed before its use can be recommended in the routine prophylaxis or treatment of CSA-AKI [65, 96].

12.5.2.3 Dexmetodomidine

Dexmetodomidine is an alpha-2 adrenoreceptor agonist which binds to receptors throughout the body including in the kidney and has an anti-inflammatory and diuretic effect [114]. While it has previously been used for it sedative properties, it has recently come under study for the prevention or treatment of IRI. *In vitro* and animal model experiments have found that treatment with dexmetodomidine either before or after an ischemic injury confers a renoprotective benefit [114]. Similarly, two recent meta-analyses of RCTs in humans showed a decreased risk of AKI after treatment with dexmetodomidine (OR 0.56 and 0.65) [103, 115]. However, both of these studies have been limited by small, single centre studies with variable quality and larger, multicentre trials are needed.

12.5.2.4 Levosimendan

Levosimendan is a calcium sensitizing inotrope which increases myocardial contractility without increasing oxygen demand, theoretically benefitting patients with low a cardiac output syndrome which risk of AKI [116]. Levosimendan has the added benefit of being an ATP-sensitive potassium channel agonist which may augment renal perfusion in addition to improving cardiac output [117]. As a result, it has been a target of interest in the treatment of CSA-AKI. Initial studies and their meta-analyses were favourable showing a reduction in rates of AKI and RRT with odds ratio of 0.43–0.51 depending on the outcome used [118, 119]. However in the last 5 years several studies have been published showing no benefit of levosimendan [120, 121]. Furthermore a recent meta-analysis found that when only trials with low risk of bias were included in the analysis there was no evidence of any benefit [122]. Given this recent evidence and the risk of adverse events including hypotension and supraventricular arrhythmias, the guidelines do not support the use of levosimendan without further investigations [65, 96].

12.5.2.5 N-Acetylcysteine

N-Acetylcysteine (NAC) is a thiol compound that reduces reactive oxygen species, which may help mitigate the inflammatory cascade associated with CPB as well as acting as a vasodilator [123, 124]. Although NAC was shown to improve renal outcomes in a rat model of CPB, this has failed to be translated into human studies [125]. Multiple RCTs and a recent meta-analysis showed no effect on rates of AKI, RRT or mortality [103, 111, 126–128]. As a result NAC has not been incorporated into practice nor recommended in the guidelines with the exception of those patients also undergoing concomitant coronary angiography [65, 96].

12.5.2.6 Sodium Bicarbonate

Given the role of hemolysis in the pathogenesis of CSA-AKI, urinary alkalinisation with sodium bicarbonate may decrease pigment nephropathy and iron mediated free radical production. An initial pilot trial exploring the use of sodium bicarbonate showed a decrease in CSA-AKI when given intraoperatively and for the first 24 h post operatively with an OR of 0.43 [129]. However, when this was repeated with a larger sample size, there was no difference found in renal outcomes, despite adequate alkalinisation of the urine [130]. This was further supported by a recent meta-analysis of five RCTs which showed no difference in rates of AKI or RRT and increased length of mechanical ventilation secondary to metabolic alkalosis [131]. Consequently, sodium bicarbonate is not recommended for the prevention of AKI in the post cardiac surgery population in the absence of another clear indication [96].

12.5.2.7 Statins

The pleiotropic effects of statins have been shown in animal models to protect against IRI through the reduction of reactive oxygen species and the upregulation of nitric oxide synthase [132, 133]. Initial observational trials in humans were also promising, showing a decreased risk of AKI in patients taking statins perioperatively, however these were plagued by confounding [134, 135]. Randomized controlled trials have failed to demonstrate a benefit of perioperative statins, and in fact have shown some potential increased risk of AKI particularly in statin-naïve patients with CKD [136–138]. As a result, the use of statins for the prevention of CSA-AKI is not recommended in consensus guidelines [65, 96].

12.5.3 Remote Ischemic Preconditioning

Remote ischemic preconditioning (RIPC) consists of inducing transient ischemia at a distal site, typically by inflating a blood pressure cuff on the arm or leg, with the aim to minimize subsequent ischemic injury at a target organ such as the kidney [139]. Although the mechanism behind this is not entirely clear it is likely as a result of a combination of neuronal, humoral and anti-inflammatory pathways which are triggered by RIPC and converge on K-dependant ATP channels in the mitochondria which are activated and decrease mitochondrial permeability, improving cell survival [139]. Given the large role of ischemia in the pathogenesis of CSA-AKI and the low cost of RIPC, multiple trials have been undertaken to assess the efficacy of RIPC in the prevention of CSA-AKI, with mixed results. While an initial double blind, sham controlled, multicentre RCT showed a promising reduction in rates of AKI (OR 0.71 favouring RIPC) it was limited by small sample size and only enrolled patients at high risk of CSA-AKI [140]. Subsequent, larger studies undertaken in a broader sample of cardiac surgery patients have failed to reproduce these results [141, 142].

12.5.4 Renal Replacement Therapy

In those patients whose CSA-AKI progresses to requiring renal replacement therapy, there is little consensus on the ideal timing, modality and dose of renal replacement. While the recent STAART AKI and AKIKI trials have both shown no benefit to early initiation of RRT in the general ICU population, the applicability of these trials to the CS-AKI population is limited by the inclusion of very few cardiovascular surgery patients (none in

AKIKI and 8% in STARRT AKI required CPB) [143, 144]. The ELAIN trial, however, was comprised of 50% post cardiac surgery patients and did show a mortality benefit to early initiation of RRT [145]. As a result it could be inferred that these results are more applicable to this population, however there is a relative paucity of randomized controlled trials specific to the cardiac surgery population. One recent trial comparing early initiation of CVVH versus late initiation of CCVHDF was stopped early due to futility when no mortality benefit was demonstrated [146]. While a recent meta-analysis showed a potential mortality benefit with early initiation (OR 0.36) the analysis consisted of predominantly retrospective cohort studies and was limited by high heterogeneity [147]. As a result, KDIGO guidelines at this point do not give a clear recommendation about the timing of initiation of RRT [101].

Guidance around the dose of RRT is also significantly limited by a lack of evidence. While the RENAL and ATN trials showed no difference in high versus conventional dose RRT in the general ICU population, there have been no trials examining this issue specifically in the cardiac surgery population [148, 149].

12.6 Pediatrics

AKI after pediatric cardiac surgery is a relatively common occurrence however it remains challenging to define, particularly in the neonatal period. The decline in creatinine that occurs after birth and ongoing glomerular development make the interpretation of serum creatinine challenging in neonates, and the change in creatinine with muscle mass make definitions using absolute creatinine unusable [150]. As a result, the two most commonly used definitions in children are the AKIN criteria, as it does not require calculation of eGFR, and the pediatric RIFLE criteria (pRIFLE) [151, 152].

As in adults, the incidence of CSA-AKI in children varies by definition employed and the population studied. In the neonatal population incidence is approximately 60%, owing to their relatively low nephron mass and the complexity of congenital repairs children typically undergo [153, 154]. The rates of dialysis are also high in the neonatal population, ranging from 12% to 27% [150, 154]. In older children the incidence of CSA-AKI falls significantly, with a recent prospective study reporting a rate of CSA-AKI of 42% in children above 30 days [155].

Many biomarkers have been studied in the pediatric population given the homogenous pathophysiology of their CSA-AKI. Both urinary NGAL and urinary IL-18 have been found to be strongly predictive of the development of severe CSA-AKI (AUC 0.72–0.99 and 0.75 respectively) [42, 43, 55].

While the association between even small decreases in renal function and mortality are well established in the adult population, the relationship in pediatric patients is less clear. Severe AKI may be associated with an increase in in-hospital mortality, ICU length of state and time of mechanical ventilation, however a long term mortality increase has not been clearly demonstrated [150, 155]. Elevated urinary NGAL and IL-18 have also been shown to be associated with increased hospital length of stay and mechanical ventilation time but has not been shown to predict mortality [43].

The pathophysiology of pediatric CSA-AKI is largely the same as in the adult population and arises from a combination of ischemic, inflammatory, hemolytic and embolic insults to the kidney [151]. Unlike adults however, there are fewer chronic comorbidities such as diabetes and vascular disease, but children may be particularly susceptible to renal injury secondary to their small nephron mass and the frequency with which CPB, and its resulting inflammatory cascade, is required. There are a number of unique risk factors in children which can help predict those at highest risk of developing AKI. As mentioned previously, younger age is a strong predictor of increased risk of CSA-AKI as is a lower gestational age in the neonatal population and low body surface area [150, 153–155]. Similar to the adult population, CPB duration is also an independent risk factor and appears to be a linear relationship, with a CBP time of >120 min conferring over a threefold increase in risk [150,

153–155]. Independent of CPB time, increasing surgical complexity also portends a higher risk of CSA-AKI [154, 155]. Children also have a higher rate of nephrotoxin administration, particularly because of the use of aminoglycosides and NSAIDs. One prospective study found that 15% of participants received gentamicin and 56% received non steroidal anti-inflammatories perioperatively [155].

The treatment of pediatric CSA-AKI also suffers from a lack of high quality, large RCTs. The mainstay of treatment primarily relies on risk factor modification, such as decreasing CPB time, avoidance of nephrotoxins and optimizing hemodynamics perioperatively [151]. In the pediatric population, fluid management to prevent overload is particularly important in treatment. Intraoperative ultrafiltration is often employed to minimize fluid gains and ultrafiltration with peritoneal dialysis in neonates has been shown to be safe and yields a 21.1% absolute mortality reduction [156]. Novel treatments have been sparsely studied in the pediatric population, although one RCT examined fenoldepam and found a decrease in urinary NGAL levels, although there was no change in rates of AKI or serum creatinine [157]. Overall, more randomized controlled trials of pharmacologic interventions in children are required.

12.7 Summary and Future Directions

CSA-AKI is common in the post cardiac surgery setting with rates upwards of 20% and approximately 2% of patients requiring dialysis. Even small elevations in serum creatinine are associated with increased short and long term mortality, as well as increased rates of in-hospital complications. Biomarkers have emerged as a promising tool for the early detection and possible treatment of those patients at highest risk of CSA-AKI, however inconsistent results have limited their clinical use.

The pathophysiology is multifactorial and poorly understood, but includes components of IRI, inflammation, hemolysis and embolic components. Overall, CPB seems to contribute to these processes but off pump cardiac surgery continues to have a significant risk of AKI. Additional risk factors for CSA-AKI include pre-existing renal function, as well as other non-renal comorbidities including congestive heart failure and cardiogenic shock, diabetes and peripheral vascular disease. Surgical factors include more complex procedures such as valve replacements and repeat sternotomy as well as anemia and hemodilution. The risk of perioperative angiography and contrast administration is less clear.

The treatment of CSA-AKI relies primarily on the avoidance of renal insults including maximizing renal perfusion in the perioperative period and minimizing nephrotoxins. Although a lack of evidence means that there are currently no novel therapies recommended for the treatment of CSA-AKI, there are a number of pharmacologic interventions which have promising results requiring further study. These include natriuretic peptides, fenoldepam and dexmetodomidine.

Areas of further study include novel biomarkers and their role in the early detection of those patients at risk of CSA-AKI and refining existing risk scores for identifying those patients who may benefit from intensive treatment. Further study is also required in the realm of novel pharmacologic strategies including fenoldepam and natriuretic peptides, in order to identify successful treatment options.

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Pediatric Cardiorenal Syndromes

13

Chiara Giorni, Alessandra Rizza, and Zaccaria Ricci

13.1 Introduction

Cardiorenal syndrome (CRS) describes a specific acute and chronic clinical picture in which the heart or the kidney are primarily dysfunctioning and secondarily affect each other [1]. This reciprocal pathogenetic relation between worsening kidney function and worsening heart function has been described about 30 years ago [2]. Recently, a more systematic classification exactly depicted the relation between heart and kidney also specifying the negative effects of decreased kidney function on the cardiovascular system [1, 3].

Currently CRS is classified into five classes: acute (I) and chronic (II) CRS, acute (III) and chronic (IV) reno-cardiac syndromes, and secondary dysfunction (V) of both heart and kidneys (i.e. during systemic clinical syndromes as sepsis, diabetes, auto-immune conditions, etc.). Although repeatedly identified in the adult population, pediatric CRS (pCRS) are currently rather precisely described, with peculiar aspects with respect to older patients. Acute CRS (type 1 or CRS I) in infants generally relates to patients undergoing cardiopulmonary bypass (CPB) [4], whereas CRS type 2 (CRS II) is related to children with chronic heart dysfunction, such as dilated cardiomyopathy (DCM) [5]. In adults, chronic cardiac abnormalities resulting in impaired kidney function are associated with adverse outcomes and prolonged hospitalizations, and the prevalence of CRS has been reported to be as high as 30% [6]. The prevalence of CRS in children is less described. The present chapter will specifically detail epidemiology, risk factors, therapeutic options and outcomes of CRS I and II, leaving reno-cardiac syndromes to specific nephrology textbooks.

13.2 CRS Type 1: Acute Cardiorenal Syndrome

Renal dysfunction in heart failure children is frequent and, although recently touched by a substantial body of literature, it is still probably underestimated [7]. In particular, acute kidney injury (AKI) is a serious complication following CPB in both children and adults. Increased procedural complexity is a risk factor for AKI following cardiac surgery.

Thanks to the recent efforts by the ADQI and KDIGO workgroups [8, 9] AKI has currently reached a standardized definition, although the specific issue of pediatric AKI definition still has some controversial aspect. With these considerations in mind, Kumar et al. described that the incidence of AKI following cardiac surgery in

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children varies widely between 11% and 80%, depending upon the institution and definition used for AKI [10]. It has been clarified that, even if probably lower severity classes in pediatric AKI may not be significantly related to patients' outcomes [11], AKI following cardiac surgery should never been overlooked. On the other side, the incidence of AKI requiring renal replacement following pediatric cardiac surgery is estimated around 5% and 10% and is reported to have an associated mortality above 30% [12] peaking to 80% in the neonatal population [13]. AKI consequent to cardiac surgery, as a direct CRS I manifestation, represents not only a marker of end-organ damage, but it may also be a predictor of worse outcomes in post cardiac surgery children [14] and it also precedes serious long-term issues such as chronic kidney disease and hypertension [15].

A number of risk factors have been identified in the development of AKI following cardiac surgery in children, including various demographic, preoperative and perioperative variables, and suggesting a multifactorial etiology associated to the variability of the perioperative and postoperative institutional practices [16]. While younger age at operation has consistently been shown to be a risk factor for AKI following congenital heart defects operations, yet there are few data on AKI among neonates and young infants undergoing cardiac surgery. Other identified risk factors of post-CPB CRS I are hypoperfusion, nephrotoxic cardiac drugs use, humoral factors as renin-angiotensin system activation, immune mediated mechanisms, metabolic products release [17]. The renal stress after surgery has also been considered secondary to central nervous system influences, to ischemic reperfusion injury, to the oxidative stress, and to the neuro-hormonal activation. In addition, surgical stress induces sympathetic activation, which leads to hemodynamic instability and renal vasoconstriction [17]. The cortical blood flow is decreased compared to the medullary blood flow; the elevation of catecholamines as vasopressin release, results in fluid accumulation. The activation of renin-angiotensin system results in an increased aldosterone production. Exposure of blood to the CPB material is another important aspect to be considered and it is particularly relevant in the younger children. For neonates and young infants, furthermore, the bypass machine prime typically consists of packed red blood cells, crystalloids, and colloids (usually albumin) to achieve the desired hematocrit: activation of inflammatory mechanism including complement and other immune mediated vasoconstrictors (endothelin and decrease of nitric oxide production and natriuretic factors release) has been described in experimental and human models, with significant effects on glomerular filtration rate (GFR) and renal function [17]. Currently, however, strategies aiming to blunt inflammation have not showed significant effects on renal dysfunction [18]. CPB for pediatric procedures, furthermore, often requires mild to profound hypothermia (down to 18 °C in selected cases) that causes intense systemic vasoconstriction, hemodilution (with consequent reduction of colloid-osmotic pressure) and low perfusion rates that are needed in order to reduce bleeding into the surgical field during heart and vessels manipulation (up to circulatory arrest in aortic reconstruction). The current trend toward open heart-surgery in very young infants has stimulated the development of miniaturized perfusion equipment with priming volumes of only 0.5–1 times the blood volume of the smallest children [19], thereby reducing the adverse effects of hemodilution and allogenic hemoderivates administration [20, 21]. The CPB is not the only risk factor for postoperative renal dysfunction; correlation between postoperative renal dysfunction and preoperative risk factors such as primary renal disease, preoperative low cardiac output, and renal injury after cardiac catheterization [22] has also been described. Another factor associated with postoperative renal dysfunction is the reduction of the cardiac output after CPB [23]. The multiple causative factors involved have a major impact in pediatric population because basal GFR, creatinine clearance and medullary concentrating ability are reduced overall in neonates and young infants (renal function reaches its complete maturity at 2 years of age).

The issue of fluid balance control is certainly another important pathogenetic mechanism

involved in the development of CRS I in children with congenital heart diseases. Fluid overload in cardiac patients (secondary to inadequate diuresis due to heart dysfunction or to excessive fluid resuscitation secondary to hemodynamic instability) has repeatedly been associated with worse outcomes [24] and renal dysfunction [25]. The use of CPB itself results in increased total body water, especially when prolonged times of extracorporeal perfusion are required, large amount of fluids are replaced and systemic inflammation is magnified, leading to accumulation of water in the interstitial space (leak syndrome). All these mechanisms may depend directly upon a reduced renal capacity of managing diuresis and body water and, in a vicious circle, may also directly cause AKI. Fluid accumulation, in a dose dependent way, has been showed to affect all organs (heart, kidneys, lungs, brain) and lead to a longer postoperative ventilation time, to a longer length of stay in the intensive care unit (ICU), and to higher incidence of postoperative infections [24, 26].

As far as diagnosis of CRS I is concerned, several novel biomarkers of heart and renal function have recently been proposed. In this light, early diagnosis of renal damage may also be associated with worsening heart function and vice versa [27]. Different sequential patterns of biomarker elevation after pediatric CPB have been evaluated and their diagnostic accuracy have been determined, distinguishing urine Neutrophil gelatinase-associated lipocalin (uNGAL) as a superior stand-alone test at the early time points after pediatric CPB, while a panel of carefully selected biomarkers as interleukine (IL)-18, renal liver-type fatty acid binding protein (L-FABP), the product of tissue inhibitor of metalloproteinase (TIMP)-2, the insulin-like growth factor binding protein (IGFBP)-7 and the kidney injury molecule (KIM)-1 have shown some value at later time points [28, 29]. It currently remains to be established if these tools can be actually implemented in pediatric critical care in order to apply timely therapeutic practices or to verify the effectiveness of renoprotective strategies [30].

The therapy of CRS I is mainly based on preventive measures, optimization of heart function and limitation of nephrotoxic agents' administration. The clear distinction between preoperative risk factors that are not modifiable and which constitute the independent factors risk of CRS I (i.e. age, surgical risk) and the modifiable variables (hemoglobin levels, hypoalbuminemia, hemodynamic optimization) may be of great help for the clinician. The increase of hemoconcentration after pediatric cardiac surgery with higher levels of hemoglobin in the first postoperative day, has been suggested to be one of the contributive modifiable risk factor to the CRS I [31].

Clearly, recent literature devoted a great focus on the effects of fluid removal. The use of ultrafiltration during CPB, conventional or modified, may limit the damaging effects of total body water accumulation. It has been showed that when a standardized volume of fluid is removed, hematocrit, hemodynamics, ventricular function, requirement for blood products, and postoperative resource use do not differ between pediatric patients receiving conventional and modified ultrafiltration for hemoconcentration after cardiac surgery [32]. More recently a meta-analysis outlined that the postoperative outcome parameters were not significantly influenced by the type of ultrafiltration method, and that the superiority of modified ultrafiltration over conventional ultrafiltration consisted in transitory clinical conditions improvements (mean arterial pressure, coagulation parameters) only in the immediate post bypass period without their persistence after ICU admission [33].

Although many interventions for AKI prevention after cardiac surgery in children are available, there is still no specific effective treatment after AKI has established. Concerning the perioperative treatment, it was recently reported that avoiding the intraoperative use of albumin and phosphodiesterase inhibitors (milrinone) may reduce the postoperative AKI by preventing direct and indirect deleterious effect on renal function [10]. Other strategies include to optimize tissue oxygen delivery, maintaining a high hematocrit and full flow rates during cooling to moderate or deep hypothermia and during rewarming [10]. An interesting observation was not recently able to associate post-operative AKI and plasma levels of different inflammation bio-

markers [18]. In this study, such mediators were not affected by the administration of glucocorticoids. Interestingly, the authors hypothesized that an association exists between the administration of milrinone and post cardiac surgery AKI. As a matter of fact, even if this association would seem to independent of inotrope score and patients' cardiac output, it must be said that no hemodynamic goals are currently clearly targeted in pediatric CRS studies [34]. Differently, inodilator drugs such as milrinone, levosimendan and nesiritide, leading to systemic vasodilation and improved renal blood flow, have a consistent rational for the prevention of AKI and CRS I treatment. Recently, Bronicki and coauthors conducted a retrospective study on nesiritide infusion in children with congenital heart diseases who showed resistance to diuretic therapy and pulmonary congestion [35]. According to these authors, nesiritide was able to significantly decrease central venous pressure and heart rate and increased urine output. Also, the serum creatinine and stage of acute kidney injury decreased significantly. Another drug that, similarly to nesiritide, apparently showed no effect in adult patients but was instead effective in a cohort of infants is fenoldopam [36]. Our group showed, during a randomized controlled trial, that high dose fenoldopam (1 μg/kg/min), administered continuously during CPB, is able to significantly reduce uNGAL levels, increase urine output and reduce the need for intraoperative vasodilators, independently of other covariates [36].

Diuretics are clearly the mainstay treatment in order to obtain an adequate urine flow after CPB in order to cope with infused fluids. Short term high dose approach with ethacrynic acid has recently showed to be effective and safe in infants and neonates undergoing major surgical procedures [37]: optimized fluid balance (due to the most aggressive approach with ethacrynic acid) in the first post-operative day led to shorter ventilation time and improved cardiac output, without increasing creatinine levels with respect to furosemide. Renal replacement therapy (RRT) is the most effective way of managing severe acute kidney injury (AKI) [38]. Peritoneal dialysis (especially when the catheter is positioned with a proactive approach, in the immediate postsurgical phase) has shown as an effective adjuvant treatment for achieving a negative fluid balance [39]. Extracorporeal RRT in the pediatric cardiac setting is reserved to the most severe cases and, in neonates, when peritoneal dialysis is contraindicated (i.e. simultaneous abdominal surgery): last generation machines and pediatric circuits have recently been described as safe and feasible in this delicate population. More timely and extensive dialytic treatments are expected in the next years thanks to this new technology [40].

Concerning sedative drugs, it has been reported that intraoperative infusion of dexmedetomidine would attenuate the renal dysfunction after pediatric open heart surgery [41, 42]: similar data have emerged in the adult literature and future studies are expected about this interesting drug.

Finally, the follow up of AKI pediatric patients after CPB has recently shown controversial data [15, 43, 44]. It seems that in contrast to the high mortality and morbidity of AKI in the acute phase, in the long-term (5 years) hypertension, reduced GFR and albuminuria are relatively common (17%, 8% and 14% respectively) although not significantly associated to anamnesis of AKI [43]. It should be highlighted that children are generally free of adult comorbidities (smoking, diabetes, vascular diseases) and may need a longer follow up to provide definitive results. As reported by Cooper et al., patients surviving a post cardio-surgical AKI episode (and then apparently restoring their renal function) demonstrate significantly increased levels of tubular injury biomarkers (IL-18 and L-FABP), compared to the age-matched patients without AKI, a follow-up to almost 7 years [44]. The clinical meaning of these pathological biomarkers level should be evaluated in the longer period (when these patients reach adulthood).

13.3 CRS Type 2: Chronic Cardiorenal Syndrome

Heart failure (HF) is a significant health care concern for children worldwide. In recent years, HF has been characterized appropriately as a clinical

syndrome including complex relationships with multiple organ systems, including the kidney. A clinical status of established HF (i.e. a patient suffering from decompensated HF after surgery for congenital heart diseases or a patient treated for dilative cardiomyopathy) with a secondary renal dysfunction (which can be either acute and chronic) has been classified as cardio renal syndrome type 2 (CRS II) [1].

Pediatric HF prevalence and long term outcomes remain largely unknown and this is true for CRS II, accordingly. Although these data are lacking, recent reports suggest that there has been a substantial increase in costs associated with care of pediatric heart transplant patients. Renal injury occurs commonly in pediatric patients with heart failure [45]. CRS II has been associated with poor prognosis, with the occurrence of worsening renal function being strongly associated with mortality in this setting [46]. CRS II is characterized by chronic abnormalities in cardiac function (e.g., chronic congestive heart failure) causing progressive and potentially permanent chronic kidney disease (previously identified as worsening renal failure).

In the setting of HF, decreased urine output and resultant fluid retention can aggravate heart failure symptoms and contribute to clinical deterioration. The physiologic interaction of the heart and kidney is complex and not definitely understood. Renal insufficiency occurring in heart failure patients is usually attributed to low cardiac output causing decreased renal perfusion or a prerenal state. This explanation might oversimplify the complex interrelationship of these two organs and it might fail to acknowledge the neuro-hormonal and vasoreactive elements in the setting of heart failure. The syndrome of HF is characterized by neuro-hormonal activation, salt and water retention and azotemia, regardless of the presence of kidney disease. The sequence of events that lead to salt and water retention and development of renal dysfunction in patients with severe low-output HF include a severe decrease in left ventricular (LV) function, which causes a reduction in cardiac output (CO) and blood pressure (BP), leading to baroceptor-mediated activation of several neuro-hormones. The sympathetic tone is enhanced, with subsequent activation of the renin-angiotensin-aldosterone system (RAAS). Over time these adaptive mechanisms become maladaptive, leading to elevated systemic vascular resistance, fluid overload, and decreased renal perfusion. Indeed, the predominant effect of neuro-hormonal activation is a severe vasoconstriction with increase of systemic vascular resistance (SVR), especially in the splanchnic bed. The renal blood flow (RBF) decreases greater in proportion to the reduction of CO. The GFR is also reduced but to a lesser extent than the RBF, suggesting a greater efferent than afferent arteriolar vasoconstriction. Therefore, the net effect of these mechanisms is that the arterial BP remains normal, maintained partly by an increase in SVR and partly by an expansion of the blood volume. Unfortunately, it occurs at the expense of renal function [47]. Elevated central venous pressure also plays an important role, as it is associated with reduced GFR even while other hemodynamic parameters (cardiac output and mean arterial pressure) are preserved [48]. The most plausible explanation is that when the central venous pressure increases, the arteriovenous pressure gradient across the kidney is decreased and the RBF, already compromised, is further reduced, leading to a significant GFR diminution [49]. Additional factors such as persistent use of nephrotoxic drugs, contrast agents for diagnostic procedures, infections or renal vein hypertension can lead to AKI during the treatment of pediatric chronic heart failure.

Studies of children with chronic left ventricular (LV) dysfunction, such as dilated cardiomyopathy (DCM), are lacking. Indeed, the association of CRS with mortality in children with dilated cardiomyopathy (DCM) is unknown. Kaddourah et al. with a modified Schwartz formula estimated GFR (eGFR) for children ≥1 year of age with DCM enrolled in the Pediatric Cardiomyopathy Registry at the time of DCM diagnosis and annually thereafter [50]. CRS II was identified when eGFR was below 90 mL/min/1.73 m^2. Children with and without CRS II were compared on survival and serum creatinine concentrations (SCr). The association between eGFR and echocardiographic measures was assessed. In this study 93

children with DCM diagnosed at ≥1 year of age were evaluated and patients with known endocrine conditions or primary essential hypertension were excluded. CRS II was identified over 60% of DCM children. Mean (standard deviation) eGFR was 62.0 (22.6) mL/min/1.73 m^2 for children with CRS and 108.0 (14.0) for those without ($P < 0.001$); median SCr concentrations were 0.9 and 0.5 mg/dL, respectively ($P < 0.001$). The mortality hazard ratio of children with CRS versus those with no CRS was 2.4 (95% confidence interval 0.8–7.4); eGFR was positively correlated with measures of left ventricular function and negatively correlated with age. Basing on this study's results, CRS II in children newly diagnosed with DCM may be associated with higher 5-year mortality and children with DCM, especially those with impaired left ventricular function, should be monitored for renal disease. As a confirmation of these data, Price and coworkers also showed that children hospitalized with decompensated heart failure who develop renal failure do have a tenfold risk of achieving the composite outcome of dying or to undergo a ventricular assist device (VAD) placement [51].

Although utilized as a surrogate of worse outcomes, use of a VAD as a bridge to transplant or destination therapy has become more common in children with end-stage heart disease (ESHD) and short-term prognosis after VAD placement are currently acceptable. In this context, renal function during VAD has been assessed by some authors because, importantly, as mechanical support evolves in the pediatric community, candidate selection should also be based on end-organ assessment. End-organ dysfunction that is deemed irreversible may be considered a contraindication to VAD implantation. However, renal recovery is challenging to predict, and several studies in adults have reported improved kidney function both in the short-term and long-term after VAD implantation. VAD implantation can also improve short-term and long-term renal function in children with ESHD [52]. Children with advanced HF commonly have renal dysfunction at the time of VAD placement. As reported by May et al., more than 50% of this population has a baseline estimated eGFR below 90 mL/min/1.73 m^2; the median eGFR in these children is 64 mL/min/1.73 m^2, consistent with stage 2 chronic kidney disease (CKD). In this observational study, AKI occurred in 60% of children after VAD implantation, but renal function recovered relatively quickly, returning to or exceeding baseline by the end of the first week after VAD implant. Patients with intact pre-VAD renal function maintained renal function throughout the study period (6 months). More impressively, patients with pre-VAD renal dysfunction experienced a significant improvement in eGFR as early as postoperative day 4 and sustained this improvement through POD 180 [52].

Finally, heart transplantation is life-saving treatment for end-stage HF. However, the impact of heart transplant on renal function is heavy. Previous analyses of renal function in pediatric heart and lung transplant recipients have shown conflicting results [53, 54]. Pradhan et al. evaluated renal function following thoracic organ transplantation in 46 children (32 heart, 9 lung, 5 heart-lung) with a median age of 4.1 years. Twenty-two percent of transplant recipients had an abnormal GFR prior to thoracic organ transplantation, which was likely related to HF. GFR% decreased following thoracic transplant. The percentage of recipients with normal renal function declined from 78% to 29% in the first 2 years post-transplant. Younger age at transplant was associated with a greater decline in GFR%, and this decline persisted after adjustment for nutritional status with body mass index or weight-for-length z-scores, that reflects loss of renal function rather than improved muscle mass. The prevalence of renal insufficiency (GFR < 75%) increased from 22% at transplant to 55% and 85% at 1 and 5 years post-transplant, respectively, while 15% had a GFR% <50 at 5 years post transplantation. Higher tacrolimus through levels over the first 6 months correlated with a lower GFR%. The nephrotoxicity of calcineurin inhibitors may be particularly important in the youngest transplant recipients [54].

Increasing evidence suggests that a greater understanding of CRS offers a unique and previously unrecognized opportunity to provide favorable clinical interventions in patients of all ages.

Early recognition of CRS and a better understanding of its pathophysiology are critical to guide therapy and improve outcomes of affected patients. Among the promising emerging methods to recognize risk for CRS II may be the use of novel renal biomarkers, possibly for a more accurate and early diagnosis and risk stratification, even in the long-term period.

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Key Concepts of Organ-Crosstalk

14

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14.1 Background

The "organ crosstalk" can be defined as the intricate biological communication between different body systems, mediated via cellular, subcellular, molecular, neural, endocrine and paracrine factors, giving rise to numerous forms of feedback. The physiological crosstalk is necessary to preserve regular homeostasis and normal functioning of the organism. However, in the disease condition, the direct and concomitant initiation of toxic cell signaling by the primary damaged organ can cause structural and functional impairment of distant organs [1]. Particularly, heart performance and kidney function are strictly interconnected and communication between these two organs occurs through a variety of dynamic and bidirectional pathways [2]. Multifactorial mechanisms leading to cardiorenal syndrome (CRS) involve not only hemodynamic parameters, such as extracellular fluid volume, cardiac output and arterial pressure, but also endothelial injury, interruption of physiological immunologic balance, cell death, inflammatory cascades, cell adhesion molecules, cytokine and chemokine overexpression, oxidative stress, neutrophil migration, leukocyte trafficking, caspase-mediated induction of apoptotic mechanisms, extracellular vesicles, small non-coding RNAs, epigenetics and oxidative stress [3–18]. These new alternative mechanisms have been recently proposed to be associated with the pathogenesis of CRS (Table 14.1).

14.2 Gene Expression

Gene expression is defined as the translation of information encoded in a gene (DNA) into protein or RNA structures that are operating in the cell. Expressed genes include genes transcribed into messenger RNA (mRNA) and then translated into proteins, as well as genes transcribed into RNA (transfer, ribosomal and microRNA), but not translated into proteins. Gene expression is cell and timing specific and gene expression analysis is the determination of the pattern of genes expressed at the level of genetic transcription, under specific circumstances or in a specific type of cell. Limited data exist regarding gene expression and gene activation in the setting of acute and chronic subtypes of CRS. In the context of CRS type 1, Virzì et al. investigated the gene expression of IL-6, IL-18, and NGAL by

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Table 14.1 New mechanisms implicated in CRS crosstalk

Epigenetic mechanisms	Modifications in gene function that are mitotically and/or meiotically heritable and that do not entail a change in DNA nucleotide sequence	Covalent modifications of DNA bases (e.g. DNA Methylation) Histone modifications RNA interference Chromatin remodeling
Prenatal programming	Environmental signals during fetal development can permanently affect composition, homeostatic systems and functions of multiple organs and systems	Nutritional Environment Other factors
Small non-coding RNA	RNA that does not encode a protein and regulates gene expression	MicroRNAs (miRNAs) Small interfering RNA (siRNAs) Piwi-interacting RNAs (piRNAs)
Extracellular vesicles (EVs)	Cell-derived vesicles, enclosed in a lipid bilayer, ranging from 30 to 2000 nm	Apoptotic bodies Microvesicles (MVs) Exosomes

quantitative real-time PCR in renal tubular epithelial cells (TECs) incubated with plasma from healthy controls (CTR), and patients with CRS type 1 or heart failure (HF). In the CRS type 1 group, mRNA expression of these factors resulted significantly higher compared with patients with HF and CTR. The authors concluded that the *in vitro* exposure to plasma from CRS type 1 patients altered the gene-expression profile of TECs characterized by an increase in pro-inflammatory mediators, the release of tubular damage markers, and apoptosis [11]. In a similar way, the same group investigated the activation of the apoptotic pathway in CRS type 1. They found that BAD and BAX gene expressions were significantly higher in monocytes treated with plasma from CRS type 1 patients compared to acute heart failure (AHF) group. On the contrary, FASL expression was similar in monocytes treated with plasma from CRS type 1 patients and AHF group [19].

14.3 Epigenetic and Epigenome

Epigenetics is responsible for phenotypic differences between cell types in multicellular organisms; it is considered a dynamic process that regulates gene expression patterns, accessibility to the genome through gene expression, and finally gene function [20–22]. The epigenome is decisive for the transcriptional outcome, allowing certain genes to be expressed while others to be not accessible to transcriptional machinery. Epigenome changes in reaction to precise signals coming from intracellular environment, neighboring cells, and extracellular factors, such as diet, drugs and nutrition. Epigenetic biochemical mechanisms include DNA methylation, cytosine modifications, covalent histone tail changes, higher-order chromatin organization and short non-coding RNA molecules, which are connected with chromatin remodeling and gene expression regulation [7, 20]. In this context, several lines of evidence are pointing to the fact that epigenetic modifications might play a specific role in chronic kidney disease (CKD) and in cardiovascular disease (CVD) development: smoking, mitochondrial dysfunction, hypertension and nephron number are significantly influenced by the in utero environment programming [23–25]. Emerging data exist regarding epigenetic mechanisms involved in the setting of acute and chronic subtypes of CRS. Unfortunately, it is still unclear how CRS risk factors are affected by histone modification, methylation and RNA interference. Within the setting of the physiopathology of kidney and heart disease, renal failure has been documented to increase cardiac histone H3 epigenetics; these findings directly link renal failure with induction of cardiomyopathy-related genes [26]. Furthermore, uremia can also affect DNA methylation, thus suggesting that epigenetic alterations are involved in CRS [20]. Recently, fascinating and promising evidence is rising about overnutrition and CRS. Nistala et al.

reported that maternal and paternal malnutrition (both under- and overnutrition) may influence fetal and prenatal programming, thus predisposing the fetus to CRS [27]. While in utero nutrient restriction has been shown to promote hypertension, CVD and CKD in offspring, high birth weight is associated with increased predisposition to CRS [28–34].

14.4 Small Non-coding RNAs

Small non-coding RNAs, which are constituted by about 18–30 endogenous nucleotides, represent an alternative intrinsic resource of gene regulation. Almost 2500 types of these molecules have been isolated in numerous life forms. They have been identified in all human cells and they are evolutionarily well conserved. Understanding the role of these non-coding molecules both in health and disease conditions is crucial due to their possible association with several critical biological functions [35, 36]. In addition, well over half of the human transcriptome is predicted to be under small non-coding RNA regulation [37]. Small non-coding RNAs control the expression of protein-coding genes through sequence-specific recognition, binding to 3′ or 5′-untranslated region (3′UTR) of target messenger RNA (mRNA) or promoter sequences, thus regulating mRNA levels by post-transcriptional mechanisms [38, 39]. Moreover, the general role of these molecules in specific cellular or physiological processes can be investigated by deleting or inhibiting miRNA processing machinery. There are growing reports on regulatory roles of these RNAs, including transcriptional gene silencing/activation and post-transcriptional gene silencing events [5, 40]. Moreover, these small RNAs are secreted from cells and enter the bloodstream directed toward targeted cells, thus denoting a new communication approach in cell–cell or cell–organ signal transduction. Different non-coding RNA exist and they have been classified into three main categories: microRNAs (miRNAs), small interfering RNA (siRNAs) and piwi-interacting RNAs (piRNAs) on the basis of their features related to the origin, structure, associated effector proteins and biological functions [41, 42].

Rana et al. have recently reported the role of cardiac miR21 and miR29b together with the inhibition of myocardium fibrosis in myocardial infarction after lowering uremic toxins levels in a rat model of CRS. The exposure to elevated serum concentrations of indoxyl sulfate (IS) was associated with an increase in miR21 expression and a reduction of miR29b in the heart. Furthermore, a significant correlation between cardiac miR21 and serum levels of IS and a significant inverse association between cardiac miR29b and serum levels of IS were observed [15]. Recently, Chuppa et al. longitudinally studied left ventricle (LV) pathology in a 5/6 nephrectomy rat model of CRS type 4 and identified novel molecular mediators. Next-generation sequencing of LV mRNA and microRNA (miRNA) was performed at physiologically distinct points in disease progression, thus identifying gene alterations in the immune system, lipid metabolism, and inflammatory pathways, as well as several miRNAs. These authors analyzed miR-21-5p–mediated targeting of PPARα (Peroxisome proliferator-activated receptor α) thus showing the therapeutic benefit of PPARα agonists on cardiac remodeling in a rat model of CKD [43].

14.5 Extracellular Vesicles

As notable discovery, microRNAs have been found in the extracellular space and in biological fluids, in a relatively stable state despite the existence of RNAse [44]. These extracellular miRNAs, excreted through various and not completely understood pathways, may be protected from degradation by several mechanisms. The inclusion in extracellular vesicles (EVs), such as microvesicles, exosomes and apoptotic bodies, as well as the formation of protein-microRNA complexes have been reported as possible mechanisms against RNAse degradation [45]. Extracellular vesicles are all cell-derived vesicles enclosed in a lipid bilayer, ranging from 30 to 2000 nm in diameter depending on their origin. In fact, three main populations of EVs have been

identified, according to their intracellular origin and dimension [46, 47]. Extracellular vesicles contain a specific subset of common proteins related to biogenesis and trafficking, as well as specific components derived from their origin cell or tissue [48, 49], such as proteins and nucleic acids [50–52]. Therefore, the study of the proteome and the nucleic acid content of EVs may provide information about the cell or tissue of origin and, importantly, their physiological state. Exosomes are 30–150 nm diameter vesicles derived from the inward budding of endosomal membranes, resulting in the progressive accumulation of intraluminal vesicles within large multivesicular bodies. They are released to the milieu by the fusion with the plasma membrane [48, 53]. Microvesicles are bigger than exosomes (100–1000 nm) and they are produced by the direct budding of the plasma membrane [54]. The first evidence of exosome-mediated transfer of mRNAs and miRNAs has been recently shown by Valadi et al., who observed substantial amounts of RNA in the exosomes of mouse mast cells [55]. Apoptotic bodies appear as a heterogeneous group of vesicles, with a size ranging from 50 nm to 5 μm and a buoyant density of 1.16–1.28 g/mL [56–58]. They contain DNA, RNA and histones, and display "eat-me" signaling molecules, causing their phagocytosis by macrophages [59, 60]. Due to their specific cellular content and high density, they may be distinguished from two other major vesicle populations, which show considerably more overlap [46].

Exosomes might play a pivotal role in the pathophysiology of kidney and heart disease, due to their action as mediators of intercellular communication and signaling mechanisms in the target cell, transfer of mRNAs, miRNAs and proteins, or the establishment of a way of cellular contents disposal [61, 62]. Circumstantial evidence has demonstrated, indeed, that these vesicles may be considered as molecular markers of renal dysfunction and structural injury, both in acute and chronic kidney damage and in graft rejection [63–70]. In the setting of CVD, platelets have been found to secrete exosomes, which may be involved in the complex cross-talk between diverse cell types in atherosclerosis plaques [71]. Moreover, cardiomyocytes as well have been shown to release exosomes able to transfer DNA and RNA to different cells [72].

14.6 Proteomics and Metabolomics

Proteomics is defined as a branch of biotechnology concerned with applying the techniques of molecular biology, biochemistry, and genetics to analyze the structure, function, and interactions of proteins produced by the genes of cells, tissues, or organisms at a certain time. It is the set of expressed proteins in a given type of cell or organism, at a given time, under defined conditions. Recent technological advances in proteomics have allowed a wide-scope analysis of protein patterns in bodily fluids, allowing the identification of numerous promising protein markers in various conditions. For instance, urine is an ideal biological fluid for proteomic analysis; it is easily collected in large amounts in a noninvasive manner. Research to determine prognostic and diagnostic value as well as clinical utility in renal, cardiac and cardiorenal disease states is ongoing [73]. In the context of "omics" sciences, metabolomics is the study of the complete set of metabolites—in a cell, tissue, organ or organism—which are the ending products of cellular processes in health and disease states. It could also be intended as a thread connecting genomics, transcriptomics and proteomics, changing completely the way to study and interpret the above stated cellular procedures [74]. It is not only resulting from changes in the expression of genes and RNA, but also from protein activity and environmental factors, including nutrition and drug therapies [75]. In a clinical context, the rapid characterization of small-molecule metabolites present in several biologic fluids (such as urine, blood, saliva) gives the opportunity to explore the interaction genotype–phenotype and genotype–environment type, thus generating the possibility to have a snapshot of the metabolic status that can help the understanding the biological network of the metabolites whether

normal or pathological [76, 77]. Metabolomics has been shown to have a substantial impact on the investigation of various CVD and renal disease [75, 77]. For instance, mass spectrometry-based profiling of plasma metabolites was performed in over 400 HF patients by Cheng et al. in order to assess the diagnostic and prognostic value of metabolomics in HF. Their results showed that metabolomics is able to provide significant prognostic value, independent of brain natriuretic peptide (BNP) and other traditional risk factors [78]. In a recent work, Bassareo et al. investigated the differences in the urinary metabolic profile and in the hematic asymmetric dimethyl arginine (ADMA) levels in young grown-up subjects who were born preterm with an extremely low birth weight (ex-ELBW) and a control group of subjects who were born at term with a weight appropriate for their gestational age. Interestingly, the authors reported a correlation between the urinary metabolic profile in ex-ELBW and their blood ADMA levels, suggesting the presence of a subclinical CRS in these subjects [74].

14.7 Inflammation

No resolving and persistent exposure to pro-inflammatory factors, such cytokines and chemokines, damages tissue, impairs organ function and is harmful in acute and chronic CRS. Cytokines, chemokines, and eicosanoids mediate cellular responses and interact with genome encoded receptors expressed on monocytes, macrophages, mast cells, astrocytes, and other cells of the innate immune system [79]. Upregulation of humoral factors by injured cells leads to stimulation of the Toll/interleukin-1 superfamily that actives nuclear factor kB (NF-kB). NF-kB translocates to the nucleus thus inducing changes in gene expression. Toll-Like Receptor (TLR) pathways result in both intra and extra-cellular up-regulation of inflammatory cytokine expression [80, 81]. Recent findings documented that inflammation is a potentially important stressor for acute and chronic cardiorenal dysfunction. Altered endothelial regulation, which may be linked to inflammation, has been documented to affect afterload–preload mismatch in HF patients consequent to greater arterial stiffness or reduced venous capacitance and increased venous pressure. Higher central venous pressures (i.e. including higher renal venous pressures) promote kidney dysfunction, injury, and release of pro-inflammatory cytokines. Furthermore, enhanced inflammatory status also contributes to renal injury and reduced kidney function. Furthermore, worsening kidney function directly affects acute/chronic cardiac disease and could contribute to poor clinical outcomes [20]. Various triggers (i.e., focal segmental glomerulosclerosis, mesangial proliferation, tubular necrosis, or interstitial fibrosis, etc.) produce pathologically distinct lesions in the kidneys. Renal vessel injury causes intravascular clotting and increased risk of extra-vascular hemorrhage; a close relationship exists between clotting and inflammation due to activation of platelets (with attendant aggregation) that stimulates the release of cytokines and chemokines to promote leukocyte recruitment. A coagulation-mediated release of mitogenic factors (epidermal growth factors, cytokines, chemokines, etc.) promotes re-epithelialization of the epithelial cell barrier, thereby limiting fluid losses. Persistent de-epithelialization increases the risk of chronic injury; however, uncoordinated epithelial hyperplasia is also detrimental (i.e., glomerular crescent formation) [20].

Ischemia, infection, and uremic milieu have the potential to stimulate diverse inflammatory components in both kidney and heart disease. In renal disease, cytokines may be produced by other tissues and cleared by the kidney. The inability to metabolize or clear cytokines in acute and chronic kidney disease may lead to an increase in serum levels that may contribute to systemic effects [8]. Stimulation of inflammation mechanisms during CRS results in the release of soluble mediators into the bloodstream that exerts harmful effects on distant organs [82]. For instance, after organ injury, monocytes (involved in both tissue damage and repair) release cytokines into the peripheral circulation that trigger pathogenic mechanisms in distant organs.

Monocyte migration with the resultant release of pro-inflammatory cytokines has been documented in CRS type 1 and type 5; oxidative stress and interleukin levels (IL-6 and IL-18) are also substantially elevated [10, 14, 82–84].

14.8 Immune Cell Signaling and Immunomodulation: The Role of Innate and Adaptive Immunity

An immune-mediated damage has been postulated as a potential mechanism involved in the pathogenesis of CRS [9]. Recent studies have highlighted the importance of both innate and adaptive immune responses to endogenous molecules induced by either tissue damage or infection [85, 86]. The innate immune system is immediately activated in infection states and inflammatory conditions in a non-antigenic-specific way. It is executed primarily by myeloid cells with the participation of some "innate" lymphocyte sub-populations and is comprised of neutrophils, monocytes/macrophages, dendritic cells (DCs), natural killer cells and natural killers T (NKT) cells. Leukocytes such as DCs and macrophages play important functions in both types of immunity by generating cytokines, chemokines and presenting antigens to lymphocytes [85, 87]. Adaptive immunity is a second line of defense responding to specific antigens in cellular and humoral response pathways. T cells polarization in response to DCs activation is complex and involves myriads of signaling cascades. The TLR pathways regulate activation of both innate and adaptive immune responses. TLRs are the major pattern recognition receptors, binding to a wide range of different molecules and, in particular, endogenous ligands produced because of tissue injury. This pathogenesis, specifically TLR-signaling, causes a rapid response mechanism to local tissue damage and it is involved in early activation of the immune response in cardiac and renal disease [88]. Although DCs are potent regulators of immunity, their role in CRS is only partially understood. DCs are antigen-presenting cells that play a central role in innate and adaptive immunology. Moreover, the dominant resident leukocyte types present in the kidney are resident intrarenal DCs suggesting a crucial role in renal immunity and inflammation. In fact, in the normal mouse CD11c+ MHC class II+ DCs are the most abundant leukocyte subset in the kidney, suggesting an important role in renal immunity and inflammation [87]. These cells are located in the interstitial extracellular compartment of the whole kidney and are tactically positioned to interact with many different factors [89–91]. Within this compartment, DCs are close to epithelial cells, macrophages, and fibroblasts, and they respond to endogenous molecules released from resident and/or infiltrating cells [8, 90, 91]. They are a heterogeneous population with different functions. Upon stimulation, DCs can convert to a mature cell type characterized by high levels of class II major histocompatibility complex (MHC class II) and co-stimulatory molecules and low phagocytic capacity. Mature DCs are specialized in T cell activation. However, DCs are also important in the innate immune response by releasing pro-inflammatory factors, such as TNF, IL-6, IL-12, MCP-1 and RANTES, interacting with NKT cells via CD40–CD40L [87, 92]. Recent studies have shown that DCs can improve or prevent injury to the kidney depending on the nature of stimulus. For example, depletion of DCs prior to IRI reduces consequent reperfusion injury and related renal dysfunction [93].Conversely, depletion of DCs prior to cisplatin-exposure resulted in worse renal dysfunction and stronger inflammation [94].

In addition, recent works tried to deepen our knowledge of pathophysiology CRS type 1 and type 5 using different *in vitro* experimental models. Monocyte cells treated by CRS type1 plasma showed up-regulation of apoptosis compared with those treated by acute HF plasma and an increase of inflammation and oxidative stress. Pro-inflammatory cytokines may induce apoptosis and necrosis through activation of death signaling receptors and, indirectly, throughout increase of reactive oxygen substrate production [10, 83]. Similarly, renal tubular epithelial cells (TEC) incubated with CRS type 1 plasma increased pro-inflammatory production, release

of tubular damage markers as neutrophil gelatinase-associated lipocalin (NGAL) and apoptosis. In a similar way, TEC incubated with CRS type 5 plasma showed a strong cytotoxic effect with a decrease of viability, activation of intrinsic and extrinsic apoptotic pathway and the deregulation of cytokine release. Furthermore, a possible relationship between endotoxin levels and renal cell death were identified in septic patients with CRS type 5.

14.9 Neurohormonal Systems in Cardiorenal Syndromes

Both heart and kidney are fundamental for the maintenance of body hemodynamic stability, through complex neurohormonal mechanisms involving autonomic nervous system (ANS), renin-angiotensin-aldosterone system (RAAS), arginine vasopressin (AVP) and endothelin [95]. CRS is a complex disease with multifactorial pathophysiology, and neurohormonal activation plays a pivotal role in this clinical scenario. Acute and chronic heart failure, a typical feature of CRS type 1 and type 2, is characterized by reduced cardiac output which leads to a fall in renal perfusion pressures, resulting in the activation of RAAS system and baroreceptors [96]. Activated baroreceptors and RAAS induce the release of AVP, which is responsible for fluid retention, further heart decompensation and tissue hypoxia [97]. In particular, AVP induces aquaporin 2 water channels expression in the principal cells of the collecting duct, thus increasing urine concentration as electrolyte-free water moves from the lumen into the interstitium and then into the circulation [98]. Moreover, direct effects of AVP on renal vascular system, low cardiac output and activated RAAS result in progressive renal impairment due to afferent renal arteriolar vasoconstriction and reduced renal perfusion [99]. Activation of RAAS and high levels of AVP are responsible for the development of hyponatremia, whose severity may underline the degree of the underlying neurohormonal activation [100] (Fig. 14.1). B-Type natriuretic peptide (BNP) and its precursor NT-proBNP are hormones secreted predominantly by the ventricles, and their levels usually

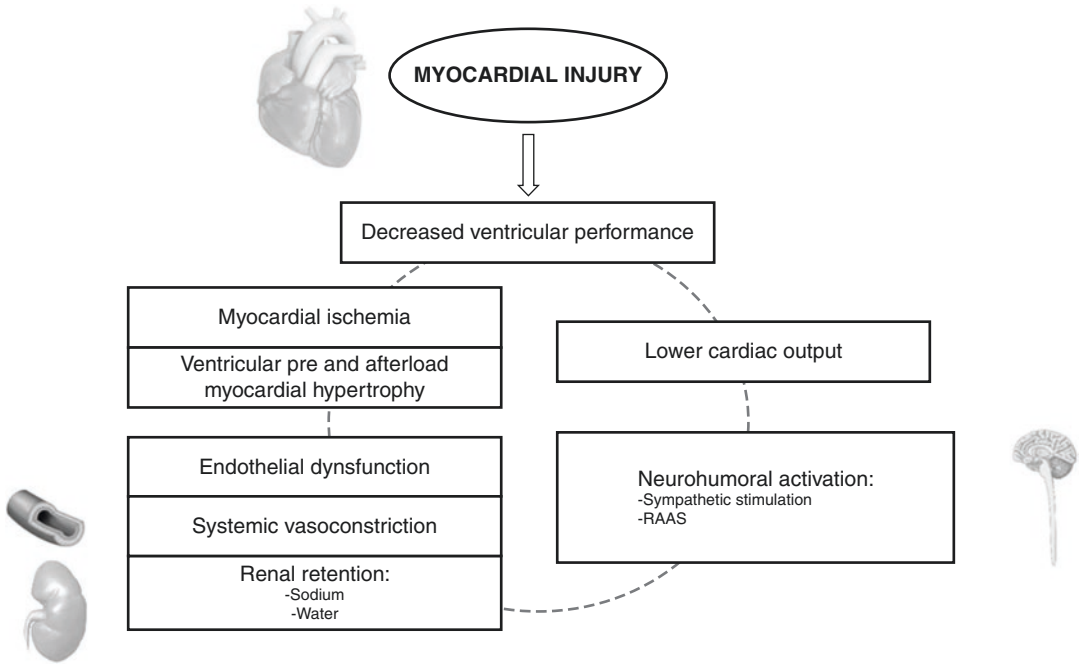

Fig. 14.1 Neurohormonal regulation in Cardiorenal Syndromes

increase in patients with acute or chronic HF. BNP release is induced by ventricular and atrial wall distension and neurohormonal activation [101]. However, increased levels of natriuretic peptides (NP) may be associated to renal dysfunction as well, and they have the potential to serve as a valuable diagnostic and prognostic tool in several CRS types [102]. The exact mechanism remains to be clarified: increased myocardial wall stress, left ventricular hypertrophy, coronary disease and cardiac remodeling may contribute to NP increase in the setting of CRS. Anyway, the relationship between BNP, renal function and the severity of HF remains to be elucidated. It is well established that patients with CKD have higher levels of both BNP and NT-proBNP compared to age- and gender-matched subjects without renal impairment, even in the absence of clinical HF, although the exact cutoff value to distinguish patients with only kidney disease and patients with CRS is not known [101].

14.10 Endocrine Dysregulation in Cardiorenal Syndromes

Progressive loss of kidney function observed in patients with CRS (in particular type 2 and type 4) is associated with anemia, altered mineral homeostasis, salt and water retention and inflammation, each of which can contribute to cardiovascular complications [103]. Among the mechanisms of progressive kidney damage and evolving functional cardiac impairment, altered calcium and phosphate metabolism plays a pivotal role. In the setting of CRS type 4, progression of renal damage is associated with a reduced activation of vitamin D in the kidney and a diminished ability of the body to excrete phosphorus [104]. Consequent hypocalcemia and hyperphosphatemia stimulate the secretion of parathyroid hormone (PTH), which increases bone absorption, renal absorption of calcium and vitamin D synthesis [105]. Moreover, elevated phosphorus levels induce the synthesis of fibroblast growth factor 23 (FGF23) in the bone, responsible for increased renal phosphorus excretion and decreased vitamin D production [106]. Progressive loss of renal function and decreased production of vitamin D exacerbated by elevated concentrations of FGF23 impair kidney ability to regulate PTH secretion. Patients may develop enlarged parathyroid glands that are no longer responsive to regulatory signals, such as vitamin D receptor activation and elevated serum calcium levels, thus requiring surgical removal [107]. Disorders of calcium homeostasis are correlated with increased rates of cardiovascular events and mortality [108]. Indeed, mineral and bone disorder associated with CKD is characterized by changes in bone characteristics (turnover, volume and strength) and changes in mineral homeostasis (imbalances in calcium, phosphorus, vitamin D and PTH), which may contribute to vascular calcification and cardiac impairment. Indeed, the decrease in vitamin D production will stimulate the RAAS, resulting in vasoconstriction and salt and water retention, which will further promote arterial stiffening [109]. Furthermore, a strong association between vitamin D deficiency and CVD is reported in the general population [110]. Among the cardiovascular effects of reduced vitamin D receptors activation: smooth muscle cell calcification, proliferation and fibrosis which lead to arterial stiffness, atherosclerosis and left ventricular hypertrophy [111].

In conclusion, controlled clinical studies with drugs investigating these new mechanisms involved in CRS patients remain at a preliminary stage, however, results from ongoing studies will undoubtedly improve future therapeutic approaches for these patients.

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Methods to Assess Intra- and Extravascular Volume Status in Heart Failure Patients

15

Maria Rosa Costanzo

Abbreviations

BIG	Bioimpedance Cardiography in Advanced Heart Failure
BIVA	Bioelectrical Impedance Vector Analysis
BMI	Body mass index
BNP	B-type natriuretic peptide
BV	Blood volume
BVA	Blood volume analysis
CCU	Coronary care unit
CM	Cell membrane capacity
CMS	Center for Medicare and Medicaid Services
CO	Cardiac output
CRT	Cardiac resynchronization therapy
CVP	Central venous pressure
ECF	Extracellular fluid
ED	Emergency Department
ELW	Extravascular lung water
ESCAPE	Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness
FDA	Food and Drug Administration
HD	Hemodialysis
HF	Heart failure
HFpEF	Heart failure and preserved ejection fraction
HFrEF	Heart failure and reduced ejection fraction
HSA	Human serum albumin
I	Current
ICF	Intracellular fluid
ICG	Impedance cardiography
IVC	Inferior vena cava
kHz	Kilo-Hertz
KIM-1	Kidney injury molecule-1
LAP	Left arterial pressure
LUS	Lung ultrasound
LVEF	Left ventricular ejection fracture
NGAL	Neutrophil gelatinase associated lipocalin
NT-proBNP	N Terminal pro B type natriuretic peptide
PA	Phase angle
PAP	Pulmonary artery pressure
PCO2 RB	Partial carbon dioxide rebreathing
PCWP	Pulmonary capillary wedge pressure
PD	Peritoneal dialysis
PIVA	Peripheral intravenous volume analysis
PLR	Passive leg raising
PV	Plasma volume
PWTT	Pulse wave transit time
R	Resistance

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RAAT	Radial artery applanation tonometry
RCV	Red blood cells volume
sCr	Serum creatinine
SV	Stroke volume
TBV	Total body volume
TBW	Total body water
TCF	Thoracic fluid content
UF	Ultrafiltration
V	Voltage
VCM	Volume clamp method
Xc	Reactance
μA	Milliampere

15.1 Introduction

Increased body fluid volume portends poorer outcomes in both acute and chronic heart failure (HF). Inadequate decongestion, defined as absence of hemoconcentration or increases in serum creatinine (sCr), is consistently associated with higher rates of HF hospitalizations and cardiovascular mortality [1–3]. Among aggressively diuresed patients, the best outcomes occur in individuals with increased sCr, Cystatin C and even with modest elevation of biomarkers of renal tubular injury [4]. Therefore, fluid overload is a greater evil than mild renal tubular injury and effective decongestion is essential for the protection of the kidney in the long term [3–7]. Withdrawal of diuretic agents in stable HF patients was associated with increased urinary levels of kidney injury molecule-1 (KIM-1), which returned to baseline with resumption of diuretic agents. Thus, in chronic HF, even subclinical fluid overload can be associated with biological evidence of tubular dysfunction [8]. Measure of blood volume with iodine-125 albumin injection demonstrated that clinically unrecognized hypervolemia is common in non-edematous HF patients and associated with increased cardiac filling pressures and worse patient outcomes [9]. Abnormal fluid handling leads to physiological abnormalities in multiple organ systems. Increased myocardial water can lead to ischemia and decreased contractility in animals and humans [10–12]. Deranged hemodynamics, neurohormonal activation, excessive tubular sodium reabsorption, inflammation, oxidative stress, and nephrotoxic medications are important drivers of harmful cardiorenal interactions in HF patients [10–13]. Elevation of central venous pressure (CVP) is rapidly transmitted to the renal veins, causing increased interstitial and tubular hydrostatic pressure, which decreases net glomerular filtration [14–20]. An increased CVP is independently associated with renal dysfunction and unfavorable outcomes in both acute and chronic HF [18–20]. Venous congestion itself can produce endothelial activation, up-regulation of inflammatory cytokines, hepatic dysfunction, and intestinal villi ischemia. Bacterial endotoxins can then enter the circulation, magnifying the inflammatory milieu created by venous congestion and neurohormonal activity [21].

In patients with renal disease, volume overload is associated with impaired oxygenation, end-organ damage, prolonged hospital stays, morbidity, and mortality. Fluid overload in patients with renal disease manifests itself as left ventricular hypertrophy, hypertension, fluid shift into the third space, and increased arterial stiffness. Furthermore, among 350,000 patients with end-stage renal disease, about 280,000 acute episodes per year were due to fluid overload [22]. Despite unequivocal evidence that excess body fluid volume is detrimental in acute and chronic HF and in renal disease, available means to identify and quantify abnormal fluid volume, monitor changes during decongestive therapies and determine when an optimal fluid volume has been achieved are poorly understood [22]. In addition, ideal methods to assess extracellular (ECF) and intracellular fluid (ICF) status remain elusive. These knowledge gaps lead to unacceptably poor HF outcomes, as underscored by the results of many acute HF trials in which, regardless of decongestive therapy, only a small minority of patients achieve optimal volume status [23, 24]. The objectives of this Chapter are to describe methods for the assessment of ECF and ICF fluid volume status, compare their relative advantages and limitations and propose research priorities in this area.

15.2 Pathophysiology of Fluid Overload in Heart Failure

In chronic HF renal retention of sodium and water results in intravascular and interstitial fluid volume expansion and redistribution. The kidney responds early to an absolute or relative decrease in cardiac output (CO) which results in arterial underfilling and consequent reduction in effective circulating blood volume (BV) [25, 26]. The consequently altered baroreceptor activity produces neurohormonal activation which further enhances renal sodium and water retention. Although sympathetic-driven vasoconstriction initially maintains organ perfusion, concomitant gradual accumulation of fluid in the interstitial compartment produces a compensatory expansion of plasma volume (PV) which maintains enlargement of intravascular volume over time (Fig. 15.1). Given that only 30–40% of total BV normally resides in the arterial circulation, and even less with systolic dysfunction, an increasingly large volume expansion must occur to maintain adequate tissue perfusion [25–27]. This initially compensatory mechanism becomes maladaptive and results in volume overload and organ congestion. Abnormally increased BV leads to increased cardiac filling pressures and later to the clinical manifestations of congestion. Depending on the volume capacity of the interstitial compartment, several liters of fluid have already accumulated before any signs and symptoms of congestion occur. Because diuretics only partially lower this fluid excess, a vicious circle is

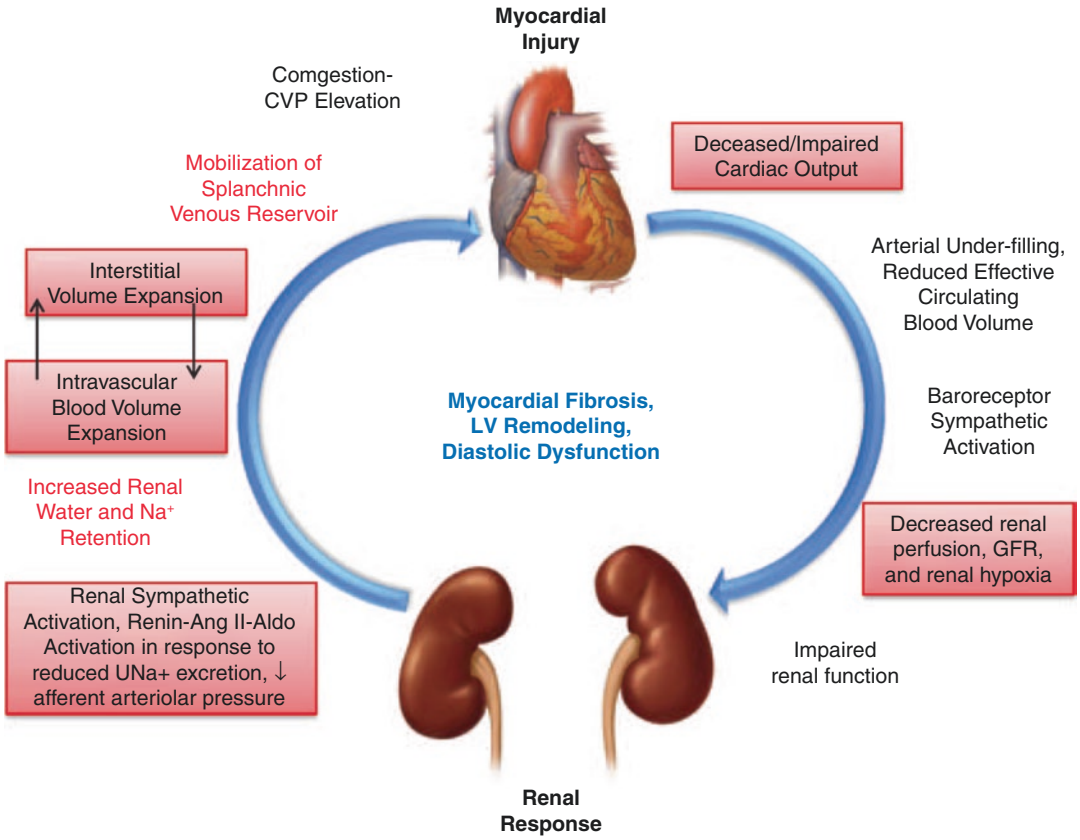


Fig. 15.1 Cardio-renal interactions in volume expansion and congestion in chronic heart failure. *CVP* central venous pressure, *GFR* glomerular filtration rate, *LV* left ventricle, Na^+ sodium, Una^+ urinary sodium. (Reproduced, with permission from [25])

established where an incomplete response to treatment is followed by gradual re-accumulation and redistribution of fluid, which in turn leads to recurrent HF decompensation [28–30]. Numerous studies have consistently shown that patients hospitalized for acute HF are at higher risk for subsequent readmissions due to recurrent HF decompensation [1, 5, 6].

Use of indicator–dilution techniques in untreated symptomatic HF patients with systolic dysfunction demonstrated that the volumes of the interstitial and intravascular compartments expanded proportionately (33–35% above normal volumes). Under normal conditions fluid retention expands PV because the interstitium has a low compliance. In contrast, in chronic HF the interstitial compartment becomes more compliant, and it is therefore able to accommodate a greater amount of excess fluid volume which persists beyond resolution of clinical congestion [9, 30, 31]. In addition, the lower capillary hydrostatic pressure, due to reduced effective circulating BV and systemic blood pressure, facilitates movement of fluid across the capillary wall from the interstitial space into the intravascular compartment. Conversely, abnormal capillary endothelial permeability coupled with reduced plasma oncotic pressure from loss of albumin promotes shift of fluid from the intravascular to the interstitial compartment. The increased tissue pressure due to net accumulation of interstitial fluid produces further PV expansion, which, in turn, promotes clinical congestion through elevation of cardiac filling pressures [26, 30]. When the ratio of interstitial volume to PV exceeds by several folds the normal 3–4: 1, response to diuretics becomes inadequate, setting the stage for the development of refractory volume overload over time (Fig. 15.2). This can precipitate acutely decompensated HF when heightened sympathetic activity triggers the shift of as much as 1 L of venous fluid from the splanchnic reservoir into the central cardio-pulmonary circulation [28, 31–35]. The ability to quantitatively assess and serially monitor total BV in the early stages of HF may permit to institute decongestive therapies before potentially nonreversible interstitial and intravascular volume expansion occurs. Importantly, red blood cell volume (RCV) can contribute to volume overload in addition to PV expansion. In hospitalized HF patients RCV is highly variable. However, the occurrence of RCV polycythemia remains poorly recognized because it can present with a low hemoglobin or hematocrit levels due to dilution in an expanded PV. In chronic HF, increased RCV is a physiologic response to low CO, tissue hypoxia, impaired oxygen exchange, and acidosis. When RBC poly-

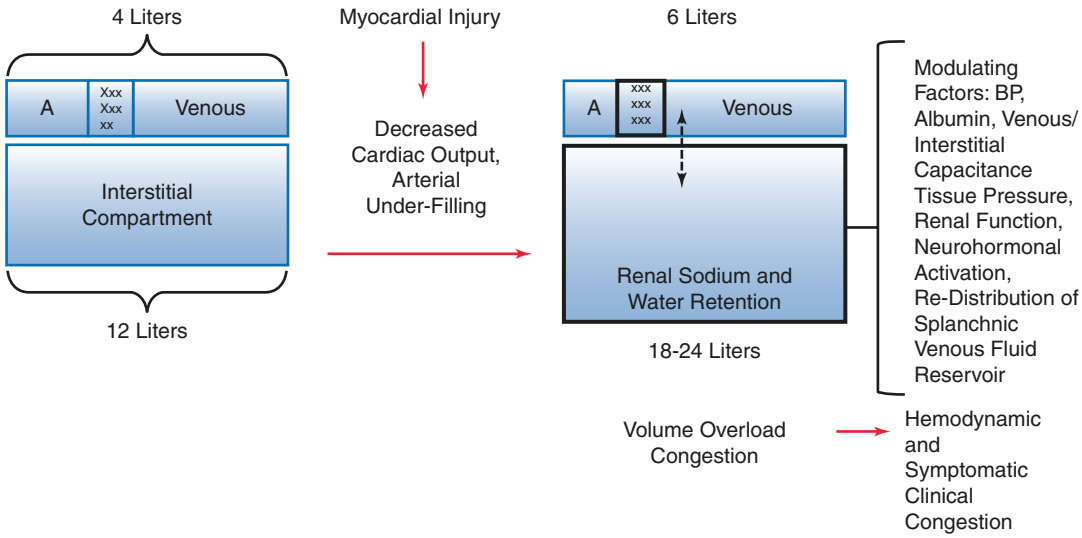


Fig. 15.2 Paradigm of interstitial and intravascular volume expansion in chronic heart failure. *BP* blood pressure, *CO* cardiac output. (Reproduced, with permission from [25])

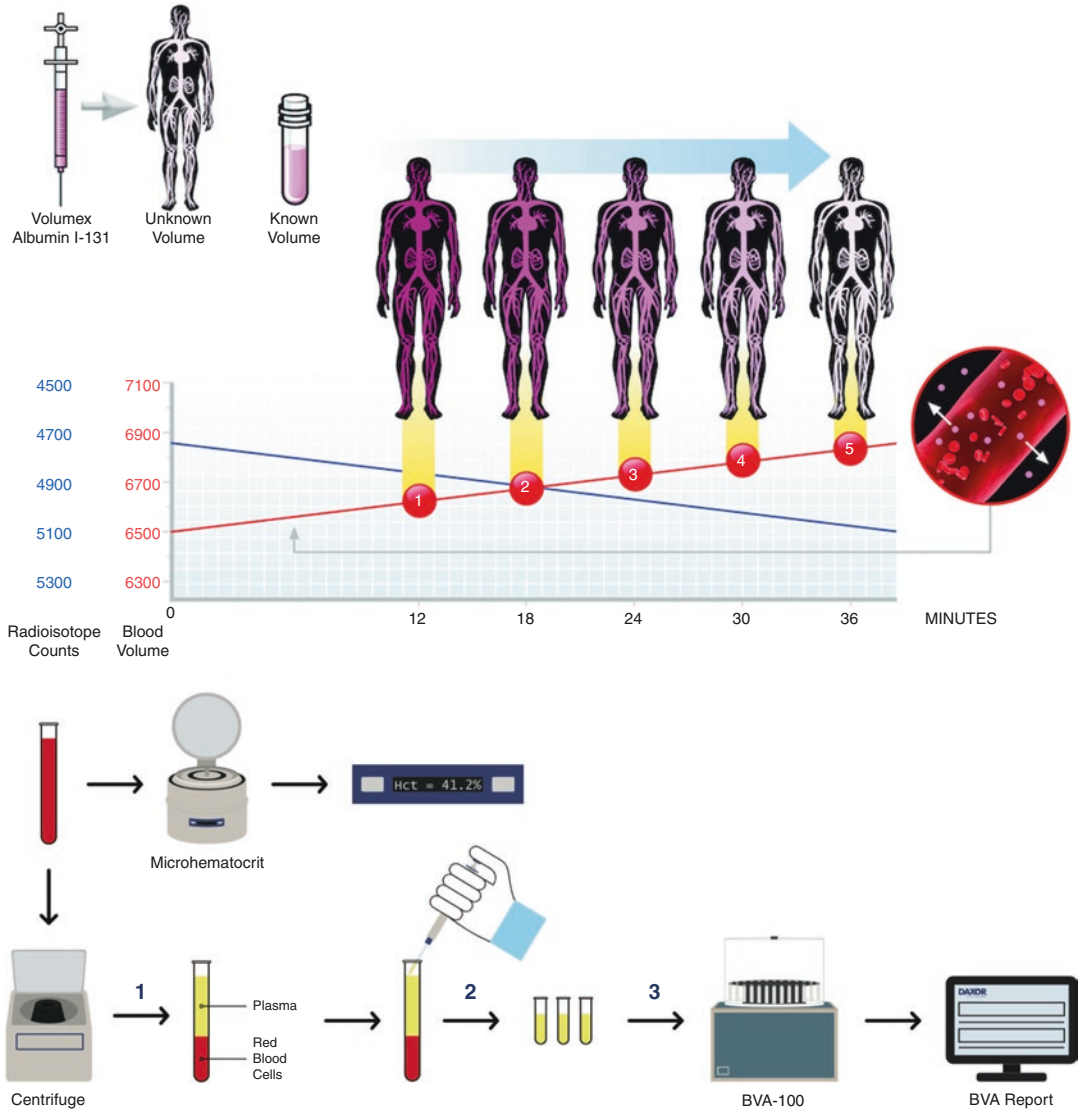
cythemia is present, diuretics may potentially contribute to higher thrombotic risk and myocardial work due to increased blood viscosity [36–38]. These facts underscore the need for accurate quantitative measurement of both RCV and PV. With PV expansion, accurate differentiation of true anemia from dilution-related anemia or identification of RVC polycythemia becomes increasingly more difficult with the sole measurement of peripheral hemoglobin or hematocrit [9, 39–42]. Precise quantitation of both RCV and PV is vital to the individualization of therapy of congested HF patients.

15.3 Blood Volume Measurement and the Indicator Dilution Principle

The indicator dilution technique permits to measure an unknown volume when a known volume of a known concentration of a tracer is added to an unknown volume of fluid [43].

After complete mixing, the concentration of the tracer is measured in a sample taken from the unknown volume. The size of the unknown volume is inversely proportional to the concentration of the tracer in the sample because the latter becomes progressively more diluted as the size of the unknown volume increases. This can then be calculated using the equation C1V1 = C2V2, where C1 is the concentration of tracer injected, V1 is the volume of tracer injected, C2 is the concentration of the tracer in a sample from the unknown volume, and V2 is the unknown volume. Nuclear medicine techniques can accurately measure a radioisotope tracer concentrations in fluid samples using the indicator dilution technique, which allows assessment of PV with human serum albumin (HSA) tagged with ^{131}Iodine or ^{125}Iodine and RCV with 51Cr-sodium chromate-labeled red blood cells. For either technique, a standard is prepared with a known quantity of tagged cells or albumin in a known volume. An identical specimen is injected intravenously, and blood samples are withdrawn once complete mixing of the tracer has occurred. Blood samples' radioactivity is compared with that of the standard to calculate the unknown volume. Although the dual-isotope/dual-tracer technique provides accurate results, it has been largely relegated to research settings due to its complexity and duration (4–6 h) [43].

Technological advances in nuclear medicine have permitted the development of a method, approved by the Food and Drug Administration (FDA) in 1998, that can provide BV results in ≤90 min (BVA-100 blood volume analyzer; Daxor Corporation Inc. New York, NY) (Fig. 15.3). Direct comparison with the double labeling techniques has shown equivalence of the two methods. However, the patient's BV status must be considered in the context of clinical status, comorbid conditions, hemodynamic values and medications, such as diuretics or vasoactive drugs, which may directly or indirectly affect volume status. In the absence of bleeding, transfusion or administration of erythropoietin peripheral hematocrit reflects a stable RCV and can be used to track changes in the patient's BV for some time after an initial BVA. Hematocrit sensors are available for continuous estimation of BV changes during decongestive therapies and can be programmed to stop fluid removal if the hematocrit exceeds a threshold set by the clinician (e.g., 5–7%) and resume therapy when the hematocrit value falls below the pre-specified limit, indicating an adequate refilling of the intravascular volume from the interstitial space [44–46]. With a changing RCV a follow-up BVA is required to assess changes in volume status. Multiple studies have confirmed the ability of the BVA-100 to assess BV and determine the causes of its abnormalities [40, 47–49]. By BVA, 43/65 non-edematous ambulatory HF patients (65%) were found to hypervolemic (mean deviation from normal values +30 ± 3%) [9]. Compared with BVA findings, the clinical assessment was correct only 51% of the time. Increased BV was associated with increased pulmonary capillary wedge pressure ($p = 0.01$) and higher risk of death or urgent cardiac transplantation over a median follow-up of 719 days (1-year event rate 39% vs. 0%, $p < 0.01$) [9]. Thus, clinically unrecognized hypervolemia is common in non-edematous HF patients and portends greater hemodynamic derangement and



poorer outcomes. Upon admission for acutely decompensated HF, 24/26 patients (92%) were hypervolemic by BVA [total blood volume (TBV) = 7.4 ± 1.6 L, increased by +39 ± 22% (range, +9.5% to +107%) above the expected normal BV]. With diuresis, TBV decreased marginally (+30 ± 16%) despite a decline in body weight by 6.9 ± 5.2 kg, and net fluid loss of 8.4 ± 5.2 L. Interstitial compartment fluid loss, calculated to be 6.2 ± 4.0 L, accounted for 85 ± 15% of the total fluid reduction [29]. These results suggest that diuretics mobilized interstitial fluid to the intravascular compartment, which remained abnormally expanded. The highly variable degree, composition, and distribution of volume overload observed in the study population underscores the importance of individualized therapy. Such tailored treatment may be facilitated by the serial quantitation of fluid overload with BVA [29]. Propensity-score control matching analysis by demographics, comorbidity, and time of treatment was performed in 245 consecutive HF admissions undergoing BVA and controls derived from the Center for Medicare and Medicaid (CMS) data and matched 10:1 for demographics, comorbidity and year of treatment.

Fig. 15.3 The BVA-100 consists of an automated well counter interfaced with a computer. The injectate is a precise amount of ^{131}Iodine-labeled HSA (10–30 mCi) in saline contained in a patented volumetric flow chamber that ensures complete dose delivery. The hematocrit is then used to calculate the RCV and TBV. The system uses volume data from five sample points and each sample is counted in duplicate. In addition, the results are corrected for mean body hematocrit, trapped plasma, and albumin transudation. The BVA-100 automatically compares each patient's results with his/her predicted normal values based on deviation from ideal weight. After measurement of patient's height and weight, a control blood sample is obtained in the supine position. The injectate is then administered and blood sampling begins after the 12 min required for mixing. Five blood samples are drawn into supplied tubes at 6-min intervals. For each sample, duplicate microhematocrit measurements are performed. Each sample is then centrifuged, and two 1-mL aliquots of plasma are placed in the BVA-100 machine with the standards and tubes for blank and background counts. Counting is performed automatically for 20–40 min, depending on the activity injected. The computer displays the data from the duplicate hematocrit measurements and the counts for the baseline, standard, and duplicate plasma samples. The computer automatically flags duplicate measurements that vary to an unacceptable degree and provides a SD measurement to assess results' validity. If, after appropriate corrections, the SD is above 3.8%, erroneous sample points are excluded. The semilogarithmic plot on the BVA-100 screen shows time of sampling on the horizontal axis and TBV in mL on the vertical axis. Each point on the graph is a separate BV volume determination. As time passes, the measured BV increases due to transudation of albumin into the interstitial space, which enlarges the volume of distribution of the tracer. The computer determines the best-fit line through the five points and then determines the true BV by extrapolating the line back to time 0. In patients with reduced cardiac output, complete mixing may take up to 20 min. Therefore, in prematurely drawn samples, the tracer's concentration will be erroneously high, and the measured BV mistakenly low. In addition, a patient with a high SD and only a borderline red blood cell deficit may have either a normal RCV or true anemia. To facilitate this distinction, the SD is presented both as a percentage and in milliliters, allowing direct comparison of the absolute amount of the patient's BV abnormality and the magnitude of the SD. If the measured volume abnormality is much greater than the SD, then the abnormality is likely true. If the volume abnormality is close to the SD, the study is equivocal. Therefore, BVA provides TBV, RCV and PV expressed in mL and as percentage deviation from the predicted normal values, normalized hematocrit and the slope of the line. The percentage deviation from normal is considered first to determine whether BV is normal, depleted, or expanded. The PV is examined in relation to RCV and TBV. Because body's homeostasis aims to maintain a normal TBV, even when RCV is depleted or expanded, PV is abnormal only when it fails to maintain a normal TBV. Expansion of PV associated with increased TBV is partly compensatory and partly pathologic. With an increased RCV, PV expansion is entirely pathologic. *BV* blood volume, *BVA* blood volume analysis, *HAS* human serum albumin, *min* minute, *PV* plasma volume, *RCV* red blood cells volume, *SD* standard deviation, *TBV* total blood volume

Decongestion strategy targeted TBV to 6–8% above patient-specific norm [50]. Of the study patients, 37% had >10% TBV excess and hypervolemia had a similar distribution in patients with reduced (HFrEF) versus those with preserved ejection fraction (HFpEF). True anemia (RCV ≥10% deficit) was present in 62% of subjects. Compared to controls, subjects receiving BVA-guided therapy experienced lower 30-day readmissions (12.2% vs. 27.7%, $P < 0.001$), 30-day mortality (2.0% vs. 11.1%, $P < 0.001$), and 1-year mortality (4.9% vs. 35.5%, $P < 0.001$) rates [50]. This analysis has the inevitable limitations of a retrospective, non-randomized study and lacks precise treatment algorithms which may have helped to place the findings in context. However, the premise that more objective assessments of volume status can better guide our clinical decisions in acutely decompensated HF is sound and impressive. Clearly these findings require independent validation with a randomized controlled trial. Greater adoption of BVA requires the demonstration of incremental benefit of BVA-guided treatment of acutely decompensated HF and a favorable cost-benefit analysis.

15.4 Bio-electrical Impedance Analysis Methods

To understand bio-electrical impedance analysis, the human body can be viewed as a conducting cylinder whose composition is shown in Fig. 15.4 [51]. Both ICF and ECF are ionic solutions and therefore good conductors of electricity (low impedance to the passage of an alternating current). The protein-

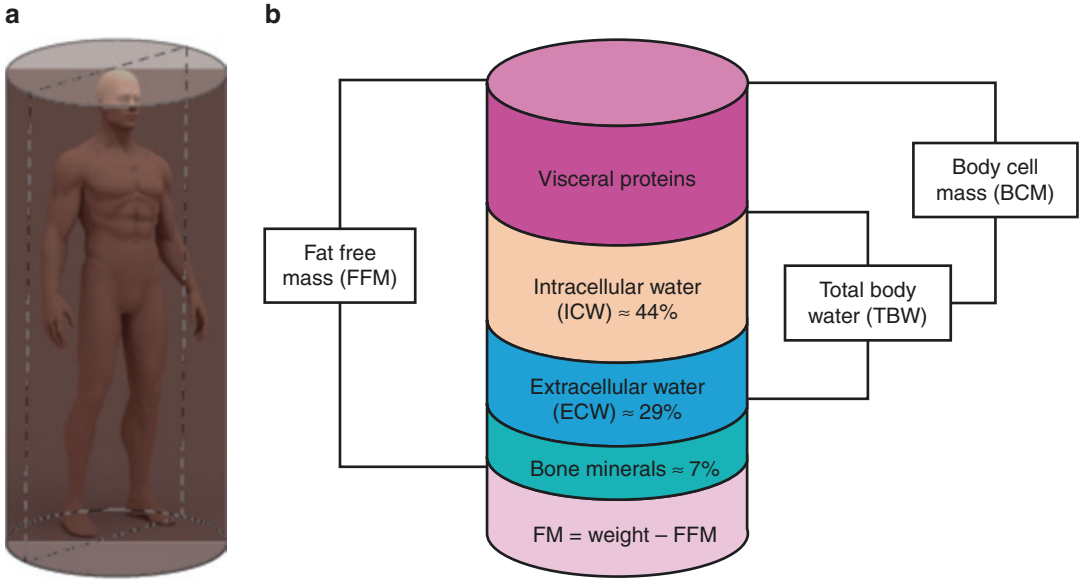


Fig. 15.4 Human body as a conducting cylinder and its body composition: (**a**) human body assumed as a conducting cylinder in BIA, (**b**) body composition schematic diagram of fat-free mass (FFM), total body water (TBW), intracellular water (ICW), extracellular water (ECW), and body cell mass (BCM). (Reproduced, with permission from: Kyle UG, Bosaeus I, De Lorenzo AD et al., Bioelectrical impedance analysis-part I: review of principles and methods. Clinical Nutrition, 2004; 23: 1430–43)

lipid-protein layers of the cell membranes function as capacitors. Bone and adipose tissue act as resistors (high impedance to the passage of an alternating current). Therefore, living soft tissues form a complex network of resistive and capacitive conductors arranged in parallel and in series. When an alternating current is applied to a living organism, the bioelectrical impedance depends upon tissue composition and the current's frequency. When electrodes are placed on living tissue, some (driving electrode) deliver the alternating current while others (sensing electrodes) are used to measure the voltage according to Ohm's Law:

$$V = (R + Xc)I$$

where V is the voltage, I is the current, and R + Xc is the complex impedance consisting of resistance (R), the opposition of the tissue to the passage of the current and reactance (Xc), which accounts for the movement of electrons determined by the characteristics of the tissue where they reside [51]. In the human body the driving and sensing electrodes can be placed in multiple configurations (far apart from each other to measure whole body impedance, or closer to each other to measure impedance of a body's segment). The alternating current can be applied at single (typically 50 kHz), dual (50 and 200 kHz) or multiple frequencies (5–1000 kHz). Single frequency bio-electrical impedance analysis (BIA) permits the calculation of TBW, whereas dual frequency BIA, with the application of predictive equations, can calculate ECF (50 kHz) and TBW (200 kHz). Because an alternating current ≤50 kHz cannot pass through cell membranes, higher frequencies are required to measure TBW. The ICF is then calculated as the difference between TBW and ECF [51].

15.4.1 Bio-electrical Impedance Vector Analysis

A plot can be created with R in the horizontal axis and X on the vertical axis. Perpendicular lines drawn from the two axes meet at various points on a line which forms the impedance vector. The angle between the impedance vector and the coordinates is referred to as phase angle (PA) and it is a measure

of the time delay (Δt) between the periodic signals of current and voltage, which vary sinusoidally at the same frequency according to the formula:

$$PA = \text{arc} - \text{tangent}\, Xc / R \times 180^{\circ} / \pi.$$

The PA may be an indicator of cell membrane integrity, distribution of ICF and ECF, and total cell mass [52–63]. The bio-electrical impedance vector analysis (BIVA) device (EFG Diagnostic, Belfast, UK) uses an alternating current of 800 μA with a frequency of 50 kHz. The first assessment consists of a direct impedance plot which measures R and X as a bi-variate vector in a nomogram [60]. Reference values adjusted for age, body mass index (BMI), and gender are plotted in the same coordinate system as three "tolerance ellipses", corresponding to the 50th, 75th and 95th vector percentile of the reference healthy population [61]. The major and minor axes of these ellipses represent, respectively, hydration status and tissue mass. The BIVA results can alternatively be displayed as a scale expressing hydration status as a percentage. This value is calculated by an independently determined equation that uses the two components of BIVA, R and Xc. The 75% tolerance ellipse is considered the boundary for normal tissue hydration. Vectors with large PA protruding outside the upper pole of the 75% ellipse signify dehydration, whereas vectors with a small PA and shorter than the lower pole of the 75% tolerance ellipse indicate increased fluid volume [61, 64–67]. Hydration values can be further subdivided into mild, moderate or severe [65]. While the length of the impedance vector is inversely related to fluid volume, the PA provides information on the relative distribution of fluid. In addition, vectors above or below the minor axis (i.e. upper-left or lower right half of ellipses) are associated, respectively, with greater or lesser soft tissue mass (Fig. 15.5).

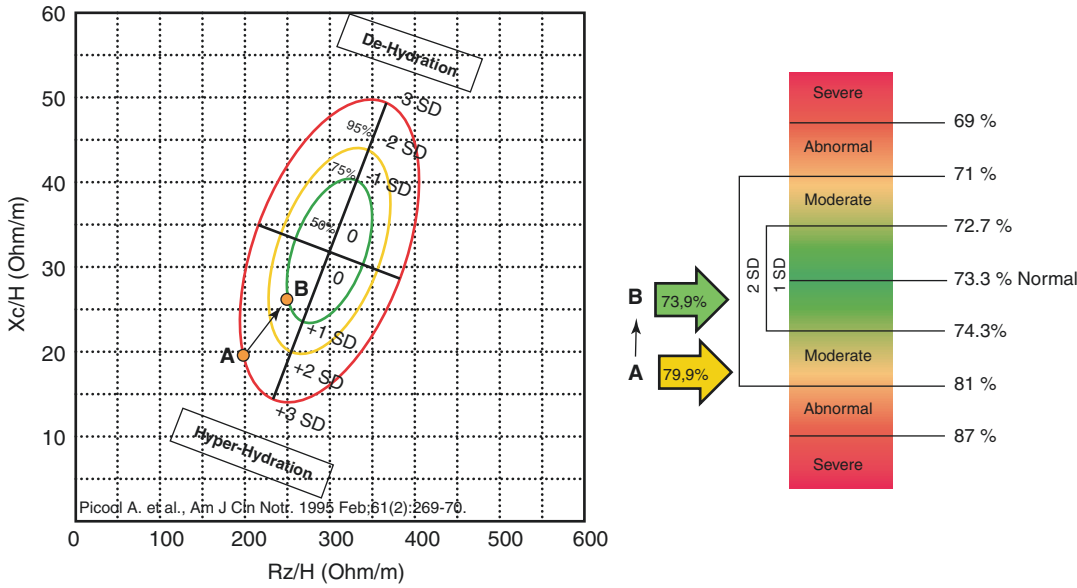


Fig. 15.5 Graphic representation of the nomogram (*left panel*) and the numerical scale (*right panel*) for BIVA. A typical example of vector migration (A to B) in response to aggressive fluid depletion therapy is reported. Corresponding values are reported in the numerical scale. Impedance (Z vector) is a combination of Resistance (R) and Reactance (Xc) across ionic solutions of soft tissues, tissue interfaces and cell membranes. Impedance at 50 kHz is represented with a complex number (a point) in the real-imaginary plane (Z vector), that is a combination of R (i.e. the opposition to flow of an alternating current through intra- and extra cellular ionic solutions, representing the real part of Z) and Xc (i.e. the capacitative component of tissue interfaces, and cell membranes and organelles, representing the imaginary part of Z). The volume of intra and extra cellular ionic solutions is (inversely) related to the R component of Z. The amount of soft tissue structures containing the solutions is (directly) related to the Xc component of Z. The arc tangent (Xc/R) is called the phase angle (Xc on the ordinate and R on the abscissa axis). *BIVA* bioelectrical impedance vector analysis

The BIVA technique is simple, can be performed at the bedside, with the patient supine on a non-conductive surface with lower extremities at 45° and upper extremities abducted at 30° to avoid skin contact with the trunk [57]. Four skin electrodes are applied, two on the wrist and two on the ipsilateral ankle. A minimal inter-electrode distance of 5 cm avoids interaction between electrodes [66]. Several studies in hemodialysis (HD) and peritoneal dialysis (PD) patients have shown that hydration vectors lengthen and the PA increases after fluid removal by ultrafiltration (UF). In addition, changes in the volume of removed fluid are significantly correlated with changes in vector components (R and Xc) both in men ($p < 0.001$) and women ($P = 0.03$) [60, 61, 65]. Assessment of fluid status by BIVA has also been done in intensive care, emergency department (ED) and other hospital settings. Concomitant evaluation of BIVA and CVP in 121 coronary care unit (CCU) patients, showed that while 93% of patients with CVP values between 13 and 20 mmHg had short BIVA vectors (indicative of overhydration), 35% of patients with CVP between 4 and 12 mmHg had normal vector length and only 10% of patients with CVP between 0 and 3 mmHg had a vector length consistent with dehydration [68]. These findings suggest that, while BIVA can identify patients with significantly elevated CVP, it cannot reliably assess fluid status in patients with CVP ≤ 12 mmHg [68]. At presentation to the ED, compared to 26 patients without cardiogenic dyspnea, 25 patients with acutely decompensated HF had higher BIVA hydration values ($p < 0.0007$), which decreased progressively in response to diuretics (76.7 ± 4.0% versus 74.4 ± 2.0%; $p < 0.0001$). Patients with baseline hydration values >80% were at higher risk of death or rehospitalization at 30 days than subjects with lower hydration values [67]. Although some correlation existed between hydration values and BNP levels, inferior vena cava collapsibility index (IVCCI) and vascular pedicle width, the data is inadequate to determine if the combined use of these values is superior to each measure alone. Among 300 patients with elevated BNP levels receiving decongestive therapy aimed at reducing BNP to ≤250 pg/mL at discharge, 72% of those who failed to achieve the target biomarker level had BIVA levels consistent with normal hydration [69]. Thus, when used together with BNP levels, BIVA may help reduce complications related to over-diuresis in patients whose BNP remains above target values due to severity of illness or concomitant chronic kidney disease [69, 70]. However, the value of BIVA relative to or combined with other measures of fluid status must be confirmed in larger prospective studies with well-defined patient populations and end-points.

15.4.2 Impedance Cardiography

Impedance cardiography (ICG) is a technology that uses changes in transthoracic impedance to calculate alterations in thoracic fluid content (TFC). Using various electrodes configurations, a small amplitude, low frequency alternating current is delivered by driving electrodes. The voltage in the sensing electrodes is measured and the average transthoracic impedance (Zo), and the small blood flow-related impedance change (ΔZ) are calculated and monitored over time. Validated formulae permit the calculation of stroke volume (SV) with the knowledge of Zo, dZ/dt and ΔZ. The CO can then be estimated as the product of SV and heart rate [51].

The ICG procedure is non-invasive, cheap, fast, portable and safe. Unfortunately, the correlation between ICG-derived variables and invasive hemodynamic measurements in hospitalized HF patients observed in early investigations was not confirmed in later studies [51, 71]. In BioImpedance CardioGraphy in Advanced Heart Failure (BIG), a prospective sub study of ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness), of 170 subjects undergoing blinded ICG measurements with BioZ (CardioDynamics, San Diego, CA), 82 also had right heart catheterization. The correlation between ICG and invasively measured CO was modest ($r = 0.4–0.6$), ICG-derived TFC was not correlated with PCWP and no ICG variable alone

or in combination was associated with 6-month hospitalization or death [71].

A newer device manufactured by RSMM Ltd. (Tel Aviv, Israel), capable of providing net lung impedance, was used in a single-blind 2-center trial (NCT01315223) where 256 HF patients with LVEF ≤35%, NYHA class II to IV and a HF hospitalization within 12 months were randomized to a control group receiving only clinical assessment or to a monitored group with lung impedance-guided therapy [72]. Measurements occurred monthly or more frequently if therapy was adjusted. All patients underwent bioimpedance measurements, but results were available to the treating physicians only for the active group. Adjustments in medications were standardized to ensure consistent responses to bioimpedance values. Over a mean follow up of 48 months net lung impedance typically decreased 3 weeks pre-hospitalization. Compared to controls, the monitored group had fewer hospitalizations and (rate per patient-year follow-up: 1.03 vs. 1.68, hazard ratio [HR] 0.66, 95% confidence interval [CI] 0.59–0.74, $P < 0.001$) and deaths (HR 0.52, 95% confidence interval 0.35–0.78, $P = 0.002$) [72]. Enthusiasm for these favorable results is tempered by the possible influence of treatment assignment on hospitalizations, lack of independent adjudication of events and a surprisingly high event rate (0.94/patient-year) in a population where 50% of subjects had NYHA Class II symptoms [73].

15.4.3 Bioimpedance Spectroscopy

Bioimpedance spectroscopy (BIS) harnesses impedance data measured over an entire spectrum of frequencies (5–1000 kHz.) [74]. The software in BIS devices is programmed to perform biophysical modeling on the impedance data, which generates the resistance associated with ECF (Re), the resistance associated with ICF (Ri), and cell membrane capacitance (C_m). After independent calculation of ECF and ICF, TBW is calculated as their sum. Compared to other BIA approaches, BIS relies less on assumptions that may be violated in disease states, such as those that fat-free mass is 73% hydrated and that ICF and ECF are normally distributed [75–77]. Furthermore, the frequency at which cell membrane capacitance is maximal (f_c) varies with clinical conditions, ranging from 30–60 kHz in normal individuals to 200 kHz in HD patients and 500 kHz in diarrheal diseases [77–80]. The ability of BIS to assess body composition and fluid compartments has been validated by comparison with the multiple dilution method in various clinical settings, including critically ill post-surgical and HD patients [74–78]. Currently only very limited data exist on the use of BIS to measure fluid volumes in HF patients. An observational study of 150 consecutive HF patients using the BCM®Body Composition Monitor (Fresenius Medical Care, Australia) was aimed at cross-sectionally compare BIS parameters with clinical evaluation, lung ultrasound, cardiac biomarkers, and echocardiographic characteristics. Two-year patients' outcomes were to be assessed to identify the best evaluative algorithm and rank the prognostic significance of the various methods (NCT02764073). Currently the study is listed on the clinicaltrials.gov website as "non-recruiting". Another single center observational study (NCT02857231) using the SOZO™ unit (ImpediMed, Qld, Australia) is enrolling 10 NYHA class III HF patients implanted with the CardioMEMS HF System (Abbott, *Abbott* Park, IL, USA) to evaluate the relationship between pulmonary artery pressure (PAP) and BIS measurements. A similar two-center study (NCT02939053) aims to establish in 30 HF patients the degree to which change in the ratio of ECF to TBW, measured using the same BIS device, correlates with change in end-diastolic PAP measured by the CardioMEMS HF. Both studies have a 30-day follow up time and anticipated completion in 2019.

15.4.4 Bioreactance

Bioreactance, which measures phase shifts of the electrical currents traversing the thorax may have a higher signal to noise ratio than BIA methods and therefore may provide a more accurate estimation of hemodynamic variables. Preliminary investigations suggest that the bioreactance method can dis-

criminate between cardiac and non-cardiac causes of acute dyspnea assess the efficacy of UF during hemodialysis and predict fluid responsiveness in spontaneously breathing patients with the passive leg raising (PLR) maneuver [81–83]. This is akin to an internal fluid challenge by mobilizing blood from the lower extremities to the right heart [84]. Patients experiencing a significant rise in SV with PLR have moved from the plateau to the steep portion of the Franck-Starling relationship and are likely to benefit from fluid administration [85]. Similarly, a shift in the same direction in patients receiving decongestive therapies may suggest that fluid removal should be reduced or stopped. Assessment of fluid responsiveness may be useful to predict hemodynamic deterioration in critically ill patients undergoing HD [85]. Notably, the PLR maneuver may not be well tolerated in acutely ill HF patients with orthopnea or major peripheral edema (Fig. 15.6).

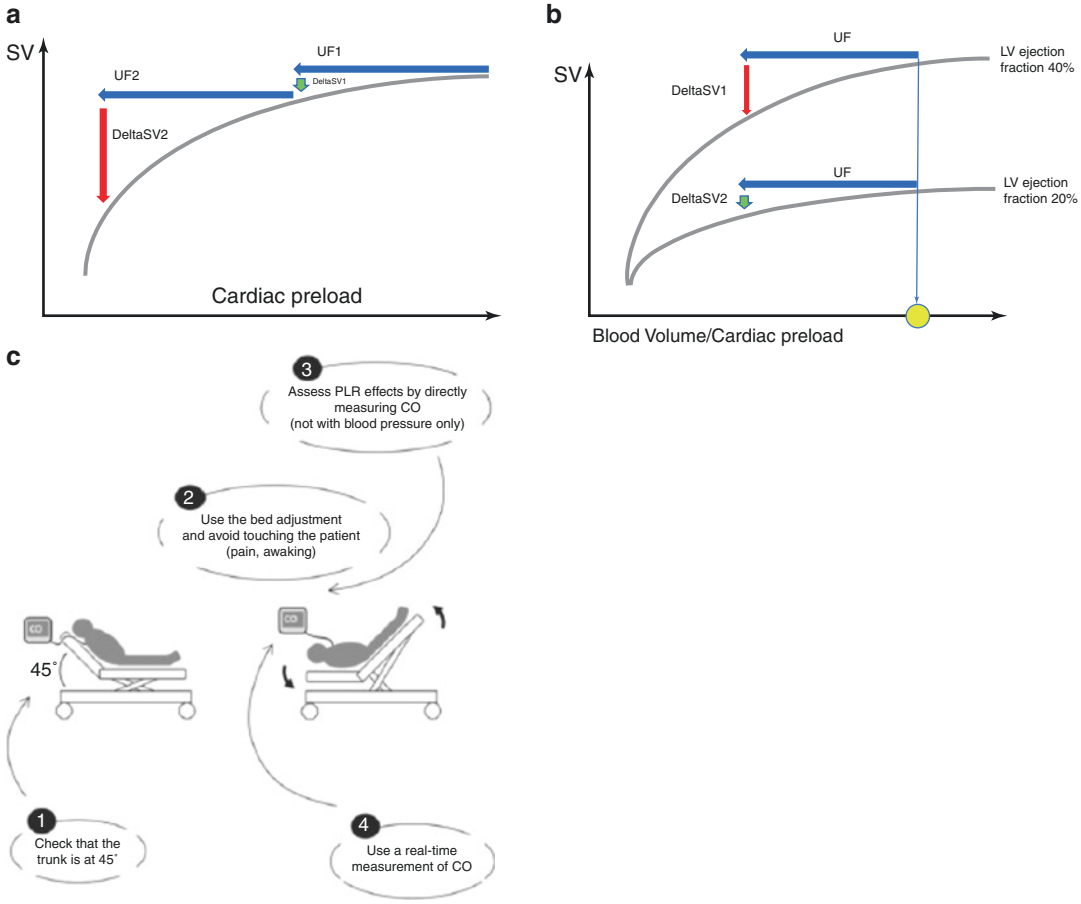


Fig. 15.6 (**a**) Franck-Starling relationship between cardiac preload and stroke volume. Because of fluid overload, most HF patients operate on the plateau of the curve. Removing fluid or decreasing preload has no significant impact on SV (UF1). After diuretic therapy or UF, patients may reach the steep portion of the curve. Their SV becomes dependent on cardiac preload and additional UF (UF2) may induce hemodynamic instability. (**b**) The passive leg raising maneuver mimics the hemodynamic effects of a fluid load. This is a reversible and internal fluid challenge. Patients experiencing a significant increase in SV during the PLR maneuver are "fluid responsive". Fluid responsive patients may experience hemodynamic deterioration during fluid removal. (**c**) Preload is not preload responsiveness. Two patients having the same blood volume or the same cardiac preload (yellow dot) may respond differently to a change in blood volume/cardiac preload during fluid removal with diuretics or UF, depending on their cardiac systolic function. *PLR* passive legs raising maneuver, *SV* stroke volume, *UF* fluid removal by ultrafiltration

15.5 Other Methods for Non-invasive Hemodynamic Monitoring

In addition to bio-electrical impedance and bio-reactance approaches, other methods have recently been developed to non-invasively monitor CO and other hemodynamic variables. These include the volume clamp method (VCM) [Nexfin (BMEYE, Amsterdam, the Netherlands)], the pulse wave transit time (PWTT), (**Nihon Kohden,** Rosbach vor der Höhe, Germany), radial artery applanation tonometry (RAAT) (T-Line system; Tensys Medical, San Diego, CA, USA) and partial carbon dioxide rebreathing (PCO2 RB) (*NICO*, Dixtal Biomedica Ind. Com, São Paulo, Brazil). In a recent meta-analysis of 37 studies consisting of 1563 high risk surgical patients, compared to bolus thermodilution, the pooled estimate of percent error of commercially available, non-invasive CO measuring devices was 47%, far above the prespecified acceptable value <30% [86]. To date there are no studies comparing the accuracy of non-invasive methods against that of bolus thermodilution in patients with acutely decompensated HF or undergoing renal replacement therapies. In addition, it is unknown whether the data provided by non-invasive CO measurements are useful in the assessment of baseline volume status and its changes with fluid removal.

15.6 Less Invasive Hemodynamic Monitoring Methods

15.6.1 Cardiac Output Monitoring by Pulse Contour Analysis

These methods estimate CO based on pulse contour analysis of the arterial waveform provided by an arterial catheter. The transformation of the arterial waveform signal from a pressure measurement to CO as a volume per time parameter requires estimation of the dynamic characteristics of the arterial vasculature [87]. Of four commercially available systems, three use internal databases or nomograms based on patients' demographics, whereas the forth uses a complex calculation to derive the parameters of interest from the oscillations of the arterial waveform. Limitations of pulse contour systems include inaccurate data obtained from over- or under-dampened waveforms, abnormal systemic vascular resistances or presence of an intra-aortic balloon-pump. In addition, for both patients with acutely decompensated HF and those receiving renal replacement therapies, the risks and logistics of an additional indwelling arterial catheter must be carefully considered, especially because the ability of pulse contour analysis to infer baseline volume status and its changes with therapeutic interventions is unknown.

15.6.2 Peripheral Intravenous Volume Analysis

The peripheral intravenous volume analysis (PIVA) device consists of a sensor that analyzes peripheral venous waveforms connected in series within an indwelling line that monitors patients' venous pressures. Venous waveform analysis is performed using fast Fourier transformation and a proprietary algorithm to derive the PIVA signal that estimates volume status, pulse and respiration rates [88]. Recently PIVA was shown to accurately identify volume overload and monitor fluid removal in HD patients [88]. Compared to that of age-matched healthy controls, PIVA signal of 18 patients with acutely decompensated HF was significantly higher at admission ($p = 0.0013$) but similar at discharge. The PIVA signal, but not BNP or chest radiographic measures, accurately predicted the amount of fluid removed by diuretics ($R^2 = 0.781$). A discharge PIVA signal >0.20 was associated with a higher risk of readmission in 120 days. While encouraging, these results are preliminary and larger controlled studies are needed to determine if PIVA can be used to quantitate intravascular volume and manage treatment across a brad spectrum of disease processes such as HF, renal failure, dehydration and sepsis [88].

15.7 Hemodynamic Data from Implanted Monitors

15.7.1 Pulmonary Artery Pressure Sensors

Elevated cardiac filling pressures portend higher risk for hospitalizations and mortality [89, 90]. Regardless of left ventricular ejection fraction (LVEF), filling pressures begin to gradually increase more than 2 weeks before HF-related hospitalizations [91, 92]. In the COMPASS-HF (Chronicle Offers Management to Patients with Advanced Signs and Symptoms of Heart Failure) study, medications adjustment in response to elevated filling pressures obtained from an implanted device was associated with a trend toward fewer hospitalizations compared to clinically-guided therapy [93]. In patients with a baseline diastolic PAP > 25 mmHg the risk of HF events decreased by 50% if the pressure could be reduced below this value [92]. However, COMPASS-HF lacked definitions of which filling pressures were consistent with "optivolemia" and therapy algorithms to achieve these targets [93]. The CardioMEMS™ PAP Sensor (Fig. 15.7) was tested in the CHAMPION trial (CardioMEMS™ Heart Sensor Allows Monitoring of Pressure to

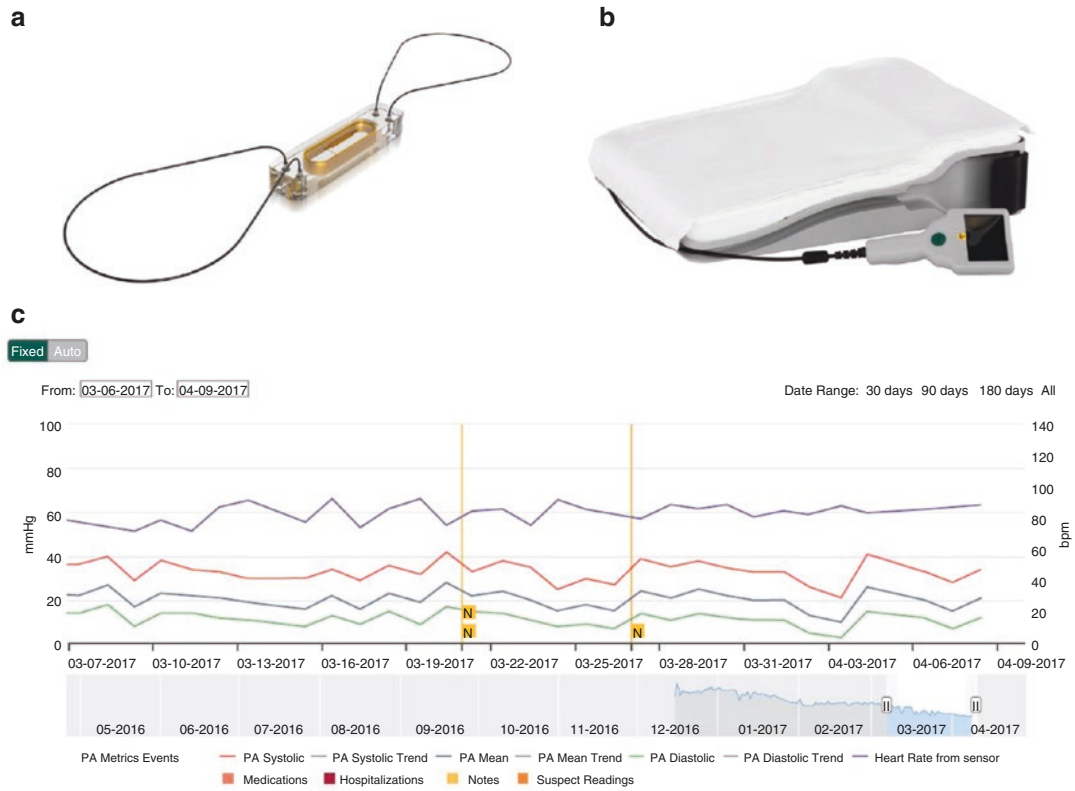


Fig. 15.7 The CardioMEMS™ PAP sensor (Abbott, Abbott Park, IL) is a coil and a pressure sensitive capacitor encased in a hermetically sealed silica capsule covered by silicone. The device has no leads or batteries. Two nitinol loops at the ends of the capsule anchor the device in the left or right pulmonary artery. The coil and capacitor form an electrical circuit that resonates at a specific frequency, and pressure applied to the sensor causes deflections of the pressure-sensitive surface, resulting in a characteristic shift in the resonant frequency (**a**). Electromagnetic coupling is achieved by an external antenna held against the patient's body. The antenna provides power to the device, continuously measuring its resonant frequency, which is then converted to a pressure waveform. An atmospheric barometer in the antenna automatically subtracts the ambient pressure from that measured from the implanted sensor (**b**). The pulmonary artery waveforms as the clinician can see through a secure website (**c**). (Reproduced, with permission from [94])

Improve Outcomes in Class III Heart Failure) [95]. Management of HF guided by PAP was associated with a 28% reduction in HF hospitalization rates after 6 months and 37% after an average follow-up of 15 months compared to clinically-based management [96]. An analysis from the CHAMPION-HF trial described in detail the pharmacological interventions that, tailored to the intracardiac hemodynamics, led to successful outcomes [97]. The pharmacological algorithm used in the CHAMPION-HF trial recommended use of sequential doses of diuretics and vasodilators to lower and maintain the PA diastolic pressure below 20 mm Hg. Importantly, the algorithm also provided guidance for de-escalation of diuretics if the filling pressures were low, to prevent hypovolemia and ensuing hypotension and renal dysfunction [97]. More than twice as many medication changes (both increases and decreases) occurred in the active monitoring group compared with the blind therapy group. Remarkably, although the average dose of diuretics from baseline to 6 months was significantly higher in the active monitoring group, the estimated glomerular filtration rate (eGFR) was similar in the 2 arms, including among patients with impaired baseline renal function (eGFR <60 mL/min/1.73 m^2). Therefore, in the CHAMPION-HF trial, the decrease in HF hospitalizations due to PAP-guided therapy did not occur at the expense of worsening renal function [97, 98]. A recent CHAMPION-HF analysis showed that PAP-guided HF management reduces also mortality in patients with HFrEF and background guideline-directed medical therapy, further highlighting the important synergy of addressing hemodynamic and neurohormonal targets of HF therapy [99]. A separate analysis of the CHAMPION-HF trial examined the impact of PAP-guided HF management in patients with LVEF ≥40%, the only prespecified subgroup of the study [100]. After an average of 17-month randomized follow-up, patients in the active monitoring group had 50% less HF events than controls (hazard ratio, 0.50; 95% confidence interval, 0.35–0.70; P < 0.0001). This is the first study to report a successful therapeutic strategy in HFpEF patients [100]. The favorable outcomes of CHAMPION-HF have been replicated in clinical practice [101, 102]. Recently, 1087 HF patients implanted with a PAP sensor between 6/2014 and 3/2016 were matched by propensity scoring to 1087 Medicare controls according to demographics, HF hospitalizations, all-cause admissions and comorbidities. Compared to controls, at 12 months post-implant, the treatment cohort had a lower risk of HF hospitalization (HR: 0.76; 95% CI (0.65–0.89), p < 0.0001) and of mortality (HR: 0.70; 95% CI (0.59–0.83), p < 0.0001) [103]. These critically important data suggests that, compared to controls, the reduction in HF hospitalizations resulting from PAP-guided therapy translates into lower mortality rates. Hopefully these results will be confirmed by the Hemodynamic-GUIDEd Management of Heart Failure (GUIDE-HF) (NCT03387813), a multicenter, prospective study which consists of a controlled, single-blind arm in which NYHA Class II-IV HF patients with either elevated NT-proBNP (or BNP) and/or a prior HF hospitalization will be randomized to either PAP sensor-guided HF therapy or standard care and of a single arm in which the outcomes of PAP sensor-guided therapy will be compared in NYHA class III HF patients enrolled on the basis of either an elevated NT-proBNP (or BNP) alone or prior HF hospitalization.

Another system like the CardioMEMS HF System (Cordella™ Heart Failure System, Endotronix, Inc., Lisle, Illinois) is being evaluated in 10 NYHA class III subjects in Ireland and Belgium (NCT03375710).

15.7.2 Left Atrial Pressure Sensors

Left atrial pressure (LAP) directly reflects LV filling pressure, the primary pressure target for HF management. Therefore, direct measurement of LAP may be a more precise target of HF therapies than right-sided pressures or PAPs. Correlations have been demonstrated in preclinical and human studies between LAP, measures of congestion and LV end-diastolic pressure when LAP is measured at the "z point," the foot of the left atrial c-wave [104]. Although both sys-

tolic and diastolic PAP are often correlated with PCWP, in patients with advanced HF, left- and right-sided filling pressures may be discordant, a finding which is associated with higher risk of poor outcomes [104–109]. Furthermore, PAP and LVEDP may be poorly correlated in acute HF and with concomitant pulmonary hypertension which can be present in 25–83% of HF patients [110]. Specifically, it is essential to know the gradient between diastolic PAP and mean PCWP, because this value reflects more changes in compliance and distensibility of the pulmonary arteries than increased filling pressures from fluid overload. The HeartPOD (Abbott, Sylmar, CA), a system for the direct measurement of LAP in ambulatory HF patients, consists of a sensor lead implanted transvenously across the atrial septum, a subcutaneous antenna coil, a patient advisory module displaying a physician-directed patient self-management plan, and remote clinician access via secure computer-based data management. The implant is powered and interrogated through the skin by wireless transmissions from the patient advisory module [111–114]. In a prospective randomized controlled study, the LAPTOP-HF (Left Atrial Pressure Monitoring to Optimize Heart Failure Therapy) trial, implanted ambulatory NYHA functional class III patients with either a previous HF hospitalization or an elevated BNP, regardless of LVEF, were randomized to either optimal medical therapy alone or LAP-guided therapy using a 1:1 ratio in 3 strata based on LVEF (>35% or ≤35%) and indication for de novo cardiac resynchronization therapy (CRT). Enrollment in the LAPTOP-HF trial was stopped early, due to a perceived excess of implant-related complications [115]. Although the overall trial was negative, when outcomes were analyzed using the endpoint of recurrent HF hospitalizations, reduction in HF events was similar in the LAPTOP-HF and CHAMPION-HF trials. This observation suggests that that LAP-guided HF therapy deserves further investigation [115]. The V-LAP system (Vectorious Medical Technologies, Tel Aviv, Israel) is a next generation LAP monitoring system which consists of a miniature (14 mm in length and 2.5 mm in diameter) percutaneous LAP sensor that is wireless, leadless, and implanted transseptally. The system includes an external wearable belt that remotely powers the implant, displays pressure readings to the patient, and transmits LAP waveform information to a web-based database. The data can be analyzed with next-generation decision-support software to extract patient-specific data (heart rate variability, valvular pathologies, early warning for arrhythmias, and diastolic and exercise hemodynamics) [94].

Another microelectromechanical system-based LAP sensor (Integrated Sensing Systems, Inc., Ypsilanti, Michigan) requires surgical implantation and it is therefore limited to patients undergoing cardiac surgery. First-in-man evaluations in patients undergoing implantation of a left ventricular assist device or other cardiac surgery have shown feasibility of the approach [94].

These implantable monitors represent a significant advance in the detection and pressure-guided treatment of hemodynamic measures of fluid overload. Because in HF patients elevated intracardiac pressures portend increased morbidity and mortality and their reduction improves outcomes, proactive pressure-guided treatment of ambulatory HF patients is unequivocally superior to therapy reactive to clinical symptoms. It remains unknown whether data provided by implantable hemodynamic monitors are closely correlated with measures of body fluid volume, such as BVA, and can accurately track rapid fluid shifts in patients with acutely decompensated HF or requiring renal replacement therapies. Future studies in these clinical settings should prospectively determine if the hemodynamic data provided by implanted sensors correlate with quantitative measures of body fluid volume and their changes with therapeutic interventions.

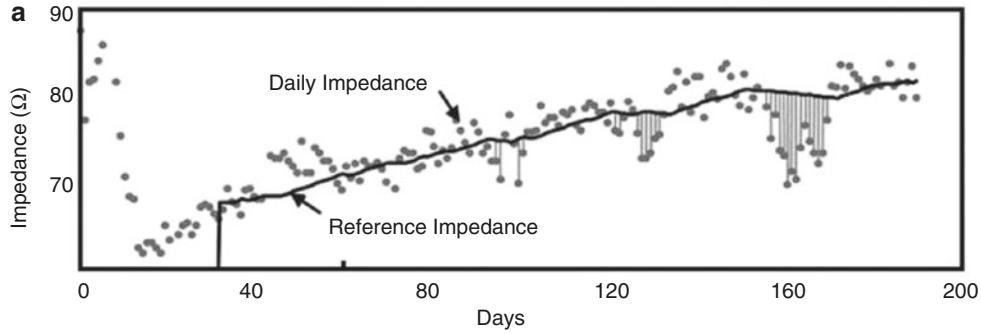
15.8 Data from Cardiac Implanted Electronic Devices

Approximately 40% of HFrEF patients receive a cardiac implantable electronic device (CIED) [116]. Some of these devices include features for evaluation of TFC. This can be measured when a small alternating current pass between the CIED

case and the lead implanted in the right ventricle. The greater the TCF, which is in the path of the electrical impulse, the lower the measured impedance. The relatively fixed position between electrodes provides more consistent impedance measurements than those from surface electrodes. Some CIEDs from one manufacturer (Medtronic Inc. Minneapolis MN) were the first to include a feature for fluid status monitoring, referred to as OptiVol [116]. This fluid index algorithm was developed in the Medtronic Impedance Diagnostics in Heart Failure Patients Trial (MIDHeFT) study [116]. This investigation used a pacemaker modified to accept an implantable cardiac defibrillator lead and downloaded software designed to automatically measure and record intrathoracic impedance in 33 patients with severe HF followed for approximately 21 months. In the acute phase of the study, patients hospitalized for decompensated HF underwent simultaneous measurement of PCWP by a pulmonary artery catheter and of intrathoracic impedance by the implanted device. In the chronic phase patients had monthly follow-up visits up to 2 years. Throughout the study clinicians and patients were blinded to impedance data. Data from 24 hospitalizations in 9 patients showed an inverse correlation between intrathoracic impedance and PCWP ($r = 0.61$, p 0.001) and the occurrence of a mean drop in average daily impedance of 12.3 ± 5.3% ($p < 0.001$) approximately 2 weeks before HF hospitalization (Fig. 15.8). From these data the OptiVol fluid status algorithm forecasted hospital admission with 76.9% sensitivity. Approximately 1.5 threshold crossings per patient-year of monitoring occurred without subsequent HF hospitalization. Notably, some false-positive crossings were associated with increased TCF, but intensification of diuretic therapy averted hospitalization [116].

The Fluid Accumulation Status Trial (FAST) prospectively and blindly evaluated 65 HF events occurring in 156 HF patients with a CIED enabled to measure intrathoracic fluid over 537 ± 312 days of follow-up [117]. True positives were defined as adjudicated worsening HF events occurring within 30 days of a fluid index above the threshold of 60 ohms-days or an acute weight gain of 3 and 5 lb, respectively, in 1 and 5 days. Unexplained detections were threshold crossings or acute weight gains not associated with worsening HF. Compared to weight, impedance had a higher sensitivity (76% vs. 23%; $P < 0.0001$) and a lower unexplained detection rate (1.9 vs. 4.3/patient-year; $P < 0.0001$) [117]. In another study 335 chronic HF patients were randomized to have impedance information available to physicians and patients as an audible alert in case of preset threshold crossings (access arm) or not (control arm). During 14.9 ± 5.4 months, the endpoint of all-cause mortality and HF hospitalizations occurred in 48 access arm patients (29%) and in 33 controls (20%) ($P = 0.063$; hazard ratio, 1.52; 95% confidence interval, 0.97–2.37), mainly due to more HF admissions [118]. These disappointing results may be due to discomfort of physicians and patients with inaction in response to an alert, delivery of the alert based on a single CIED parameter, and the lack of prespecified guidelines for the evaluation and treatment of TCF changes triggering the alerts.

Several studies have been conducted for risk stratification of HF patients based on combinations of data obtainable from CIEDs. Unfortunately, the performance of the various proposed indices in predicting impending worsening HF cannot be meaningfully compared: device, manufacturer, analytic methods, assessed parameters, end points, frequency of evaluation, type of risk stratification, length of follow-up, and results vary significantly between studies. However, all analyses have some common aspects: (1) the relative weight of each measure contributing to the final risk index cannot be determined, which may lead to wrong therapeutic interventions, (2) lack of standardized therapies in response to elevated indices; (3) development of risk scores in HFrEF patients with indications for CIEDs; and (4) lack of data on whether protocols targeting a given risk index improve HF outcomes (Table 15.1) [2, 5–7, 119–122]. The newest risk stratification tool based on multiple data obtainable from CIEDs is the HeartLogic alert algorithm, available in the COGNIS (Boston Scientific, St. Paul, MN) CRT-defibrillator device. To develop the algorithm, data collected


a
Impedance (Ω)
90
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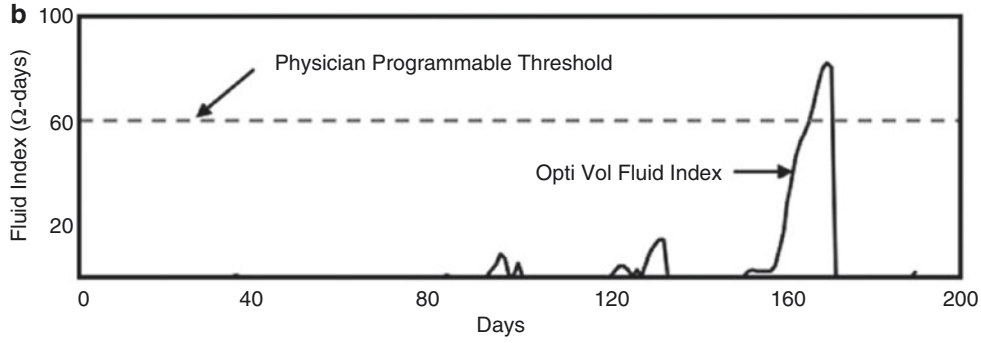
70
Daily Impedance
Reference Impedance
0
40
80
120
160
200
Days


b
Fluid Index (Ω-days)
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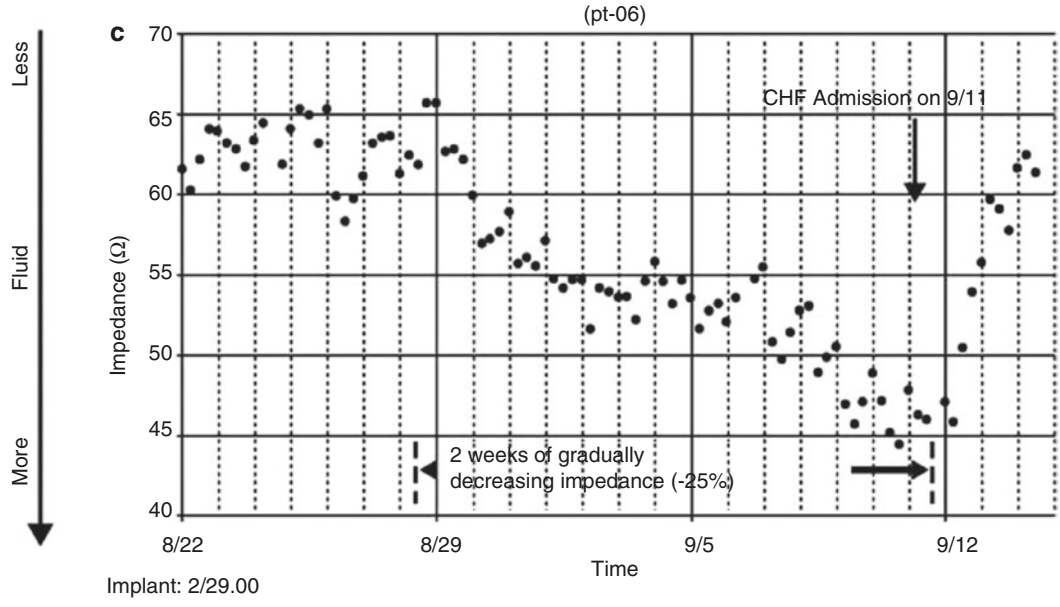
(pt-06)
c
Less
Fluid
More
Impedance (Ω)
70
65
60
55
50
45
40
CHF Admission on 9/11
2 weeks of gradually
decreasing impedance (-25%)
8/22
8/29
9/5
9/12
Time
Implant: 2/29.00

Fig. 15.8 Daily impedance is defined as the average of 64 measurements made every 20 min for 5-h. After activation of the ventricular fibrillation detection feature measurement of impedance begins and cannot be reset. For each patient, reference impedance, the value calculated as the mean of the last 4 average daily impedance values, is first obtained 34 days post-implant to avoid inaccurate readings caused by local edema and inflammation. Thereafter, in each patient, the reference impedance trend established with the OptiVol algorithm slowly adapts to fluid changes (**a**). Any cumulative consecutive negative deviations in the average daily impedance from the reference impedance are plotted to create the OptiVol fluid index, which reflects the magnitude (ohms) and duration (days) of impedance reduction from the reference value (ohm-days) (**b**). Although the fluid index threshold is nominally programmed at 60 ohms-days, it can be adjusted between 30 and 180 ohms-days based the clinician's estimation of the optimal fluid status for a given patient. When the average daily impedance is above the reference impedance for 2–3 days, the fluid index resets to zero. Impedance before and during hospitalization for heart failure. As the patient experienced worsening heart failure and eventual hospitalization, intrathoracic impedance decreased. After diuresis and resolution of heart failure symptoms, intrathoracic impedance increased to the pre-symptomatic level. *CHF* congestive heart failure, *Pt* patient (**c**). (Reproduced with permission from: Wang L. Fundamentals of Intrathoracic Impedance Monitoring in Heart Failure. Am J Cardiol 2007;99[suppl]:3G–10G)

Table 15.1 Studies of heart failure risk stratification using variables from cardiac implantable electronic devices with 1-year follow-up

Study (sample size)	Study type	Blinding	Variables evaluated in score	Frequency of evaluation	Selected outcomes
MultiSENSE; Boehmer et al. [2] (N = 500/400)	Multicenter, nonrandomized	Investigators, Events comm.	S1, S3, respiration, thoracic impedance, heart rate, activity	Daily	HFE detection; Sensitivity = 70% [95% CI, 55.4–82.1]
IN-TIME; Hindricks et al. [5] (N = 333/331)	Multicenter, randomized	None	Arrhythmias, %CRT, PVCs, activity, abnormal ICE	Daily (working days)	CCS (Algorithm vs. SOC): 61 (18.9%) vs. 90(27.2%); $P = 0.013$; deaths: 10 vs. 27
7 studies Cowie et al. [6] (N = 921/1310)	Combined analysis	N/A	Thoracic impedance, AF burden, VRAF, VT, patient activity, heart rate, HRV; %CRT	Monthly	HFH ↓; Hazard ratio, 10.0; 95% CI, 6.4–15.7; $P < 0.001$
PARTNERS HF, Whellan et al. [7] (N = 694)	Multicenter, observational	Events comm.	AF, ≥60 Ω Fluid Index, activity, night heart rate, HRV, device therapy	Monthly	HFH ↓; Hazard ratio, 4.8; 95% CI, 2.9–8.1; $P < 0.0001$

ACS acute coronary syndrome, *ACG* automatic gain control, *AF* atrial fibrillation, *A/V Arrh.* atrial and ventricular arrhythmias, *BIV* biventricular, *CCS* clinical composite score, *CEC* clinical events committee, *95% CI* 95% confidence interval, *CRT-D* cardiac resynchronization therapy-defibrillator, *Dev set* development set, *ER* event rate, *HF* heart failure, *HFE* heart failure event, *HFH* heart failure hospitalization, *HR* heart rate, *HRV* heart rate variability, *HTN* hypertension, *HzR* hazard ratio, *ICD* implantable cardioverter defibrillator, *ICE* intracardiac electrogram, *LV* left ventricle, *M* month, *N/A* not applicable, *NNP* negative predictive value, *NYHA* New York Heart Association functional class, *PGA* patient global assessment, *pt.* patient, *PVC* premature ventricular contractions, *RVR* rapid ventricular response, *SE* sensitivity, *SP* specificity, *TL* telemonitoring, *UAR* unexplained alert rate, *Val set* validation set, *VRAF* ventricular rate during atrial fibrillation, *vs.* versus, *Y* year

from multiple device sensors were used in combination with clinical baseline and HF events data. Initial analyses identified heart sounds (S1 and S3), thoracic impedance, respiration, heart rate, and activity as predictive of an HF event [123]. Changes in these features from each patient's baseline were aggregated and weighted based on an individual's daily risk for worsening HF. The HeartLogic index value is updated daily, and an alert is issued when the index crosses the nominal threshold of 16 [123]. In the Multisensor Chronic Evaluation in Ambulatory Heart Failure Patients (MultiSENSE) study, this alert index forecasted HF events with a 70% sensitivity and a median of 34-day warning [123]. A post-hoc analysis of the MultiSense study showed that among 900 patients (average event rate: 0.20/pt-year), 145 HF events occurred over 1 year in 88 patients with evaluable HeartLogic alert algorithm. The risk of a HF event during periods in alert status was tenfold that occurring during periods out of alert status (0.80 versus 0.08/pt-year) [124]. Sub-stratification showed that, compared with the lowest risk group (low NT-proBNP and not in alert status), the highest risk group (high NT-proBNP levels and in alert status) had a 50-fold increased risk of an HF event (1.00/pt-year versus 0.02/pt/year) [124]. However, CIED-based HF scores have limitations. The HeartLogic index can rise above the nominal value of 16 due to tachypnea and rapid shallow breathing. Without a position sensor, it is impossible to discern whether the respiratory abnormality is due to pulmonary edema or to sleep disorder breathing, conditions requiring different interventions [119]. The ongoing Multiple Cardiac Sensors for the Management of Heart Failure (MANAGE-HF) study compares remote monitoring with versus without HeartLogic alerts to drive HF care (NCT03237858).

Taken together, the data obtainable from CIEDs, although useful as early warning of HF decompensation to trigger early intervention to avoid hospitalization, have specific limitations regarding assessment of body fluid status. These include: (1) estimation of fluid overload limited to the thorax; (2) inability to precisely quantify the amount of excess volume and its changes with fluid removal; (3) restriction to patients with CIED indications, resulting in the exclusion of HFpEF patients who comprise more than 50% of the HF population in the U.S. and Europe.

15.9 Ultrasound Methods

15.9.1 Lung Ultrasound

Extravascular lung water (ELW) reflects the water content of the lung interstitium, which is determined by lung permeability and cardiac filling pressures. Lung ultrasound (LUS) is increasingly used for ELW assessment through the analysis of B-line artifacts (Fig. 15.9) [125]. According to international consensus, B lines are discrete laser-like vertical hyperechoic reverberation artifacts that arise from the pleural line, extend to the bottom of the ultrasound screen without fading, and move in tandem with lung sliding [125]. Comparison with data from computed tomography and invasive hemodynamics confirms a direct relationship between B lines and ELW. Examination of ELW by LUS can be performed with any type of echography device at any transducer frequency, is highly feasible, reproducible and has a short learning curve [125–127]. Briefly, both sides of the anterior and lateral chest are scanned from the second to the fourth or fifth intercostal spaces, at parasternal to midaxillary lines, for a total of 28 scanning sites in each of which the number of B lines is recorded as a value from 0 (no detectable B lines) to 10 (a fully white screen). The sum of B lines produces a score that quantifies the degree of ELW [125–129]. According to a recent meta-analysis, three or more B lines in two or more bilateral lung zones can be considered diagnostic for pulmonary edema (sensitivity, 94%; specificity, 92%) [130]. A B-line score cutoff $\geq$15 is significantly correlated with clinical congestion scores, E/E′ ratio, NT-proBNP levels, increased LV filling pressure, larger LV volumes, LV mass index, left atrial volume index, tricuspid regurgitation velocity, and estimated systolic PAP [125, 131]. In a recent systematic review of 6 studies including 438 acutely decompensated HF patients, the

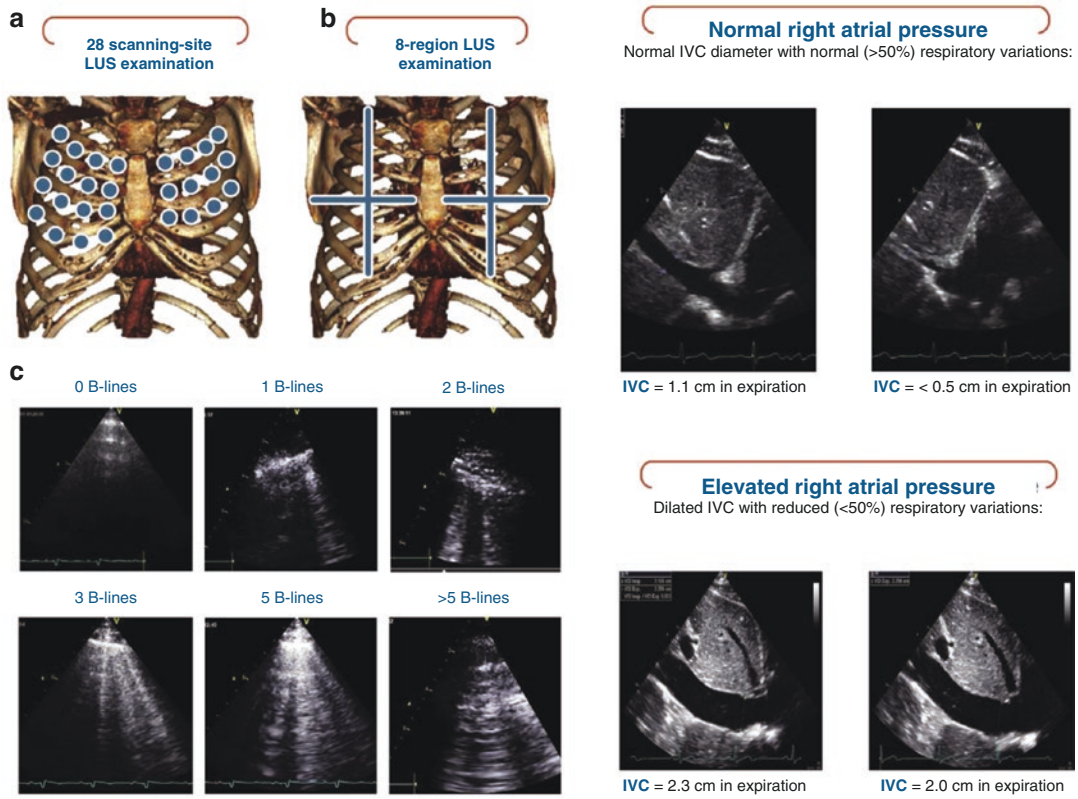

Fig. 15.9 Lung ultrasound and quantification of inferior vena cava diameters through respiratory cycles. (**a**, **b**) Two techniques for quantifying pulmonary congestion using lung ultrasound (LUS). With the 28 scanning-site LUS technique, a precise quantification of extravascular lung water can be achieved; 16–30 comets (also called B-lines) detected in the entire lung are evocative of moderate pulmonary congestion and >30 comets are evocative of severe pulmonary congestion. The 8-region LUS technique is a semiquantitative technique. A positive region is defined by the presence of ≥3 B-lines in a longitudinal plane between 2 ribs and ≥2 positive regions on each lung, which suggest significant pulmonary congestion. LUS lasts <5 min using both techniques. (**c**) Upper images: Normally aerated lung and regular interstitium, the only image that can be visualized below the pleural line is the reflection of the chest wall from the probe to the parietal pleura (A lines), or a few vertical artifacts can be detected (images with 1 and 2 lung comets). (**c**) Bottom images: Progressive extravascular lung water accumulation as shown by the increasing number of lung comets. Right panels: right atrial pressures can be assessed with IVC diameters as shown in the upper and lower right panels. (Reproduced with permission from: Gired N, Seronda MF, Coiro S et al. Integrative Assessment of Congestion in Heart Failure Throughout the Patient Journey. J Am Coll Cardiol HF 2018; 6:273–85)

number of B lines decreased in as few as 3 h after therapy initiation and were mostly cleared in 4.2 ± 1.7 days [132]. In HD patients, interdialytic weight gain is consistently associated with number of B lines [133–136]. A decrease of 2.7 B lines has been shown to occur for every 500 mL of volume removed by UF [133]. In patients with both decompensated or chronic HF the number of B lines is positively correlated with BNP levels [137, 138]. In contrast, this relationship is inconsistent in HD and PD patients [133–136]. Importantly, B lines lack specificity, as those due to edema are like those due to interstitial fibrosis. Compared to those seen in HF, B lines associated with the adult respiratory distress syndrome have an irregular distribution and fragmented pleural line. Moreover, subcutaneous emphysema or morbid obesity reduce the image quality required to evaluate B lines [127]. Therefore, as for all other methods used to assess fluid status, B lines

cannot be considered in isolation, but rather in the context of clinical, hemodynamic and echocardiographic evaluation.

15.9.2 Inferior Vena Cava Ultrasound

The diameter of the inferior vena cava (IVC) is typically measured from the long-axis subxiphoid view between 5 and 30 mm from the IVC and right atrial junction during end-expiration and after sniff. The diameter of the IVC changes with respiration, reflecting the elasticity of this capacitance vessel. In spontaneously breathing subjects, intrathoracic pressure decreases during inspiration, thereby increasing venous return and causing collapse of the IVC. Conversely, during expiration, venous return decreases, leading to an increase in IVC diameter [139]. In acutely decompensated HF, when volume overload dilates the IVC to the limits of its elasticity, the respiratory cycle is associated with only minimal change of IVC diameter [139]. This reflects the non-linear pressure-diameter relationship of the IVC so that, above a threshold pressure (i.e., CVP >20 mmHg), no further increase in IVCD can be observed [140, 141]. Indeed, a respiratory variation of IVC diameter ≤ 15% was highly sensitive and specific for the diagnosis of acutely decompensated HF [142]. In 75 patients undergoing pulmonary artery catheter-guided therapy for acutely decompensated HF, evaluation of multiple echocardiographic methods for estimation of right atrial pressure revealed that IVC diameter ($r = 0.40$, $P < 0.0001$), IVC diameter during inspiration ($r = 0.49$, $P < 0.0001$) and percent change of IVC diameter ($r = 0.41$, $P < 0.0001$) had the highest correlation with right atrial pressure [141]. Therefore, determination of IVCCI $[(IVCD_{max} - IVCD_{min})/IVCD_{max}]$ in acutely decompensated HF patients may also help to optimize fluid removal rates while avoiding hypotension.

In 24 acutely decompensated HF patients undergoing UF, IVCCI was calculated before UF, at 12 h, and after completion of therapy. After removal of an average 5780.8 ± 1994.6 mL over 20.3 ± 4.6 h at a rate of 287.6 ± 96.2 mL/h, IVCCI increased significantly ($P < 0.001$). Hypotension occurred in 2/24 patients whose IVCCI increased by >30%. In all the other patients, an increase in IVCCI was not associated with hemodynamic instability [139]. These results suggest that IVC ultrasound is a rapid, simple, and non-invasive method for bedside monitoring of intravascular volume during UF and may be helpful in adjusting fluid removal rate. The accuracy of IVC measurements is influenced by the presence of a prominent Eustachian valve, patient's position and ability to follow instructions and intra and inter-observer variability (Fig. 15.9).

15.10 Biomarkers

The use of natriuretic peptides to assess volume status and guide decongestive therapies cannot be recommended because fluid overload is not the sole cause of increases in the levels of these biomarkers [143, 144]. The removal of fluid to achieve pre-specified natriuretic peptide levels is untested in acute heart failure. Serum creatinine (sCr) is the most widely used biomarker to guide fluid removal due to the belief that its level reflects both renal filtration function and tubular status [5, 7]. However, sCR was established and validated as a measurement of renal function only at the point of steady-state (constant production from the metabolism of muscle creatine phosphate and unchanging glomerular filtration and urinary flow to excrete creatinine at a constant rate). Therefore, it is unfortunate that sCr is the only widely available measurement of renal function in patients with acute illnesses, such as acutely decompensated HF, where the rates of creatinine production and excretion may be altered. In addition, sCr concentration can be normal with documented tubular injury due to delayed achievement of detectable changes of this analyte [145]. Generally, hemodynamically driven sCr increases resolve with treatment in 24–72 h, whereas the cellular derangements due to acute tubular damage may last for weeks. Therefore, the duration of sCr elevation has a greater predictive effect on morbidity and mortality than the extent of this biomarker's elevation

[146]. Indeed, the use of increases in sCr as an endpoint for acutely decompensated HF trials has been challenged. Evaluation of the relationship between changes in sCr and 60-day outcomes in Diuretic Strategies in Patients with Acute Decompensated Heart Failure (DOSE) subjects revealed that increases in sCr from baseline to 72 h (DOSE's coprimary endpoint) was associated with lower risk for the composite outcome of death or HF events. Conversely, there was a strong relationship between improved renal function and unfavorable 60-day outcomes [3]. Thus, sCr changes are an unreliable surrogate endpoint in trials of fluid removal therapies. An alternative to creatinine, cystatin C, is a protein produced in all nucleated cells and distributed in extracellular fluid. It is freely filtered and mostly reabsorbed and catabolized by the proximal tubule. Cystatin C is not affected by muscle mass or diet and is less strongly associated with age, sex, and race than creatinine, but smoking, inflammation, adiposity, thyroid diseases, malignancy, and glucocorticoids influence cystatin C levels, diminishing their value as a measure of renal excretory performance [7]. Estimation of GFR using creatinine, cystatin C, or both has not been validated in acutely ill patients, in whom these estimates may be inaccurate compared to 4-h urinary creatinine clearance for detection of renal function changes [147].

After the discovery of neutrophil gelatinase-associated lipocalin (NGAL), which is secreted in the urine and the plasma by a damaged kidney, it was shown that the expression/secretion of urine NGAL occurred within 3 h of the event (sepsis, nephrotoxins, obstruction, ischemia); and that the amount of secreted protein (from 20 ng/mL to 5 mg/mL) was proportional to the severity and time of resolution of the stimulus [148]. A growing body of evidence suggests NGAL is not expressed when sCr increases due to volume stressors. A systematic study of thousands of genes encoding for several biomarkers including NGAL, KIM-1, tissue inhibitor of metalloproteinase-1, and clusterin, found that these molecules were detectable after a brief dose of ischemia, yet none of these genes were expressed after near-fatal volume depletion, despite a similar rise in sCr in the two models [149]. Although not yet widely used, in the setting of any method of fluid removal, the levels of biomarkers of tubular injury could potentially help distinguish a rise in sCr due to a hemodynamically mediated decrease in GFR or actual tubular injury [145, 149, 150]. An analysis from the Low Dose Dopamine or Low-Dose Nesiritide in Acute Heart Failure with Renal Dysfunction (ROSE) trial showed that in the context of aggressive diuresis of fluid-overloaded HF patients, worsening renal function, as defined by creatinine-based estimation of GFR, occurs without obvious renal tubular injury [4]. Although there were no consistent changes in NGAL, *N*-acetyl-β-D-glucosaminidase, and KIM–1 suggestive of significant tubular injury, a small subset of patients had modest increases in these biomarkers' urinary concentrations [4, 151]. Yet even in these patients, an increase in biomarkers of tubular injury did not worsen outcomes, suggesting that fluid overload was a greater evil than some degree of renal tubular injury [4–7, 152].

15.11 Prospective and Conclusions

Fluid overload in HF and renal disease patients is unequivocally associated with increased morbidity and mortality. The staggering number of HF re-hospitalizations underscores the inability to accurately estimate the magnitude of fluid excess and to determine when an optimal fluid status has been achieved after treatment. The most accurate method to measure ECF and RCV is BVA. Unfortunately, BVA is not widely used largely due to the perceived complexity of the method. Studies evaluating the correlation between BVA and other measures of fluid volume assessment, such as hematocrit, biomarkers, hemodynamic values and BIA methods are sorely lacking. Therefore, it remains unknown whether once BVA is performed before institution of decongestive therapies, fluid removal can be monitored with easier, more rapid and less expensive methods. All bioelectrical impedance methods have not undergone rigorous comparison with BVA or invasively obtained hemodynamic

data, and therefore their sensitivity and specificity in quantifying fluid excess at baseline and in their ability to detect volume changes in response to fluid removal therapies remains unknown. Possibly BIS may have advantages over other BIA methods as it harnesses a wide spectrum of current's frequencies and it relies less on assumptions that may be violated in disease states, such as HF and kidney disease. Regrettably only two very small studies are correlating BIS with data from an implanted PAP sensor, and their results are not yet available. Bioreactance devices may be promising, but their value is greater in assessing fluid responsiveness in critically ill or surgical patients than in assessing fluid volume and its changes with therapeutic interventions in acutely decompensated HF patients. Therapy guided by implanted hemodynamic monitors is clearly associated with reductions in re-hospitalizations regardless of LVEF. Recent analyses have shown a strong signal toward decreased mortality in NYHA class III HF patients receiving PAP-guided therapy. Risk scores have been developed with data obtainable from CIEDs, such as heart sounds, activity, respiratory rate and TFC. Although these risk scores may forecast HF events with enough warning to avert hospitalizations, they do not provide quantitative fluid volume data, and cannot be used in patients without an indication for a CIED. Ultrasound methods, such as the evaluation of ELW and IVCCI, are promising, but they have not undergone meaningful comparisons with other methods of fluid volume assessment. Biomarkers such as natriuretic peptide have unquestionable diagnostic and prognostic value. However, due to the multitude of factors which contribute to their elevation, they cannot be used for the quantitation of fluid excess or to guide HF therapy. The use of elevation in sCr, worsening renal function and acute kidney injury as interchangeable terms has resulted in the premature discontinuation of decongestive therapies and the resulting poorer outcomes of fluid overloaded HF patients. The task ahead is daunting, but not insurmountable: the initial step is to confirm the ability of BVA to precisely quantify fluid overload and achievement of an optimal BV after treatment; subsequently correlations should be evaluated between BVA and other techniques which can performed easily, serially and inexpensively; in the ambulatory setting, hemodynamically-guided therapy can be used for early detection of fluid overload and prevention of HF events requiring hospitalization; parameters from CIEDs may help to stratify the risk for HF events with enough warning to enable timely interventions for the prevention of HF decompensation; in the near future wearable devices detecting data similar to that provided by CIEDs may become available for all HF patients, regardless of LVEF, without the requirement for an invasive procedure. As for CIEDs-derived risk indices, those arising from wearable devices must provide targets sufficiently specific to trigger the correct therapy.

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Novel Biomarkers of Acute Cardiorenal Disease

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16.1 Brief Terminology of Acute Cardiorenal Disease

Cardiorenal syndromes (CRS) types 1–5 comprise acute or chronic conditions of heart problems injuring the kidney and vice versa. In type 1 cardio-renal syndrome acute heart impairment leads to acute kidney impairment whereas in type 3 reno-cardiac syndrome acute kidney impairment leads to acute heart impairment. Both types of CRS are known as acute cardiorenal disease. The term of heart or kidney *impairment* summarizes functional (dysfunction/insufficiency/failure) and structural (damage/stress/injury) abnormalities. Acute kidney impairment (AKI, syn. Acute kidney injury/insufficiency) considers functional and structural acute kidney abnormalities.

16.2 Major Pathomechanisms of Cardiorenal Syndromes (CRS) Types 1 and 3

Pathophysiological understanding of CRS 1 and 3 may enable interpretation of test results of novel biomarkers. In an attempt to identify major pathophysiological mechanisms and to address the utility of biomarkers for CRS types 1 and 3, recommendations from a consensus conference held under the auspices of the Acute Dialysis Quality Initiative (ADQI) are provided [1, 2]. Results and recommendations of this conference are the basis of this chapter, updated with recent key publications. Complex pathomechanisms of CRS type 1 (acute cardio-renal) and 3 (acute reno-cardiac) have been recognized in recent years to be intertwined. Both syndromes are bidirectionally linked with each other by direct and indirect effects of kidney impairment on the heart, and effects of kidney impairment on remote organ function with indirect effects on the heart. On the other hand, worsening cardiac impairment can further complicate kidney impairment and produce a vicious cycle between CRS types 1 and 3.

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CRS type 1 is characterized by a rapid worsening of cardiac function leading to AKI and most frequently appears in the setting of acute decompensated heart failure (ADHF) but also in acute coronary syndrome (ACS) [3]. CRS type 1 follows ischemic (e.g. myocardial infarction) or non-ischemic (e.g. valve dysfunction, aortic dissection, pulmonary embolism) cardiac events. Up to 40% of patients hospitalized for ADHF develop AKI [4].

Classical mechanisms of CRS type 1 include low cardiac output and neurohormonal activation and release of vasoactive substances resulting in low renal perfusion and possible renal ischemia with AKI. In addition, high central venous pressure, increased intra-abdominal pressure leading to venous congestion, activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS) and release of other vasoactive substances such as endothelin, anemia and a marked alteration of immune and somatic cell signaling have all been implicated as important contributors of AKI (Fig. 16.1).

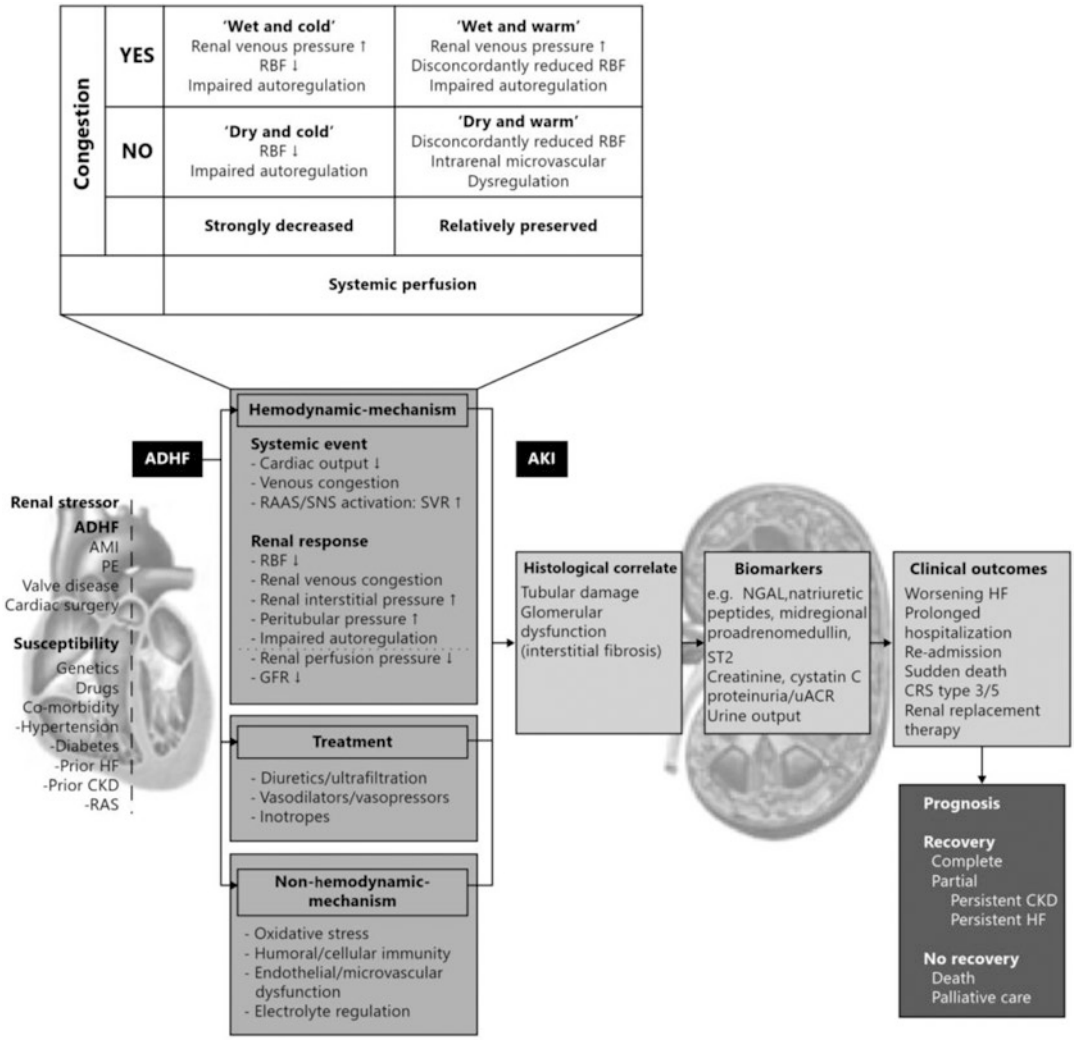

Fig. 16.1 Pathophysiology of CRS type 1 (reproduced with permission from ADQI). (Reproduced with permission from Haase Michael, Müller Christian, Damman Kevin, et al. Pathogenesis of Cardiorenal Syndrome Type 1 in Acute Decompensated Heart Failure: Workgroup Statements from the Eleventh Consensus Conference of the Acute Dialysis Quality Initiative (ADQI). © 2013 S. Karger AG, Basel)

CRS type 3 initiated by AKI has been shown to cause inflammation in experimental renal ischemic models, which then induced cytokine expression, leukocyte infiltration into the heart, cell death by apoptosis, and impaired cardiac function [5]. Combined with this finding is the well-known significant physiological derangements, such as fluid and electrolyte imbalance and uremia, that underpin remote organ failure and finally affect heart structure and function, which in turn may cause further kidney impairment. Acute salt and water retention, volume overload, and the immediate effects of uremia on the myocardium are all postulated mechanisms in precipitating ADHF in CRS type 3 [6]. The mechanisms whereby AKI leads to cardiac dysfunction have been proposed to include two principles: direct effects of AKI on the heart, and effects of AKI on remote organ function with indirect effects on the heart (Fig. 16.2) [7].

16.3 Biomarkers of Acute Cardiorenal Disease

Not every patient with AKI or acute heart impairment will develop CRS 1 or 3. Therefore, early identification of patients with acute heart *OR* acute kidney impairment who will subsequently develop acute impairment of the apparently still unaffected organ is one of the major clinical challenges in the prevention of CRS types 1 and 3. Established and novel heart and kidney biomarkers may add valuable information for such risk assessment potentially enabling prevention of CRS types 1 and 3.

This chapter focusses on evidence of the ability of novel biomarkers to *early diagnose or predict* CRS type 1 (i.e. before kidney impairment) or CRS type 3 (i.e. before heart impairment). Such information basing on biomarker test result may be useful for guiding acute treatment including adapted medication or ultrafiltration therapy. Biomarker information may also be used for hospital discharge decisions or guiding treatment in the ambulatory setting, both aiming at avoiding an episode of early rehospitalization. Furthermore, the value of novel biomarkers to predict de-novo development or worsening of preexisting of CKD following CRS type 1 or 3 is assessed here.

Novel kidney biomarkers may be used for early diagnosis of acute kidney impairment in the setting of CRS type 1, whereas they could be also useful to early screen for patients at risk for CRS type 3.

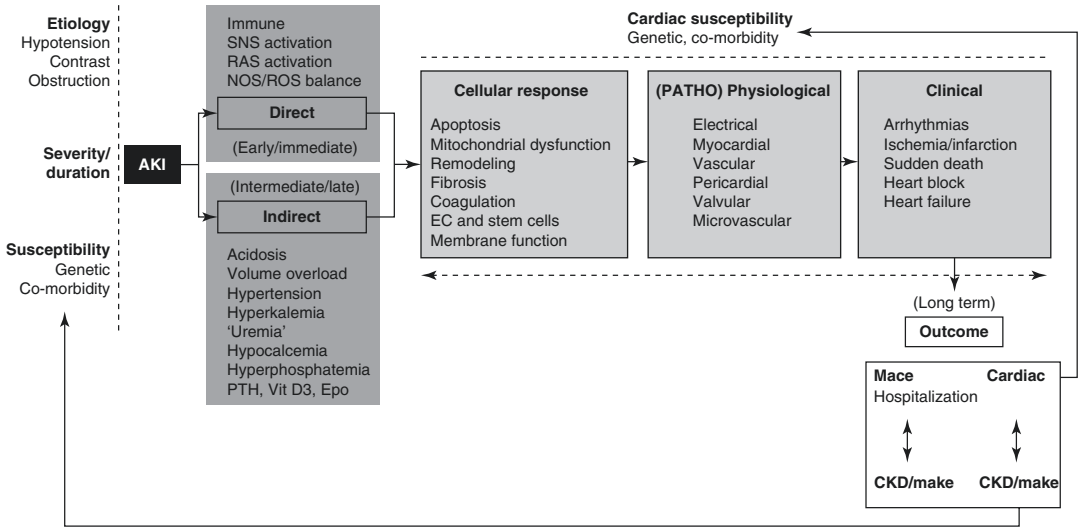

Fig. 16.2 Pathophysiology of CRS type 3 (reproduced with permission from ADQI). (Reproduced with permission from Haase Michael, Müller Christian, Damman Kevin, et al. Pathogenesis of Cardiorenal Syndrome Type 1 in Acute Decompensated Heart Failure: Workgroup Statements from the Eleventh Consensus Conference of the Acute Dialysis Quality Initiative (ADQI). © 2013 S. Karger AG, Basel)

16.3.1 Biomarkers for Early AKI Detection After Cardiac Impairment (CRS Type 1)

Classically, in CRS type 1 excessively increased cardiac biomarkers such as (nTpro)BNP and troponins are associated with development of acute kidney impairment [8]. Also, ECG and echocardiography are useful clinically available diagnostic tools for identification and characterization of cardiac impairment in the setting of impending CRS type 1.

Acute cardiac impairment may harm the kidney through several pathways as described above. Early recognition or even prediction of a loss in glomerular filtration or injury/stress to the renal tubular cells, both associated with complications and adverse outcomes [9, 10], is one of the clinician's tasks in this scenario. Novel biomarkers of AKI should be able to inform the clinician about present glomerular filtration status and renal tubular cell status. Finally, AKI appears to be related to increased rates of subsequent chronic kidney disease, and patients with AKI should therefore be monitored closely.

16.3.1.1 Biomarkers of Glomerular Filtration

Routinely, serial serum creatinine measurements are used to recognize declining glomerular filtration rate in patients with acute heart impairment typically such as ADHF or ACS. However, there must be awareness that, as soon as serum creatinine significantly increases, CRS type 1 is already established and prevention of this type of CRS no option anymore. Surprisingly, there is evidence for both, harm and benefit for the patient once cardiac impairment and treatment leads to AKI. On the one hand, AKI (here: acute serum creatinine increase) was associated with a poorer outcome for patients with ADHF, specifically AKI was independently associated with heightened risk for death and prolonged hospitalization [3, 11].

On the other hand, patients with a linear increase in serum creatinine was paradoxically associated with improved outcomes. The relative change in eGFR from baseline to 72 h demonstrated a similar relationship; for every 10% worsening in eGFR, the risk of adverse outcomes decreased. However, when, in the same study, evaluating WRF as defined for the secondary safety endpoint of DOSE (>0.3 mg/dL increase in creatinine at any time from baseline to 72 h) vs. those without WRF, there was no evidence of increased risk for the composite endpoint [12]. Therefore, the authors argue against using linear changes in serum creatinine as a surrogate endpoint in trials of decongestive strategies.

Others found during decongestive therapy in ADHF [13], that a significant reduction in NT-proBNP was not associated with AKI (here: acute serum creatinine increase). However, it is still unclear whether this finding may suggest that in ADHF patients it may be warranted to strive for an optimal decrease in NT-proBNP, even if this induces WRF.

Interestingly, the combination of a cardiac function parameter and a kidney function ratio identified distinct phenotypes of AKI (here: serum creatinine increase) with different clinical presentation and prognosis. Specifically, in patients with ADHF, the subgroup of patients with both, an elevated (NTpro)BNP and BUN/creatinine ratio had a cardiorenal profile characterized by venous congestion, diuretic resistance, hypotension, hyponatremia, longer length of stay, greater inotrope use, and substantially worse survival compared with patients without AKI [14].

In patients with acute myocardial infarction, lower eGFR at hospital admission was an independent predictor of subsequent AKI (CRS type 1) [15]. Together with (NTpro)BNP at presentation, eGFR may assist in the prediction of CRS type 1 and may be useful for corresponding risk stratification in patients with acute myocardial infarction.

Serum Cystatin C

Beside serum creatinine, serum cystatin C, a 25-kDa glomerularly filterable protein produced by all nucleated cells at a constant rate, has been used as biochemical surrogate for renal function. Serum cystatin C measured at admission in patients hospitalized for treatment of ADHF was more predictive of longterm all-cause mortality

and readmission for ADHF than serum creatinine or serum BNP [16, 17]. Given the prognostic value and its biochemical characteristics, serum cystatin C may also have value for earlier diagnosis of an acute loss of kidney excretory function in CRS type 1.

Determination of Renal Function and Injury Using Near-Infrared Fluorimetry in CRS

Cardiac arrest and cardiopulmonary resuscitation lead to experimental cardiorenal syndrome type 1. ZW800-1, a small near-infrared fluorophore being developed for clinical intraoperative imaging, is favorable for evaluating cardiac and renal function noninvasively.

Glomerular filtration rate (GFR) is considered to be a critical measure of excretory kidney function. Reduction of GFR indicated kidney pathology and is a critical diagnostic criterion for acute and chronic kidney disease. However, measurement of GFR in vivo and in the clinical setting remains challenging, leading to undesirable reliance on surrogate markers such as serum creatinine [18]. Rapid quantification of GFR can be achieved in physiologic and AKI rat kidney models using intravital fluorescent ratiometric two-photon kidney imaging [19]. However, this technology has not yet been tested in human AKI or in cardiorenal syndrome. Real-time, non-invasive in-vivo measurement of GFR may be possible using near-infrared fluorophores as few biologic compounds absorb in the near-infrared. Such novel technique, near infrared fluorimetry, combines use of biomarkers with imaging and has been successfully tested in experimental cardiorenal syndrome using inulin clearance as gold standard with correlation coefficients $R > 0.9$ [20].

16.3.1.2 Biomarkers of Acute Renal Tubular Damage/Stress

This paragraph is dedicated to common understanding of acute tubular damage biomarker test results referred to as early AKI diagnosis or subclinical AKI, respectively. The consensus definition of AKI is currently based on changes in serum creatinine and urine output. However, recent data have challenged this paradigm. A pooled analysis of prospective cohort studies highlighted the prognostic relevance of combining routine kidney function parameters (acute serum creatinine increase) with kidney injury markers [9, 10]. There is evidence that positive kidney biomarker test result identifies critically ill and emergency department patients with such AKI subtypes with incrementally increasing risk of adverse outcomes [21, 22].

As a consequence of combining markers of glomerular filtration function with markers being able to indicate renal tubular cell status and as a shown in Fig. 16.3, the combination of simultaneous assessment of a functional and damage markers can help stratify patients into four subgroups: no marker change, functional kidney impairment alone (e.g. "hemodynamic acute kidney impairment"), damage alone ("subclinical acute kidney impairment"), or change in both functional and damage markers. This four groups categorization permits identification of a new category of patients who may have 'subclinical' AKI, i.e. a positive test result of damage marker without a simultaneous loss of kidney function possibly due to renal function reserve or decreased creatinine production (Fig. 16.3, upper right quadrant). In these conditions, e.g. nephrotoxic drug exposure, loss of function may not develop at all or be seen at some time interval after detection of acute tubular injury. Patients with subclinical AKI are at higher risk for adverse outcomes including need for acute initiation of acute renal replacement therapy and mortality, than patients without an increase in damage biomarker levels [23]. Hemodynamic AKI includes cardiorenal syndrome, prerenal azetomia, hepatorenal syndrome and RAAS inhibition.

These findings on AKI subtypes have been confirmed for several novel kidney biomarkers, such as neutrophil gelatinase-associated lipocalin (NGAL), Interleukin-6, KIM-1 and midkine but also as a trend for proteinuria [24]).

On the basis of these studies using novel kidney for outcome prediction, kidney biomarkers have been suggested to complement serum creatinine- or urine output-based criteria for AKI (Fig. 16.4) [2].

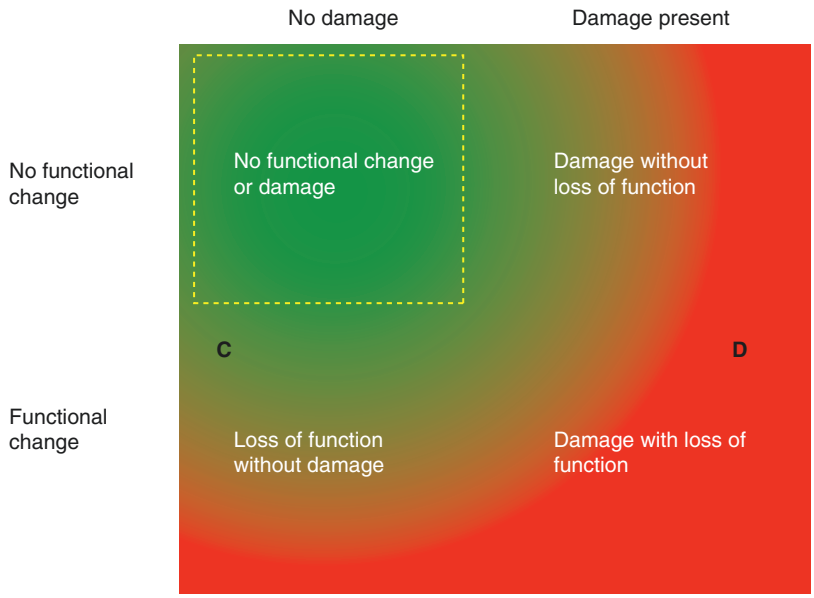

Fig. 16.3 New spectrum or subtypes of acute kidney impairment (AKI) based on combination of functional and damage biomarkers (reproduced with permission from ADQI). (Reproduced with permission from McCullough Peter A., Shaw Andrew D., Haase Michael, et al. Diagnosis of Acute Kidney Injury Using Functional and Injury Biomarkers: Workgroup Statements from the Tenth Acute Dialysis Quality Initiative Consensus Conference. © 2013 S. Karger AG, Basel.) As illustrated, the combination of functional and damage biomarkers allows the clinician to differentiate a normal state of kidney function from subtypes of acute kidney impairment. The current criteria for diagnosis include the lower two quadrants. Patients negative for functional and kidney damage markers are considered to have no AKI (Box A). The ability to detect a state of damage alone (Box B) allows an expanded criterion for diagnosis of AKI. This may represent 'subclinical' AKI in which loss of function might develop several days after detection of kidney damage or not at all due to renal function reserve or decreased creatinine production, however, still associated with impaired outcomes. The bottom left quadrant (Box C) indicates a dynamic change in renal filtration of serum creatinine but without detectable kidney damage that may be physiologic such as seen in patients with 'hemodynamic AKI' including cardiorenal syndrome, prerenal azetomia, hepatorenal syndrome and RAAS inhibition. The right lower quadrant (Box D) represents patients with functional and damage criteria of AKI associated with the worst prognosis

16.3.1.3 Biomarkers of Acute Renal Tubular Damage/Stress After ADHF/ACS

In accordance with the concepts above, the use of biochemical markers for detection of loss of GFR and development of acute tubular damage has been suggested to overcome limitations of serum creatinine. Two important characteristics of biomarkers should be their defined role in the pathophysiology of the syndrome and their clinical actionability. Below, evidence for several novel kidney biomarkers potentially related to pathophysiology of CRS type 1 is presented. This chapter is limited to the biomarkers below, shown in alphabetical order, although further candidate biomarkers are being tested for suitability for the early diagnosis/prediction of AKI in patients with ADHF including osteopontin, *N*-acetyl-β-D-glucosaminidase, stromal cell-derived factor-1, endoglin, galectin-3 and exosomes. However, at this stage, data are too limited to draw any conclusions for use of the latter candidate biomarkers.

Angiotensinogen

Increasing evidence revealed that the intrarenal renin-angiotensin system (RAS) plays a vital role in maintaining hemodynamic balance and cardiorenal interaction, which are often disrupted in patients with ADHF [25, 26]. In animal studies, activation of the intrarenal RAS is an initial response to hypoperfusion in cardiac and renal

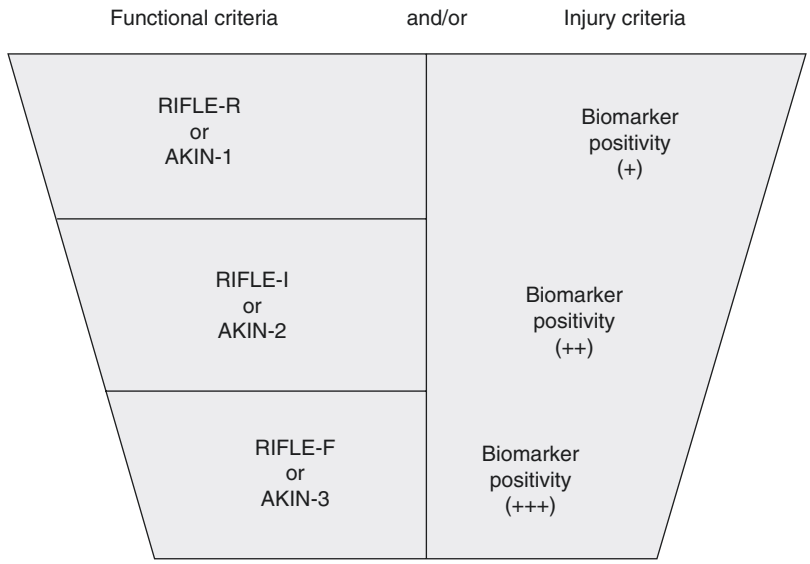

Fig. 16.4 Novel criteria for acute kidney impairment (reproduced with permission from ADQI). (Reproduced with permission from McCullough Peter A., Shaw Andrew D., Haase Michael, et al. Diagnosis of Acute Kidney Injury Using Functional and Injury Biomarkers: Workgroup Statements from the Tenth Acute Dialysis Quality Initiative Consensus Conference. © 2013 S. Karger AG, Basel.) In order to diagnose acute kidney impairment (AKI) selecting the worst criterion (function (RIFLE/AKIN/KDIGO) or damage) is recommended. In the appropriate clinical setting, this new damage biomarker criterion will enhance the ability of RIFLE/AKIN/KDIGO to define AKI. There are currently insufficient injury biomarker data to support staging of AKI, however AKI stages basing on renal function changes are suggested to remain. The semiquantitative trend for increasing biomarker severity associated with increasing kidney damage is suggested by the literature and is displayed by darkening background color as well as the symbols: +/++/+++

injury, and is also an important contributor to the progression of the disease [25, 27]. Intrarenal angiotensinogen (AGT), a principal substrate of the local RAS, is mainly formed in the proximal tubule cells and secreted into the tubule lumen [28]. Urinary AGT (uAGT) level correlates with intrarenal AGT and angiotensin II, and has been shown to be an indicator of intrarenal RAS activity in clinical studies [29]. In a prospective, two-stage, multicenter cohort study by Yang et al. [30] in 317 patients with ADHF, uAGT peaked on the first hospital day in patients who subsequently developed AKI (32.8%). The adjusted highest quartile of uAGT on admission was associated with a 50-fold increased risk of AKI compared with the lowest quartile. For predicting AKI, uAGT (AUC = 0.84) outperformed urinary neutrophil gelatinase-associated lipocalin (AUC = 0.78), the urinary albumin/creatinine ratio (AUC = 0.71), and the clinical model (AUC = 0.77). The uAGT level independently predicted the risk of 1-year mortality (adjusted odds ratio, 4.5) and rehospitalization (adjusted odds ratio, 3.6). The authors concluded that uAGT is a strong predictor for acute CRS and 1-year prognosis in ADHF [30].

KIM-1

Similarly to NGAL, urinary kidney injury molecule-1 (KIM-1), a specific marker of renal tubular damage, has also been implicated for modifying the susceptibility to heart failure risk [31]. These data suggest that acutely upregulated biomarkers of kidney damage, such KIM-1, may circulate to have distant pathophysiologic effects on the heart, including myocardial inflammation, destabilization of atherosclerotic plaques and susceptibility to ischemic events (CRS Group 3).

Atici et al. [32] investigated the usefulness of a series of novel renal biomarkers in 111 patients with acute decompensated heart failure to predict cardiorenal syndrome. For KIM-1, they did not

detect a statistically significant correlation between KIM-1 concentrations in urine and the occurrence of cardiorenal syndrome.

L-FABP

Liver fatty acid binding protein (L-FABP) is localized in the proximal tubule and is shed in the urine on kidney injury L-FABP, were associated independently with 3-year mortality after AKI [33]. Donors with acute kidney injury at the time of their hospital admission had higher L-FABP concentrations in urine samples collected at organ procurement. Higher L-FABP concentrations also correlated with lower 6-month recipient estimated GFR, but this effect was seen only in patients with delayed graft function [34, 35]. In an observational study with 281 consecutive patients with ADHF and 37% of those developing AKI, urinary L-FABP concentrations were significantly higher in patients with AKI than in those without. Urinary L-FABP concentration measured at hospital admission was an independent predictor of AKI in ADHF patients. Receiver operating characteristic analysis showed that baseline urinary L-FABP level exhibited 94.2% sensitivity and 87.0% specificity [36].

NGAL: Biological Characteristics

Neutrophil gelatinase-associated lipocalin (NGAL, also known as lipocalin 2, siderocalin or24p3) appears to be that one with most comprehensive experimental and clinical data available in ADHF and ACS as to date. A recent critical evaluation of the literature on NGAL highlights biological characteristics and clinical value of this biomarker in the prediction of AKI in different clinical settings as shown in the following [37]. NGAL was originally isolated from the supernatant of activated neutrophils and identified as a polypeptide covalently bound to gelatinase [38]. NGAL is expressed in a variety of human tissues, including lung, liver and kidney, in various pathologic states. Human NGAL consists of a single disulphide-bridged polypeptide with a molecular weight of 25 kDa) covalently bound to gelatinase from human neutrophils. While the majority of NGAL is in a monomeric form, NGAL also occurs as dimers and trimers, as well as in a complex with neutrophil gelatinase [38]. The 25 kDa monomeric NGAL form is secreted by injured kidney tubule epithelial cells, whereas the dimeric form is the predominant form secreted by neutrophils [39]. The major ligands for NGAL are siderophores [40], which are ferric ion-specific chelating compounds [41]. The iron status of NGAL is a critical determinant of biological activity. Iron-containing NGAL binds to cell surface receptors such as megalin, gets internalized and releases its bound iron. The increased intracellular iron concentration drives the regulation of iron-dependent genes. NGAL has been implicated in multiple biological processes, including attenuation of apoptosis [42] and differentiation of renal tubule epithelial cells and nephrons [43]. NGAL has also been implicated in the pathophysiology of heart failure, myocarditis and in coronary atherosclerosis [44–46].

Preclinical studies identified NGAL to be one of the most upregulated genes and proteins in the kidney very early after AKI in animal models [47]. NGAL protein expression was detected predominantly in tubule epithelial cells that were undergoing proliferation and regeneration, suggesting a role in the repair process. Serendipitously, NGAL protein was also detected in the urine and plasma in animal models of AKI, where it preceded the increase in plasma creatinine concentrations. The urine NGAL is derived predominantly from epithelial cells of the distal nephron, although a fraction may come from the systemic pool escaping reabsorption due to proximal tubular injury [48]. Plasma NGAL originates not only from the damaged kidneys (via tubular backleak) but also from extrarenal organs.

Recent evidence has emerged to implicate a potentially important pathophysiologic link between NGAL and CRS. NGAL induces cardiomyocyte apoptosis by increasing intracellular iron accumulation [49]. Renal NGAL expression rapidly increased following acute inflammation and/or injured renal tubular epithelia, in particular following damage from IRI and toxin exposure [10]. Administration of recombinant NGAL to mice induced an acute inflammatory response with compensatory changes in cardiac functional

parameters reflecting its potential role as cardiorenal biomarker [49]. Beyond a potential inflammatory role of NGAL in CRS, there is first evidence for its involvement in fluid status regulation given that mineral corticoid receptor activation induces NGAL promoter in the cardiovascular system and upregulation of NGAL expression in the heart and aorta and its plasma levels mediating subsequently developing vascular fibrosis [50].

NGAL: Clinical Trials

Across clinical settings of AKI, NGAL appears to be a strong marker of acute renal tubular injury. Many studies have shown that NGAL rises 24–48 h before creatinine, and thus shows promise in being a powerful marker for early detection of kidney damage [51, 52]. There are few studies examining NGAL in patients with heart failure, and these studies were conducted in mostly small cohorts showing preliminary evidence that elevated admission serum NGAL levels predict AKI in patients with ADHF whereas serum creatinine was of limited value. In patients with ADHF, serum NGAL strongly correlated with kidney function markers. Higher NGAL levels at hospital admission have been associated with adverse cardiovascular outcomes or death [53]. Of note, NGAL levels were found to be largely determined by underlying impairment of renal rather than myocardial function. At hospital discharge, plasma NGAL level was a stronger predictor of 30-day all-cause death and ADHF readmissions than BNP. Such comparison with BNP suggests that ongoing acute tubular damage in CRS type 1 is of importance for future development of CRS type 3.

In a study where patients were admitted with ADHF, elevated plasma NGAL with a cut-off value of 170 ng/mL at time of admission was associated with development of type 1 CRS within 48–72 h [54, 55]. Other studies have found that among patients admitted for ADHF, those who subsequently developed WRF (defined as creatinine rise >0.3 mg/dL) had significantly higher NGAL values than those who maintained steady renal function. Patients with an admission NGAL >140 ng/mL were at 7.4-fold increased risk of developing worsening kidney function during hospitalization, validating the accuracy with which NGAL can predict kidney injury [56]. A recent study demonstrated that in patients admitted to hospital with AHF, and who developed WRF during hospitalization, plasma NGAL levels are significantly increased compared with patients without WRF. A cut-off of 134 ng/mL plasma NGAL has been related to WRF with good sensibility and specificity [52].

Furthermore, it was reported that both serum and urine NGAL levels correlate with various markers of renal function, such as serum creatinine, cystatin C, and albuminuria [57]. Of studies comparing the value of urine NGAL with that of plasma NGAL for predicting AKI in patients with ADHF some found that both markers were similar in this regard while others found plasma NGAL to be superior to urine NGAL. Specifically, in contrast to the serum value of NGAL and its predictive value, some studies demonstrated that urinary NGAL did not reliably predict persistent renal impairment or all-cause mortality in ADHF [58, 59]. Some authors have suggested that serum and urinary NGAL represent different aspects of the nephron's function. Whereas higher serum NGAL correlates well to reduced glomerular filtration function, urinary NGAL is more a marker of impaired natriuresis and diuresis in the setting of ADHF [60]. Urine NGAL level in decompensated HF patients may not be a significant predictor of diuretic dose requirement, but possibly a good marker for predicting AKI [61].

Such conclusions were not supported by the results of the AKINESIS study [62]. AKINESIS was a multicenter, prospective cohort study enrolling patients presenting with AHF requiring intravenous diuretic agents. The primary outcome was whether plasma NGAL could predict the development of WRF, defined as a sustained increase in plasma creatinine of 0.5 mg/dL or >50% above first value or initiation of acute renal replacement therapy, within the first 5 days of hospitalization. The main secondary outcome was in-hospital adverse events. Nine hundred twenty-seven subjects were enrolled (mean age, 68.5 years; 62% men). The primary outcome occurred in 72 subjects (7.8%). Peak plasma

NGAL was more predictive than the first NGAL, but neither added significant diagnostic utility over the first serum creatinine (areas under the curve: 0.656, 0.647, and 0.652, respectively). There were 235 adverse events in 144 subjects. The first NGAL was a better predictor than peak NGAL, but similar to the first creatinine (areas under the curve: 0.691, 0.653, and 0.686, respectively). In a post hoc analysis of subjects with an estimated glomerular filtration rate <60 mL/min/1.73 m^2, a first NGAL <150 ng/mL indicated a low likelihood of adverse events. The authors concluded that plasma NGAL was not superior to serum creatinine for the prediction of AKI or adverse in-hospital outcomes. However, in ADHF patients, the combination of plasma NGAL with serum creatinine was superior to serum creatinine alone in the diagnosis and early treatment of AKI with a better outcome including renal protection and a decreased hospital stay. This finding from a case series with random assignment of 12 patients in each group was reported from Angeletti et al. [63].

Proenkephalin

It has been known for long that the endogenous opioids including enkephalins also have roles in cardiovascular regulation [64, 65]. Proenkephalin A (PENK) is widely expressed, and cardiac cells secrete enkephalins, which have local effects on opioid receptors. Cardiodepressive through a negative inotropic effect and lower blood pressure and heart rate, opioid receptors, especially the delta-receptor that binds enkephalins, are widely distributed, with highest densities in the kidney [66]. Opiate administration in ADHF has been associated with poor outcomes [67]. Fontana et al. [68] reported elevated met-enkephalin levels in severe ADHF compared with less severe acute HF. In several acute disease conditions, elevated plasma levels of a PENK fragment (amino acids 119–159) have been associated with renal dysfunction and poor outcomes. Recently, PENK was demonstrated to be an independent predictor of major adverse cardiac events, including death, reinfarction, and rehospitalization for HF in patients presenting with acute myocardial infarction [69]. This also has been shown more recently for stable ambulatory patients with HF [70]. PENK predicts acute kidney injury after cardiac surgical procedures [71] and in patients with sepsis [72].

In a recent multicenter observational trial of the GREAT Network including 1908 patients with ADHF, PENK independently predicted worsening renal function (odds ratio 1.6) with a model receiver-operating characteristic area of 0.69. PENK was associated with the degree of AKI. PENK concentration was an independent predictor of 1-year mortality ($p < 0.0005$) and 1-year death and/or HF (hazard ratio 1.3). PENK levels independently predicted outcomes at 3 or 6 months and were independent predictors of in-hospital mortality, predominantly down-classifying risk in survivors when added to clinical scores. Basing on these results, the authors concluded that, following ADHF, circulating PENK levels reflect cardiorenal status and provide short-term and long-term prognostic information on both mortality and cardiovascular morbidity. PENK predicted AKI and could be used in conjunction with different clinical risk scores for in-hospital mortality [65].

TIMP-2/IGFBP7

Potential kidney biomarkers for CRS type 1 prediction are tissue inhibitor of metalloproteinase-2 (TIMP-2) and insulin-like growth factor-binding protein (IGFBP7). TIMP-2/IGFBP7 concentrations in urine appear to identify severe AKI in critically ill patients [73] and, during long-term follow-up recognize patients with increased risk of acute renal replacement and mortality after critical illness. A review by Kellum and Chawla [74] noted, that TIMP-2 and IGFBP7 may increase in response to inflammation, oxidative stress, ultraviolet radiation, drugs and toxins [75–77]. Such response on a wide variety of insults may help explain why they correspond to risk for AKI, a syndrome known for its multiple etiologies. Even if insults may not actually destroy cells, TIMP-2 and IGFBP7 may signal in autocrine and paracrine fashions [78]. Therefore, TIMP-2 and IGFBP7 have been recently described as an ‘alarm’ spreading to adjacent cells [74]. Also, the

authors reasoned, that detection of cellular stress may be more useful than detection of injury or cell death [79]. Increased TIMP-2/IGFBP7 concentrations in urine may be seen as an alarm of the stressed cells exiting any of the specific cell cycles 0–2 too early or too late which may also indicate a risk signal for apoptosis [80] or later kidney fibrosis because if the cell exits a phase too soon, or stays in a phase too long, the normal repair and recovery process can become maladaptive [81, 82]. Both TIMP2 and IGFBP7 have been implicated in the G1 cell-cycle arrest phase noted to occur during the very early phases of cellular stress [75–77]. Specifically, it has also been shown that renal tubular cells also go through this G1 cell-cycle arrest phase following stress due to a variety of insults [83]. Induction of cell-cycle arrest is not only associated with increased risk for AKI but may also serve as a mechanistic link between AKI and CKD [82]. Sustained cell-cycle arrest will result in a senescent cell phenotype and lead to fibrosis.

Despite increasing evidence for the clinical usefulness of cell cycle arrest markers (TIMP-2/IGFBP7) for AKI in critically ill patients and in patients undergoing cardiac surgery, there is sparse data on these biomarkers in CRS. Only two studies on TIMP-2/IGFBP7 predicting CRS were identified, both showing that IGFBP7, TIMP-2, and the combination of both, adequately predicted cardiorenal syndrome type 1 in patients who initially had developed ADHF [32, 84].

Biomarker Combinations

The question whether a combination of kidney biomarkers would be more useful than measurement of a single biomarker for prediction of CRS type 1 or prediction of worsening CRS type 1 was also investigated during the last years.

First, a prospective multicenter study enrolling 317 patients with ADHF in the exploration cohort and another 119 patients in the validation cohort, both patient cohorts with ADHF, found that the highest quartile of uAGT on admission was associated with a 50-fold increased risk of AKI development (CRS type 1) compared with the lowest quartile.

The uAGT level independently predicted the risk of 1-year mortality (adjusted odds ratio, 4.5) and rehospitalization (adjusted odds ratio, 3.6). Best performance for diagnostic risk reclassification of AKI and 1-year mortality was shown for a combination of uAGT and uNGAL in an independent multivariate model incorporating important clinical AKI risk factors [30].

Subsequently, to identify novel urinary biomarkers for progressing cardiorenal syndrome type 1, in a prospective multicenter study, 213 patients with ADHF and AKI were enrolled, of whom 50 patients presented with worsening acute kidney injury. The highest tertile of uAGT (odds ratio, OR 11) and uNGAL (OR 5) independently predicted AKI progression compared with the lowest tertile. These three urinary kidney biomarkers improved risk reclassification compared with the clinical model alone (category-free net reclassification improvement for primary (progressing AKI) and secondary outcomes (progressing AKI with subsequent death) ranging between 0.60 and 0.93). Basing on the findings that urine concentrations of AGT, NGAL and that of an inflammatory biomarker at the time of AKI diagnosis predicted AKI progression and worsening of AKI with death in ADHF the authors concluded that these renal injury biomarkers, when added to the clinical risk model, may identify a subpopulation of patients with CRS type 1 that is at the highest risk for the most adverse outcomes [85]. Improvement of risk prediction may improve care of ADHF, guide patient counseling, optimize management, and facilitate clinical trials for acute CRS treatment.

Another prospective multicenter study chose a somewhat different approach combining cardiac (proNT/BNP) and kidney biomarkers (NGAL) to predict AKI (CRS type 1) in 101 patients with ADHF admitted to the emergency department (ED). Compared to patients without AKI, those with AKI had a longer in-hospital length of stay (LOS) (mean LOS 13.1 ± 13.4 days vs. 4.8 ± 3.7 days, $p < 0.001$) and higher in-hospital mortality [6/26 (23%) vs. 2/75 (2.6%), $p < 0.001$]. Among the biomarkers assessed, baseline NT-proBNP (4846 vs. 3024 pg/mL; $p = 0.04$), BNP (609 vs. 435 pg/mL; $p = 0.05$) and NGAL

(234 vs. 174 pg/mL; p = 0.05) were each higher in those who developed WRF. In logistic regression, the combination of elevated natriuretic peptide and NGAL were additively predictive for AKI (CRS type 1). Rates of AKI were considerably higher in patients with elevation of both classes of biomarker. Comparable results were observed in a separate cohort of 162 patients with ADHF from a different center. The authors concluded that in ED patients with ADHF, the combination of NT-proBNP or BNP plus NGAL at presentation may be useful to predict impending CRS type 1 [86].

Finally, a case-control study which measured a combination of novel kidney biomarkers in 61 asymptomatic children with dilated cardiomyopathy (DCM) and LV ejection fraction (LVEF) < 55% found that children with DCM had higher tubular injury marker concentrations (incl. NGAL, KIM-1) in urine compared with healthy and age-matched controls while all conventional kidney function markers were within normal limits in the DCM cohort. A combined model using cut-off values of tubular injury biomarkers and BNP resulted in distinction between patients with mildly depressed LV (55 > LVEF ≥ 45) and those with LVEF < 45%. This data suggests that asymptomatic children with LVEF < 55% might have subclinical kidney injury that cannot be detected with conventional kidney function markers. Also, TIM in conjunction with other cardiac function markers may be utilized to distinguish asymptomatic children with DCM and moderate or worse LV dysfunction (LFEV < 45%) from those with mild LV dysfunction (55 > LVEF ≥ 45%) [87].

Interpretation of Test Results of Markers of Acute Tubular Damage/Stress

The ability to detect a state of acute tubular damage alone (biomarker positivity) allows an expanded criterion for diagnosis of AKI. This may represent 'subclinical' AKI in which loss of function might develop several days after detection of kidney damage or not at all due to renal function reserve or decreased creatinine production, however, still associated with impaired outcomes. Kidney biomarker positivity in the absence of detectable kidney damage may indicate a dynamic change in renal filtration of serum creatinine but that may be physiologic such as seen in patients with 'hemodynamic AKI' including cardiorenal syndrome. The presence of functional and damage criteria in patients with CRS type 1 is associated with the worst prognosis. Taken together, there is first evidence that acute tubular damage markers contribute to distinguishing a potentially adaptive from a maladaptive reaction of the kidney in response to ADHF. Therefore, measurement of novel kidney biomarkers in clinical practice might prove useful. Such approach would consider rapid reversibility of renal function loss before acute tubular damage may occur.

16.3.2 Markers to Predict or Indicate Cardiac Impairment After AKI (CRS type 3)

In CRS type 3 two major clinical questions need to be addressed: Are there novel (kidney) biomarkers which can indicate diuretic resistance as major risk factor for hypervolemia and cardiac impairment? Are there novel cardiac biomarkers early indicating cardiac impairment?

For novel kidney biomarkers indicating AKI we refer to Sect. 16.3.1.

16.3.2.1 Novel Kidney Biomarkers for Early Diagnosis of Diuretic Resistance

Serum hypochloremia at hospital admission is associated with neurohormonal activation, diuretic resistance, most likely as part of AKI, and worsening cardiac impairment [88, 89]. Sodium-free chloride supplementation was associated with increases in serum chloride and changes in several cardiorenal parameters [88]. Of interest, renal tubular resistance is the primary driver for loop diuretic resistance in acute heart failure [90]. Specifically, further studies point towards distal tubular compensatory sodium reabsorption being a major underlying reason of diuretic resistance [91].

Novel biomarkers, such as NGAL and ST2 indicate that diuretic unresponsiveness is associ-

ated with atherosclerosis, glomerular and tubular renal dysfunction and abnormal electrolytes. However, these markers were of limited clinical use to predict diuretic response at hospital admission for acute heart failure [92].

Once patients are identified with AKI, the furosemide stress test serves as a novel assessment of tubular function with robust predictive capacity to identify those patients with progressive AKI putting them at risk for cardiac impairment [93]. Overall, in the setting of early AKI, furosemide stress test urine output volume outperformed biochemical biomarkers for prediction of progressive AKI, need for RRT, and inpatient mortality. Using a furosemide stress test in patients with increased biomarker levels improves risk stratification [94, 95].

16.3.2.2 Novel Kidney Biomarkers for Early Diagnosis of Cardiac Impairment

Plasma NGAL concentrations at discharge can be a significant predictor for prognosis among patients in the Coronary Care Unit with a combination of NGAL and BNP providing a remarkably accurate prediction of major cardiovascular events. Measurement of NGAL at hospital discharge may enable identification of high-risk patients and adjustment of patient management [96]. Increased serum cystatin C concentration is an independent risk factor for heart failure in older adults and appears to provide a better measure of risk assessment than the serum creatinine concentration [97]. Higher levels of Cystatin C seem to be associated with increased left ventricular mass and concentric left ventricular hypertrophy and they could be an independent predictor of major cardiovascular events in a 12 month follow-up period of non-ST elevation acute coronary syndrome (ACS) patients [98].

Interleukin 18 (IL-18, molecular weight 18 kDa) has been indicated as associated with atherogenesis, coronary artery disease, lipidic plaque instability and myocardial infarction; high IL-18 levels have also been described in acute decompensated heart failure (ADHF) patients with clear impact on long term cardiovascular outcomes [99]. Combination of heart-type fatty acid-binding protein (H-FABP) and liver-type (L)-FABP seems to play a role in defining both kidney and heart injury, since H-FABP levels have been correlated with BNP levels in patients with ADHF. Both serum H-FABP and urinary L-FABP may be able to detect ongoing myocardial damage involved in the progression of ACS [100]. Finally, serum H-FABP appears as an independent predictor of cardiac events on 1-year follow-up evaluation in patients with ACS, also showing a greater predictive capacity for cardiac events rather than troponin [100].

16.3.2.3 Novel Cardiac Biomarkers of Plaque Destabilization Before Troponin Rise

Coronary plaque destabilization is considered as a primary event for acute coronary syndrome. In this respect, it is conceivable that markers of plaque (de)stabilization which have hitherto not been established in clinical practice can give an indication of a developing myocardial infarction even before the rise of highly sensitive troponins. These include choline, glycogen phosphorylase isoenzyme BB (GPBB), heart-type fatty acid-binding protein (H-FABP), angiopoietin-2, ischemia-modified albumin and myeloperoxidase (MPO). For example, heart-FABP (H-FABP) is a non-enzymatic protein increasing during cardiac ischemia and it holds more than 80% sensitivity for diagnosis of acute myocardial infarction in the period of 30–210 min after symptoms' onset [101], faster than CK-MB activity and cardiac troponins but there is limited data in patients with cardiorenal disease as is for the other mentioned novel cardiac biomarkers.

In summary, the comparison of these new markers with the highly sensitive troponins is either pending or has not shown any benefit in the diagnosis of patients with acute chest pain [102] Further studies are needed to make a direct comparison of a single measurement of these markers at earliest possible To allow for the onset of symptom onset and to verify a potentially additive prognostic value beyond that of highly sensitive troponins.

16.3.2.4 Novel Biomarkers of Cardiac Dysfunction

Cardiac biomarkers are commonly employed in daily clinical practice. BNP is a vasopeptide hormone released by left ventricle in response to wall stress and modified by a prohormone (proBNP). ProBNP and BNP are found in the kidney and glomerular filtration process has a role in the clearance of NT-proBNP. BNP/NT proBNP ratio is the best diagnosis and prognostic markers in patients with acute renal failure [103]. The PRIDE study has highlighted how NT-proBNP levels in patients with eGFR b60 mL/min/1.73 m^2 are the best predictors of clinical outcomes [104]. BNP and NT-proBNP provide fundamental information in patients with renal dysfunction although it has been to remember that NTproBNP seems to be reduced in patients undergo hemodialysis by high-flux membranes. Troponins are highly sensitive and specific for ischemic myocardial injury and they correlate with outcomes in kidney disease patients [105, 106].

A number of new markers for the diagnosis and prognosis of patients with ADHF are currently undergoing clinical testing. Promising candidates appear to be midregional pro-ANP, (pro) adrenomedullin, copeptin, and galectin-3. Exemplary, to date, galectin-3 may be one of the novel cardiac biomarkers to be considered for use in addition to BNP or NT-proBNP for risk stratification and potential therapeutic intervention. The strongest evidence of a cardiorenal link between AKI and the development of cardiac fibrosis is the β-galactoside-binding lectin galectin-3 [107, 108]. Galectin-3 mRNA expression in renal tubules was shown to be upregulated early after IRI and toxin-induced AKI and persisted for 7 days following injury [107]. Importantly, galectin-3 has been implicated in the development of myocardial fibrosis and heart failure in an experimental model of AKI [108]. Moreover, inhibition of galectin-3 can mitigate the formation of cardiac fibrosis [109]. Galectin-3 use appears to be in line with current Heart Failure Guidelines (American College of Cardiology Foundation and American Heart Association [ACCF/AHA]). Galectin-3 binds to cardiac myofibroblasts and induces collagen synthesis and cardiac remodeling. Values above 26 ng/mL are associated with a pronounced risk of early hospitalization or increased mortality. In the course of disease, galectin-3 levels appear to be relatively constant. Therefore, the marker offers no gain in the diagnosis of acute heart failure compared with the natriuretic peptides. The concentration is also independent of classic heart failure therapy, so it is not eligible for pharmacological monitoring. In summary, galectin-3 identifies patients who may benefit from more intensive therapy or surveillance.

However, the determination of above described novel markers of ADHF has not been established in the routine so far, presumably because with BNP/NT-proBNP a meaningful parameter has already been introduced.

16.4 Summary

Novel biomarkers early indicating acute kidney or cardiac impairment are already available. Such biomarkers may be valuable for prevention or early recognition of CRS types 1 and 3 interrupting the well-known cardiorenal vicious cycle. Troponins and acute renal tubular damage/stress markers (TIMP-2/IGFBP7, NGAL and others) may signal whether there is tissue damage or not and serum cystatin C and BNP/NTproBNP signal whether there is organ dysfunction or not. As such, prevailing pathophysiology of acute heart and kidney impairment may be, at least in part, early clinically addressed.

Biomarkers reflecting different aspects of acute cardiorenal/renocardiac syndrome pathophysiology are needed to allow patient phenotyping to inform prognosis and treatment. Future research may be directed at identification and implementation of specific biomarkers indicating prevailing pathophysiology in CRS types 1 and 3.

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Novel Biomarkers of Chronic Cardiorenal Disease

17

Peter A. McCullough

We are in the midst of chronic disease epidemics of chronic kidney disease (CKD) and heart failure (HF). There is now widespread recognition that CKD contributes to the initiation and progression of HF and vice versa. Cardiorenal syndromes can be thought of as organ failure syndromes where one organ system influences the progression of disease in the other according to the primum movens [1]. Heart failure through a variety of mechanisms including hemodynamic, neurhumeral, and cell signaling promote the progression of chronic kidney disease. This progression can be punctuated by episodes of acute kidney injury (AKI). Advancement of CKD directly leads to derangements in cardiac function and ultimately sodium and water retention, volume overload, neurohumoral changes, micronutrient abnormalities, all of which result in left ventricular and ultimately right ventricular dysfunction. Over 87% of patients with CKD approaching dialysis have structurally abnormal hearts as seen on echocardiography [2]. This chapter will explore the role of blood and urine biomarkers in the areas of screening and detection, diagnosis, prognosis, and management of cardiorenal syndromes [3].

It is recognized that approximately half of all patients diagnosed with HF have preserved left ventricular ejection fraction (HFpEF) and half have HF with reduced ejection fraction (HFrEF). The determinants, pathophysiology, contribution of ischemia, and relationship to arrhythmias with HFrEF are much better understood than HFpEF [4]. It is believed that a core pathophysiologic process involved in both forms of heart failure is cardiac fibrosis and the crosslinking of procollagen to collagen which is regulated in part, by the renin-angiotensin aldosterone system [5]. Once this structural event has occurred in the interstitium of the myocardium, it is unlikely that any form of neurohumoral modification will reverse, degrade, or influence the cross-linked collagen matrix. Thus, there is considerable interest in upstream use of neurohumoral antagonism to prevent or retard the progression of cardiac fibrosis in patients who ultimately develop HF. Some of these same core pathophysiologic processes may be determinants of the progression of CKD, particularly diabetic nephropathy. Hence it is not surprising that biomarkers developed for one organ system may have clinical relevance to the other. Most importantly has many other chapters have pointed out, measures of renal filtration function (serum creatinine and cystatin C) and the estimated glomerular filtration rate (eGFR) calculate with either assay or both, is a strong prognostic factor in cardiovascular outcomes, particularly heart failure hospitalization and death [6]. In a similar fashion, the degree of albuminuria or proteinuria, while a powerful predictor

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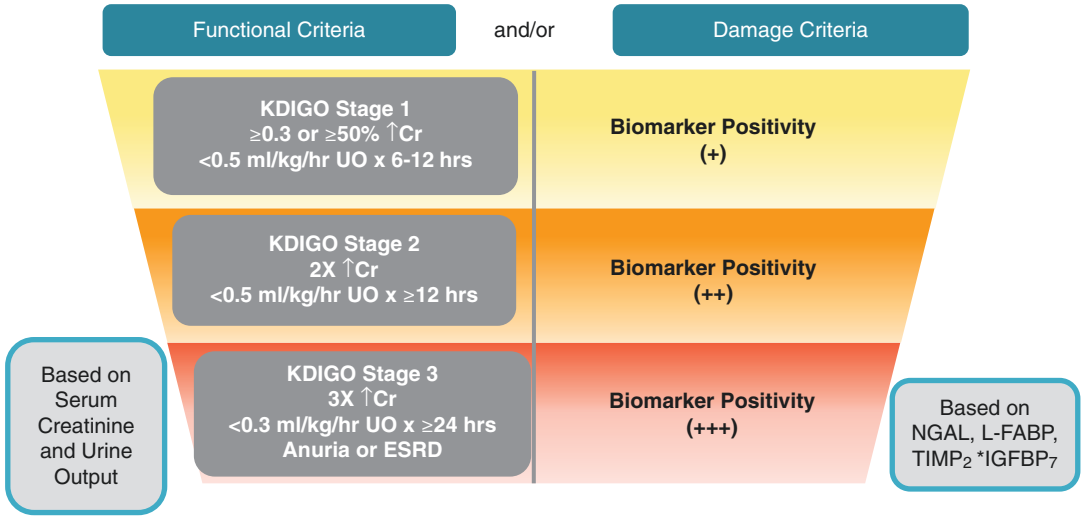
of the progression of kidney disease, is also associated with an array of atherosclerotic and myocardial disease outcomes [7].

There are new laboratory and imaging technologies that reveal the presence of cardiac and possibly renal fibrosis. The 2013 guidelines for HF from the American College of Cardiology recommend several biomarkers for the assessment and management including natriuretic peptides (B-type natriuretic peptide [BNP], N-terminal pro B-type natriuretic peptide [NT-proBNP]), ultrasensitive troponin I or T, galectin-3 and ST2 [8]. Numerous studies have demonstrated the usefulness of chronic serial measurements of BNP or NT-proBNP in the monitoring of myocardial disease [9, 10]. In addition, either peptide has proven to be useful as entry criteria for clinical trials HF patients, primary to exclude HF mimics. With the advent of more sensitive assays for troponin, it has been shown that the majority of patients with HF have chronic elevations which are related in a graded fashion to heart failure hospitalization and death [11, 12]. Galectin-3, a novel biomarker produced by cardiac macrophages and pericytes, is a member of the family of animal lectins, which selectively binds β-galactoside residue on the cell surface of fibroblasts, and via the transforming growth factor-beta pathway, signals the production and secretion of procollagen in the extracellular space [13]. Galectin-3 has been demonstrated to be elevated in blood in the presence of HF and is prognostically related to death independently and complementary to the natriuretic peptides [14]. Soluble ST2 is a decoy ligand for the interleukin-33 receptor present in the myocardium and its levels are quantitatively related to the severity of HF and are predictive of future HF hospitalizations and death [15, 16]. Interestingly, among young individuals in the Framingham Heart Study, ST2 levels anticipate the future development of HTN during adulthood [17]. In simplistic terms, ST2 can be thought of as a link between the immune system and left ventricular dysfunction. All four markers, ultrasensitive troponin I or T, BNP or NT-proBNP, galectin-3 and ST2 can be integrated into a chronic Myocardial Injury Summary Score (MISS) as shown below.

Fortunately, an integrated biomarker score such as MISS is amenable to comparison against cardiac imaging correlates such as advanced echo echocardiography with strain rate assessment and cardiac magnetic resonance imaging (cMRI) to give inferences on internal validity. Ultrasonography with strain rate imaging is an emerging technology for the assessment of cardiac fibrosis. In order to determine the healthy distensibility of the left ventricle over a course of treatment, ultrasound post-processing technology that is able to detect changes in motion to subtle for the human eye to appreciate is needed. Given that the muscle fibers of the left ventricle are laid out in a cross hatch formation from the apex to the base (near the mitral valve) and that the chambers are synchronized in their pumping, the overall expansion and contraction of the muscle follows a very complex sequence of events. Any damage to the myocardium due to lack of blood, infection or other events will change this expansion and contraction significantly. Ultrasound strain imaging provides a non-invasive, non-radiation method to assess the heart's ability to expand and contract properly and can detect subtle changes in these events. Cardiac magnetic resonance imaging using gadolinium has demonstrated that the presence of late gadolinium enhancement is indicative of myocardial tissue fibrosis and is the reference standard. The finding of cardiac fibrosis on cMRI is prognostic for cardiac arrhythmias and death in a variety of cardiomyopathies [18]. In summary, strain rate imaging is emerging as the most sensitive technique to evaluate the subtle effects of CKD on myocardial function with the ability to detect physiologic changes that cannot be seen on conventional echocardiography and likely will be complementary to cardiac MRI [19].

The diagnosis of AKI is best substantiated by measures of renal function and damage as shown in Fig. 17.1. In the setting of diuresis for acute HF and use of drugs that attenuate the renin-angiotensin system, cystatin-C performs as a more reliable indicator of renal filtration than serum creatinine [20, 21]. There are a vast number of protein biomarkers under investigation for the detection and prognosis of AKI as shown in



KDIGO=Kidney Disease International Global Outcomes, NGAL = neutrophil gelatinase associated lipocalin, L-FABP = L-type fatty acid binding protein, TIMP-2*IGFBP-7 = tissue inhibitor of metalloproteinase-2 (TIMP-2) and insulin growth factor binding protein-7 (IGFBP-7)

Fig. 17.1 Complementary functional and damage markers in the assessment of AKI. *KDIGO* Kidney Disease International Global Outcomes, *NGAL* neutrophil gelatinase associated lipocalin, *L-FABP* L-type fatty acid binding protein, *TIMP-2*IGFBP-7* tissue inhibitor of metalloproteinase-2 (TIMP-2) and insulin growth factor binding protein-7 (IGFBP-7)

Fig. 17.2. The three most relevant and approved by regulatory bodies in different areas in the world are: neutrophil gelatinase associated lipocalin (NGAL) (siderocalin-2), human L-type fatty acid binding protein (L-FABP), and the multiplied product of two cell cycle arrest markers in urine, tissue inhibitor of metalloproteinase-2 (TIMP-2) and insulin growth factor binding protein-7 (IGFBP-7). NGAL has the particular advantage of being measurable in plasma and not depending on urine collection with similar test performance in prospective studies [22]. Serial NGAL measurements in blood or urine can anticipate the development of severe AKI (KDIGO Stage 2 or 3) and anticipate its duration. NGAL appears to be most responsive in the setting of critical illness and has lesser utility in patients with heart failure or those receiving intravascular contrast agents. L-FABP appears to be ideally positioned as an early detection marker of contrast-induced acute kidney injury (CI-AKI) [23]. Finally, serial TIMP-2*IGFBP-7 has clinical value for the anticipation of stage 2/3 AKI in the setting of clinically illness when the test is strongly positive (>2.0) or strongly negative (<0.3) on one or more values [24]. Intermediate values (0.3–2.0) resolve into strongly positive or negative over serial measurement in the vast majority of cases.

There are a host of renal biomarkers in development that will complement the urine albumin:creatinine ratio in the detection of chronic renal injury including those outlined in Table 17.1 that can be organized into a chronic Kidney Injury Summary Score (KISS) analogous to the MISS score as proposed in the following paragraphs.

One of the difficulties faced by CKD clinical trials is the lack of indicators of improvement or worsening of kidney function over time outside of the time-honored measurement of serum creatinine and assessment of proteinuria. This paper proposes an integrative approach for promising renal biomarkers tested in acute and chronic settings. Since most of these markers have a skewed distribution to the left, they are amenable to logarithmic transformation, and hence, can be put on a summative scale in order to detect harm

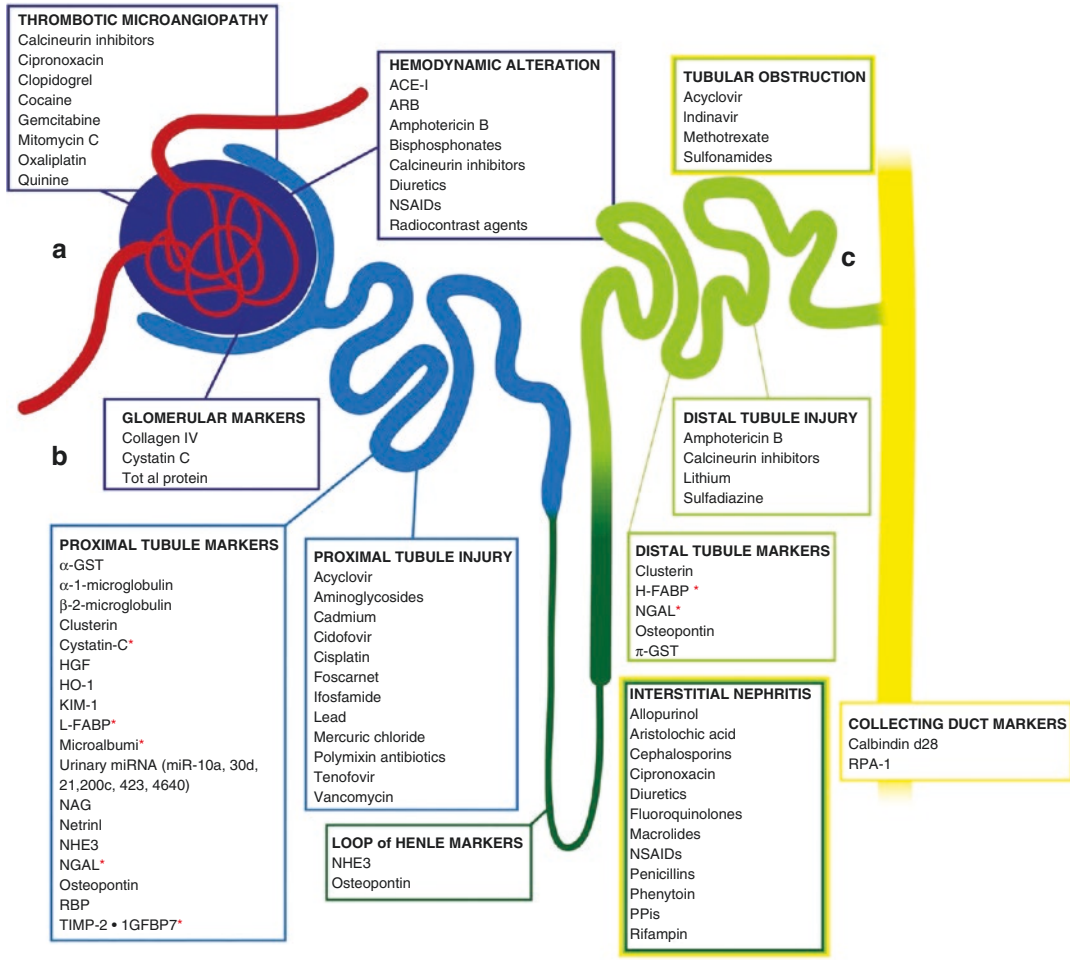


Fig. 17.2 Wide range of biomarkers for naturally occurring and drug or toxin-induced AKI in development with commercially available assays in one or more region indicated by red asterixes

Table 17.1 Biomarkers measured in blood and urine that comprise the myocardial injury summary score (MISS) and kidney injury summary score (KISS)

Components of myocardial injury summary score measured in whole blood, plasma, or serum	Components of kidney injury summary score measured in urine and blood (eGFR)
B-type natriuretic peptide (BNP) OR N-terminal pro B-type natriuretic peptide (NT-proBNP)	Tissue inhibitor of MetalloProteinases-2 (TIMP-2) × insulin-like growth factor binding protein-7 (IGFBP-7), also known as the commercially available NephroCheck® test
Ultrasensitive troponin I or T	Neutrophil gelatinase associated lipocalin (NGAL):creatinine (Cr) ratio
Galectin-3	Kidney injury molecule-1 (KIM-1):Cr ratio
ST2	L-type fatty acid binding protein:Cr ratio
	Interleukin-18:Cr ratio
	Alpha glutathione *S*-transferase (αGST):Cr ratio
	Pi glutathione *S*-transferase (piGST):Cr ratio
	N-acetyl-β-D-glucosaminidase (NAG):Cr ratio
	Cystatin-C:Cr ratio (uCysC:Cr)
	Estimated glomerular filtration rate (eGFR)
	Albumin:Cr ratio (ACR)

(movement to the right or positive) or benefit, movement to the left or negative from zero. Given the absence of information on relative importance, the initial calculation of KISS is divided by the number of renal markers and as a result is unweighted. Unfortunately, unlike for the MISS score, there is no imaging correlate that can be used for the kidneys to provide a degree of internal validity.

The proposed method for MISS and KISS involves calculation of biomarker indices, representing from one or more biomarkers (Table 17.1) measured in a panel, typically in batch mode at the end of a clinical trial [25]. The basic metric is the ratio of the peak value for a biomarker seen after a treatment to the baseline value before treatment. Both the baseline and post-treatment values may represent single assay measurements, or a single value determined from multiple measurements with rules used to ensure robust assay estimates.

The basic component for the score is defined as: $\text{Biomarker(i)}_{\text{Peak}}/\ \text{Biomarker(i)}_{\text{Baseline}}$.

The composite score across multiple biomarkers (i) for a given patient (j) would be defined as:

$$\text{MISS or KISS}(\text{j}) = \Sigma \log_{10}\left[\text{Biomarker}(\text{i})_{\text{Peak}} / \text{Biomarker}(\text{i})_{\text{Baseline}}\right] / \text{total number of biomarkers measured}\, \text{i} = 1, \text{n}$$

The composite score has these features:

1. Individual biomarker values, which may be measured on different scales, are normalized to a ratio value, without units, which can be combined. Use of ratios addresses, in part, the fact that the variability associated with individual biomarkers may be dependent on the magnitude of the values themselves, which make some statistics based on original values (especially, mean values) less suitable for comparing differences between treatment groups.
2. The MISS and KISS values are estimated at a patient level, so that a lack of change in some biomarkers can be compensated for by increases by others in the panel of biomarkers, reflecting different patient-to-patient expressions of biomarker changes.
3. The logarithmic transformation addresses the observed right-skewing in the distribution of underlying biomarker values, which are bounded by zero but may have relatively large values compared to mean or expected values. Log_{10} values between −1 and + 1 cover the range from original ratios of 0.1–10 for individual biomarkers. No change in a biomarker value from baseline to post-treatment use would result in a ratio of 1 and a log score of 0 (which is appealing). It may be reasonable to limit extreme ratios values below 0.1 or above 10 to those values. If that was done, then the total MISS or KISS score for 5 biomarkers, for example, would be dived by 5 and the range would be between −1 and + 1 as shown in Fig. 17.3.

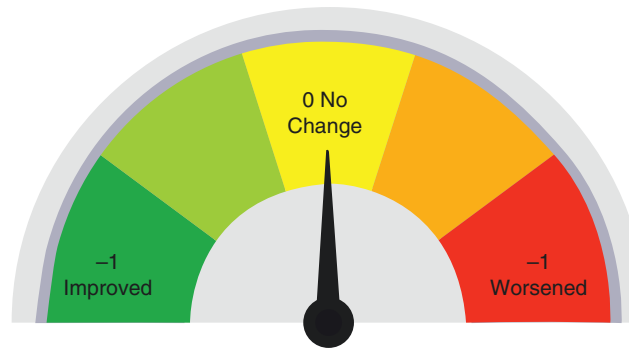


Fig. 17.3 Example dashboard of a MISS or KISS score indicating disease progression

4. For values that go down over time, such as the eGFR, then a negative value would need to be assigned to this term in the equation
5. The MISS and KISS values can be treated as ordinary statistics for purposes of summary, analysis, or sample size estimation for future trials.

17.1 Conclusions

Clinical development of novel therapies for both acute and chronic cardiorenal syndromes are in need of biologic measures of acute injury and disease progression that precede major adverse renal and cardiac events such as AKI, HF hospitalization, end-stage renal disease requiring dialysis, and death [26]. This chapter has summarized several clinically available biomarkers and has proposed both myocardial and kidney injury summary scores comprised of measured biomarkers and integrated into organ specific scores than can be used in future analyses and prospective studies of cardiorenal syndromes.

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18 Mechanisms of Kidney and Heart Cross-talk in Acute Kidney Injury

Negiin Pourafshar and Mark D. Okusa

18.1 Introduction

The kidney and heart are closely linked. Any condition that affects one organ, complicates the function of the other organ and dysfunction of both organs results in worse patient outcomes [1]. These relations would result in clinical pathology termed cardiorenal syndrome [2]. A report from the Acute Decompensated Heart Failure National Registry (ADHERE) national data base revealed that more than 60% of patients hospitalized with acute decompensated heart failure (ADHF) have moderate kidney disease [3], and a previous multivariate analysis showed that glomerular filtration rate (GFR) is the strongest predictor of mortality in patients with ADHF, exceeding functional class and ejection fraction [4]. Previous studies have revealed that baseline renal function impairment was linked to a higher risk of death and death or rehospitalization in ADHF patients [5].

Different pathways between heart and kidney characterize the pathophysiological relation of the two organs [6, 7]. The term "cardiorenal syndrome" (CRS) has been expanded to characterize a condition in which renal function impairment is a consequence of heart failure [8], however; the definition has not been clear [9]. Previously, there have been multiple different categories described for CRS, including type I, acute cardiorenal syndrome; type II, chronic cardiorenal syndrome; type III, acute renocardiac syndrome; type IV, chronic renocardiac syndrome; and type V, secondary cardiorenal syndrome [10], nevertheless, these categories are not commonly used. Currently the term renocardiac syndrome is applied to define the undesirable consequences of decreased renal function on the cardiovascular system [10].

Unfortunately, the vague description and the difficulty of these conditions creates inaccuracies in the evaluation and treatment of these condition [9]. Nevertheless, current advances in the field have improved our understanding of organ interactions to facilitate the management of the clinical entities that associate with these two organs [11].

In acute renocardiac syndrome, acute kidney injury (AKI) is thought to be the primary initiating event and cardiac failure is thought to be the subsequent consequence of AKI [12]. A number of mechanisms by which AKI could lead to cardiac injury, have been described (Fig. 18.1). Severely impaired kidney function, leads to systemic immunological reactions, activation of sympathetic nervous and renin–angiotensin–aldosterone systems, and increased oxidative

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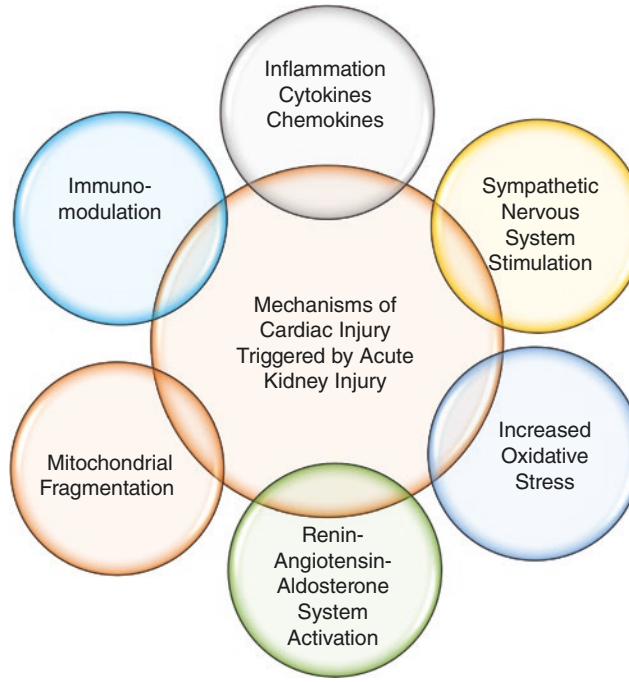

Fig. 18.1 Different mechanisms by which AKI triggers cardiac injury

stress [13, 14], resulting in sodium retention and fluid accumulation, hypertension, acidemia, and electrolyte disorders [15]. Moreover, AKI leads to accumulation of neutrophils, macrophages/monocytes and lymphocytes in the kidney [16] that contributes to increased systemic cytokines such as TNF-α, IL-1, IL-6 and IL-8 [12]. These cytokines are thought to initiate cardiac myocyte apoptosis [12, 13] and renal ischemia reperfusion leads to capillary vascular congestion [17–19]. It has been shown in previous studies that increased levels of proinflammatory cytokines are related to increased mortality [12, 20].

Unfortunately, the consequences of AKI on the heart have not been illuminated satisfactorily to date. This chapter updates the recent findings on distant cardiac effect of AKI [21].

18.2 Acute Renocardiac Syndrome

There continues to be an increase in AKI in the overall population [22, 23]. Previous studies have shown that, acute renal function decline, eventually results in cardiovascular complications such as ADHF, acute myocardial infarction (MI) and arrhythmias [24]. It has been reported that renal failure could lead to a substantial decrease in survival when compared to other organ failures [25]. AKI is related to major adverse kidney events, including worsened renal function and end stage renal disease (ESRD), as well as other major adverse cardiovascular events, such as MI, stroke, and ADHF [26].

AKI may lead to significant alterations in the heart function including left ventricular (LV) dilatation, and end-systolic and end-diastolic fractional restrictions [6]. Unfortunately, studies of the role of AKI on cardiac function, in humans are rare [27–29]. Previous animal studies have shown the effect of hemodynamics on renocardiac syndrome including the effect of renal venous pressure [30], intra-tubular pressure [30], on glomerular filtration rate (GFR) [31]. The animal studies revealed that elevated serum urea in AKI, results in significant blunting of vessel reactivity to endothelium dependent endogenous agonists which would further cause endothelial dysfunction with subsequent diminished organ perfusion [32, 33].

In addition to hemodynamic changes, there have been other mechanisms affecting cardiac

function including sympathetic nervous system (SNS), renin-angiotensin aldosterone (RAAS), coagulation systems [6], oxidative stress and nitric oxide equilibrium [13]. Moreover, mitochondrial dysfunction induced by AKI contributes to cardiac apoptosis [34]. We herein discuss the significant mechanisms by which AKI affects cardiac function (Fig. 18.1).

18.3 Mechanisms of Cardiac Injury Triggered by AKI

Induction of Systemic Inflammation: Role of Inflammation, Cytokines and Chemokines. AKI is known to initiate inflammation with resultant cytokine expression, leukocyte infiltration, apoptosis, and cardiac dysfunction [24]. It has been shown that increased leukocyte infiltration significantly enhances the risk of acute MI [35, 36], therefore, blockers of leukocyte activity could decrease the extent of injury [37–39]. Adhesion molecules that are upregulated by markers such as tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1), facilitate leukocyte infiltration and subsequent inflammation [13]. The interface of adhesion molecules, such as ICAM-1, on endothelial cells with their counter-receptors on leukocytes results in rolling, tethering and transmigration of leukocytes across the vessel wall [40]. Kelly et al., reported that in rats subjected to bilateral renal ischemia there was an increase in ICAM-1, TNF-α and IL-1 mRNA expression in the heart associated with evidence for leukocyte infiltration and functional changes comprised of left ventricular end diastolic diameter, left ventricular and systolic diameter and decreased fractional shortening by echocardiography [18].

Previous animal studies have illustrated that following AKI cardiac histologic changes observed including cellular apoptosis and vascular congestion [17, 18]. AKI results in cardiac infiltration of macrophages [41] and cardiac hypertrophy [42]. Burchill et al. found that in rats subjected to subtotal nephrectomy, AKI led to cardiac fibrosis and hypertrophy a few days after AKI [42]. Bozkurt et al. highlighted the link between TNFa and cardiac fibrosis was demonstrated through the continuous infusion of TNF-α which led to reduced LV function, cardiac myocyte shortening and LV dilation. Discontinuation of TNF-α infusion led to partial reversal of these changes [43] and selective blockade of TNF-α restricted cardiac apoptosis [18] .

In transgenic mice overexpression of TNF-α selectively in the heart using a murine alpha-myosin heavy chain promoter, led to premature death, biventricular dilation, myocyte apoptosis and transmural myositis [44]. The mechanism of TNF induced cardiac dysfunction is thought to be due to directs effects on myocytes as well as indirect effects of TNF-α inducing coronary vasoconstriction [45]. Lastly, chronic treatment with IL-1 caused an increased in myocardial P-Selectin expression and leukocyte infiltration of the heart resulting in myocardial dysfunction, and augmented cardiac myeloperoxidase activity, an effect reversed by neutralizing P-selectin [46]. These results suggest that adhesion molecules contribute importantly to the pathogenesis of cytokine induced myocardial dysfunction.

Sympathetic Nervous System Stimulation. There are inadequate studies regarding the role of the SNS in acute renocardiac syndrome. Stimulation of SNS, at first preserves cardiac output, however; it promotes apoptosis [47], neointimal formation and modifies immune system function [24]. Studies suggested that SNS has effects on intrarenal hemodynamics and increases renin secretion by the kidney. Moreover, it will worsen cardiac function through mechanisms including direct effects of norepinephrine, cardiac myocyte apoptosis, fluctuations in myocardial calcium homeostasis, as well as rise in myocardial oxygen requirement [14, 48, 49]. Furthermore, it has been suggested that SNS activation enhances neuropeptide Y production, which is a vascular growth-promoter, responsible for neointimal development, vasoconstriction, and impairment of immune system function [50]. It appears that the activation of the systemic nervous system stimulates apoptosis [47], and affects immune system function [24] which would result in initiation of cascade of inflammation with ensuing decline of organ function.

Renin-Angiotensin-Aldosterone System Activation. RAAS activation in AKI leads to angiotensin II release, vasoconstriction with subsequent failure of extracellular fluid homeostasis. Stimulation of the RAAS excites renin secretion by the kidneys with subsequent vasoconstriction and decreased oxygen delivery and aggravation of ischemia [6]. Angiotensin II can stimulate NADPH oxidase in multiple sites including endothelial cells [51, 52], vascular smooth cells, renal tubular cells [53], and cardiomyocytes [54] with production of reactive oxygen species [55] and resultant oxidative stress, inflammatory mediators release, and extracellular matrix regulation [56]. The hormone may also have a direct role in modifying myocardial structure [57], and apoptosis in cardiac myocyte cultures [58]. In heart failure patients, other than angiotensin II [59]; high plasma renin activity (PRA) is also linked to increased mortality [60]. A previous study showed increased cardiac morbidity and mortality with elevated renin levels [61]. Recently, direct renin blockers have been studied to provide data on the role of PRA separate from the classical RAAS pathway [62]. ALOFT trial showed that aliskiren which is active blocker of renin site of renin [63], reduced PRA, urinary aldosterone in stable HF patients [64]. However, the direct role of PRA and renin blockers in adverse cardiac outcomes, is still debatable [65].

Increased Oxidative Stress. The inflammatory cytokines are characteristically thought to produce decreased cardiac inotropic effects, nonetheless the form of the inotropic response is multifaceted. An instantaneous response can be either stimulatory or depressant and is affected by Nitric oxide (NO) developed from NO synthase (cNOS), sphingolipid mediators, arachidonic acid (AA), and variations in intracellular Ca^{2+} [66]. A delayed response is regularly cardiodepressant and results principally from the NO generated from inducible NOS (iNOS), the production of reactive oxygen species (ROS), and changes in β-adrenergic receptor (β-AR) signaling [66].

Immunomodulation: the Role of Immune system. Both innate and adaptive immune responses are important for tissue damage or infection [6, 67]. The innate immune system is immediately activated in infection states and inflammatory conditions. The adaptive immune system performs as a second line of defense [68–70]. The kidney dendritic cells reside in the interstitial extracellular compartment and are activated by innate immune system in response to hypoxia and the release of danger associated molecular patterns (DAMPS) [71, 72]. The early immune response entails activation of dendritic cells and dual activation of interleukin (IL-)12/interferon-γ (IFN-γ) and IL-23/IL-17 signaling pathways [73–75] . As discussed earlier, the renal injury activates the inflammatory pathways resulting in stimulation and infiltration of leukocytes with resultant myocardial hypertrophy, apoptosis and fibrosis due to cellular proliferation and inflammation [18, 69, 76]. Immediately (<1 min) following ischemia reperfusion injury cytokines are released into the circulation from the kidney [16] The systemic inflammatory response leads to cardiac immune cell infiltration and adherence of neutrophils to the vascular endothelium, which is a critical early in the course tissue injury [77, 78]. After adherence and chemotaxis, neutrophils liberate reactive oxygen species, proteases, myeloperoxidase with direct tissue damage along with stimulation of cytokine release with resultant cardiac injury [79, 80].

Role of Mitochondria in AKI-Induced Cardiac Injury. The kidney and heart both utilize oxidative phosphorylation for energy needs, therefore they have abundant mitochondria. It can be presumed that mitochondrial damage would contribute to AKI and heart dysfunction. Brooks et al., described a notable morphologic modification of mitochondria in AKI models [81]. Mitochondrial fragmentation was seen prior to cytochrome release and cellular apoptosis. A decrease in mitochondrial fragmentation and cardiac apoptosis (which are seen in AKI) has been observed to be caused by a dynamin-related protein 1 inhibitor (Drp 1). A previous study confirmed that AKI resulted in cardiac mitochondrial damage via Drp1 activation. Drp1 is a regulator of mitochondrial fragmentation. Drp1 is primarily in cytoplasm; however, situations that activate the molecule result in transferring to the outer

membrane of mitochondria with resultant mitochondrial splitting. This has been revealed in studies of small RNA knockdown experiments [81]. Drp1 stimulation during cardiac injury resulted in left ventricle failure [82]. Drp1-dependent remodeling causes cytochrome c release from mitochondria [83] which is through mitochondrial DNA distribution [84]. Also, it appears that inhibition of Drp1 by overexpressing dominant-negative mutant interdicted the release of cytochrome c and reduced apoptosis [85]. While mechanisms of AKI induced mitochondrial fission in the heart is uncertain, the data endorse that it could be a novel therapeutic focus in cardiac failure stimulated by AKI.

18.4 Possible Interventions Against Cardiac Injury in AKI

Studies regarding appropriate management and prevention of cardiac injury induced by AKI are deficient. Treatment strategies are challenging; inhibition of volume overload is essential to reduce the possible decline in cardiac and renal function and different inotropes and vasodilators have been evaluated for the effect on heart and kidney function [86], however, diuretic use to ameliorate clinical symptoms in ADHF patients in the setting of renal injury remains controversial as the data on the mortality benefit in patients with AKI is debatable [87, 88]. In fact, studies did not recommend use of diuretics for AKI apart from treatment of volume overload [88, 89]. Angiotensin-converting enzyme inhibitors (ACEIs), are suggested to be beneficial for cardiovascular mortality in patients with mild kidney injury [90]. These medication's effects on hemodynamics, and ventricular remodeling may support their positive cardiovascular outcome, however their use in non-dialysis patients with severe AKI remains controversial.

Another interesting and conflicting area of study is renal sympathetic nerve denervation (RDN) to block the effect of the SNS which increased renin release through induction of beta-1 receptors in the juxtaglomerular apparatus as well as alpha-1B receptors of the collecting ducts to boost reabsorption of sodium and alpha-1A receptors of renal vasculature to endorse vasoconstriction. It is suggested that renal nerves could play a role in renal inflammation and podocyte injury due to β-adrenergic receptor activation as well as release of neuropeptides, and renin release from with subsequent increased plasma angiotensin II levels and other pro-inflammatory cytokines including tumor necrosis factor and IL-1β from immune cells [91]. Previous animal studies showed that renal denervation diminished inflammation [92], however the outcomes of clinical trials are variable. It should be noted that due to the concern for worsening renal function, RDN may not be appropriate in patients with AKI. Therefore, to date, several questions continue to remain unanswered about the function of renal nerves in prevention and management of acute renocardiac syndrome. In general, it appears that an improved perception of the pathophysiological mechanism through further clinical trials is needed to offer a possible target for intervention.

18.5 Long Term Prognosis of Acute Renocardiac Syndrome

Previous studies showed that AKI signifies severe renal and cardiovascular results when matched with similar cardiovascular risk factors. Evidence confirms increased long-term coronary events and mortality in AKI patients [93, 94]. Prior studies have revealed that patients who had severe AKI requiring temporary dialysis had more coronary events than those without severe AKI, which emphasizes the role of AKI as a cause of cardiovascular mortality [95].

In an observational study which examined hospitalized patients recovered from dialysis-requiring AKI showed a substantial correlation of AKI with higher risk of all-cause mortality independent of CKD progression and coronary events [96]. Such study may propose aspects particular to AKI rather than CKD progression which can play a role in coronary artery disease.

A study of more than 18,000 patients with AKI exhibited that AKI was related to long-term cardiovascular events, even after multivariable adjustment [26], They revealed that contrasted to patients with MI, those patients with both MI and AKI are almost twice as likely to be admitted for ADHF contrasted to patients with MI alone. The study concluded that AKI is possibly worse for an individual than is an MI exposure [26]. A study by Wu et al., indicated that the AKI detrimental outcome on long-standing cardiovascular risk is similar to the risk from diabetes mellitus (DM) [96]. DM is a coronary heart disease risk comparable which contributes to a 10-year risk of coronary death [97]. Moreover, it should be noted that several studies proposed that AKI elevates the risk of CKD advancement [98–101], and CKD is an important risk factor for cardiovascular disease [102].

These findings highlight the possible value of inhibiting cardiovascular injury by targeting AKI patients, and dialysis-requiring AKI with consequent improvement should be considered as a risk group for cardiovascular disease [96]. Recognition of risk factors implicated in renal injury could be the greatest reasonable method to avoid and defer the unfavorable consequences [102].

18.6 Conclusion

Cardiac and kidney function are firmly interrelated and interaction among these organs occurs across a multiplicity of pathways (Fig. 18.1). It is believed that the connection among cardiac and renal injury signifies the pathophysiological methods that relate in harmful ways to cause acute renocardiac syndrome.

Aggressive risk modification, and appropriate secondary intervention are crucial. The ample pathogenetic characterization of cellular and subcellular arrangements in cardiac and renal interaction and the use of new biomarkers could aid in the choice of the best therapeutic option and enhance survival. Furthermore, future trials are needed to provide outcomes which could provide applicable therapeutic strategies. Until such results are accessible, it seems rational to aim for recognized treatment focuses with an individualized patient-oriented approach.

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19 Kidney and the Heart in Multiorgan System Failure

Nevin M. Katz

19.1 Introduction

The interaction between the heart and the kidney in critical care patients is key to sustaining adequate *perfusion* of the whole body and individual organs. This interaction is of great importance in preventing and reversing *multiorgan system failure.* Perfusion of the whole body and of individual organs is determined by fluid balance, hemodynamics, arterial obstructive disease, and oxygen delivery.

19.2 Fluid Balance and Kidney and Heart Interaction

Fluid balance in critically ill patients is an important issue, and can be an especially challenging issue in patients with acute kidney injury or chronic renal failure. Achieving and maintaining an optimal fluid balance is an important goal of critical care.

The complexity of the interaction between the heart and kidney is highlighted by the development of the classification of "cardiorenal syndromes." [1] This interaction is related to multiple physiologic abnormalities including heart failure, hypertension, pulmonary dysfunction, renal failure, fluid overload, electrolyte abnormalities, and multiorgan system failure. Components of this physiologic complexity include increased stimulation of the renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system activation, and arginine vasopressin stimulation.

Hypovolemia is often related to blood loss, or inadequate fluid replacement, and is usually not related to renal dysfunction. In contrast, *hypervolemia*, or *fluid overload*, is an important complication of acute and/or chronic renal failure, as well as heart failure. Fluid overload causing edema of organ systems leads to *multiorgan system failure*. Organs particularly vulnerable to injury in this situation include the lungs, brain, heart, kidney, liver, and gastro-intestinal tract. Management in this situation often includes pharmacologic agents which promote diuresis, and may include renal replacement therapy (RRT) with continuous or intermittent dialysis or hemofiltration. Early initiation of RRT has been associated with reduced mortality in critically ill patients [2]. These patients typically have multiorgan system failure. The favorable effect of continuous versus intermittent RRT, in the ICU on renal recovery at hospital discharge, has been reported [3].

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19.3 Hemodynamics

One of the most important aspects of critical care is achieving an adequate cardiac output. John W. Kirklin, mentor for many cardiac surgeons of his day, and Eugene H. Blackstone, his research associate, were among the first to quantify the importance of preventing low cardiac output in the postoperative period after cardiac surgery. Kirklin and Blackstone came to the conclusion that if the postoperative cardiac index is less than 2.0 L/min/m^2, the probability of cardiac death rises steeply and immediate intervention is warranted [4, 5]. Optimizing hemodynamics to achieve adequate cardiac output and oxygen supply-demand balance is central to the management of critically ill patients.

Optimal critical care requires continuous monitoring, proactive rather than reactive measures, and rapid and effective responses when new issues arise. Optimal hemodynamic management is dependent on adjusting the hemodynamic parameters of heart rate/rhythm, preload, afterload, and contractility so that perfusion of the body and its critical organs meets metabolic demands. To accomplish this efficiently, management needs to be based on specific hemodynamic-related targets.

The concepts, principles, and technology of hemodynamic monitoring and management have evolved over many years, and we can now focus on an increased number of hemodynamic targets. Balancing and adjusting hemodynamic management to achieve these targets provides the opportunity to maximize the effectiveness and efficiency of the therapeutic options we now have (Fig. 19.1).

19.4 Hemodynamic Targets

The classical parameters to adjust cardiac output are heart rate/rhythm, preload, afterload, and contractility. If the patient is postoperative cardiac surgery, an additional parameter for correction, is the surgical result, if it is not optimal. Further surgery or catheter interventions for coronary artery obstructive disease, valvular disease, or cardiac tamponade may be required. This may also include additional correction of vascular obstructions, such as stenosis of a renal artery.

Adjusting the basic hemodynamic parameters of afterload and contractility with pharmacologic therapy will determine the specific Frank-Starling ventricular function curve on which the patient's heart is performing. Adjusting preload can then lead to the position on that curve with the best possible cardiac output.

The technology of ventricular assist devices (VAD's) and ECMO provide the means to achieve adequate hemodynamic and perfusion targets. Mixed venous oxygen saturation has been the classical measure of perfusion adequacy.

Classical hemodynamic targets for critical care patients have guided hemodynamic management (Table 19.1). The wide range of acceptable pressures and flows reflects the wide range of conditions with which patients present. Although cardiac output and filling pressures are classically monitored with pulmonary artery (PA) balloon occlusion catheters, advanced central venous and arterial catheters are now available that provide continuous key hemodynamic data and are less invasive.

19.5 Afterload Therapy: Afterload Reduction and Treatment of Vasoplegia

It is well-recognized that decreasing afterload while maintaining adequate myocardial perfusion increases cardiac output for a given preload and creates another set of ventricular function curves for a given contractile state. The type and amount of adjustment varies according to a patient's preoperative and postoperative conditions. Patients with hypertension or atherosclerotic disease require a higher perfusion pressure to avoid ischemic cardiac, cerebral, renal, and mesenteric complications. If LV function is depressed, cardiac performance can usually be improved by reducing afterload. In postoperative patients after mitral repairs or mitral valve replacement for severe mitral regurgitation, lowering afterload may be beneficial as the ventricle

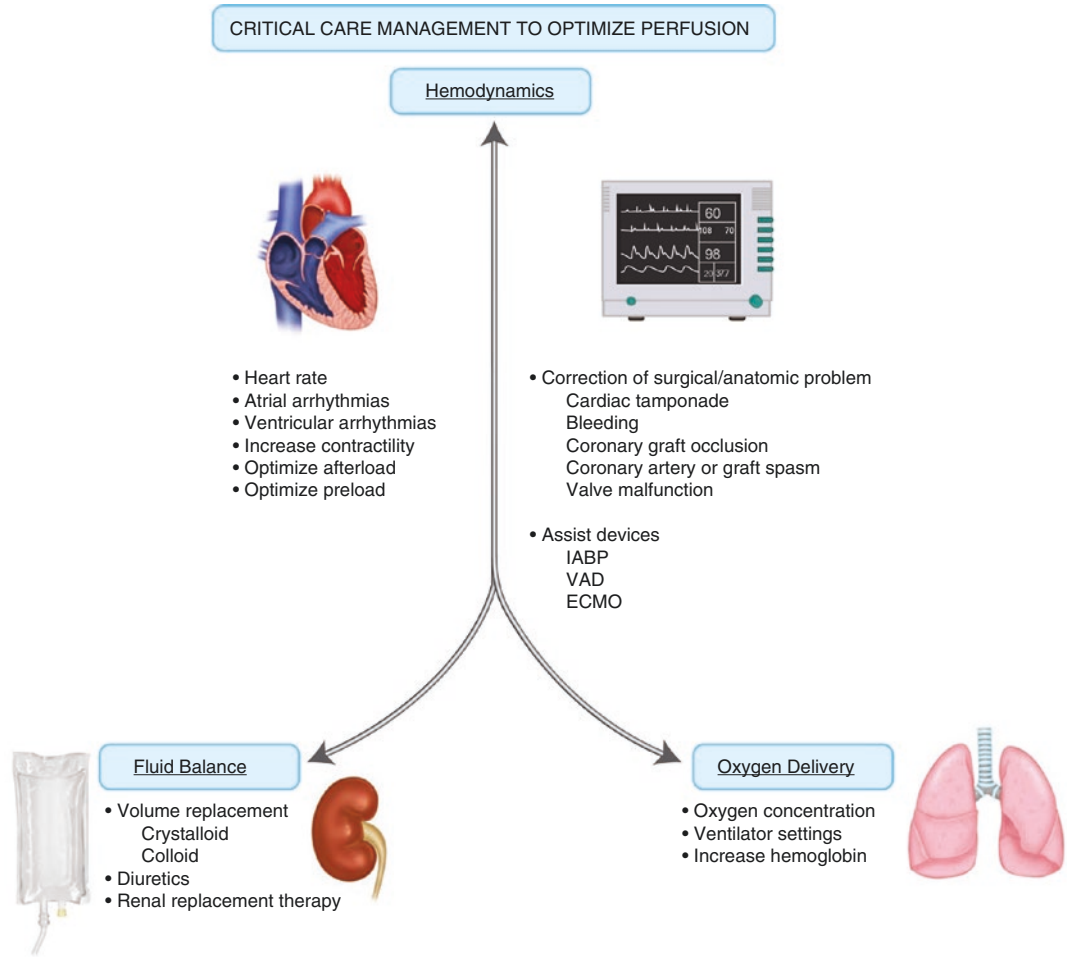

Fig. 19.1 The critical care management to optimize perfusion and reduce factors causing the cardio-renal syndrome includes: optimizing hemodynamics, fluid balance, and oxygen delivery

Table 19.1 Classical hemodynamic targets used to guide hemodynamic management

Cardiac Output (Cardiac Index) C.I. 2.2–4.4 L/min/m^2
Pressures
Systemic BP:
Systolic 90–140 mmHg
MAP 70–90 mmHg
LAP or PCWP (5–18 mmHg)
RAP or CVP (5–15 mmHg)
Systemic vascular resistance (SVR) (900–1400 dynes/sec/cm^5)
Mixed venous oxygen saturation (S_vO_2)
Pulmonary artery—60–80%
Central venous—70–80%

adjusts to the competent valve and the corresponding sudden postoperative increase in left ventricular afterload due to the competent valve.

Afterload can be reduced by using vasodilators, or by unloading the ventricle with an intra-aortic balloon pump or ventricular assist device. Several pharmacologic agents can be employed. The vasodilator nitroprusside has been shown to decrease afterload and improve left cardiac function in patients with aortic stenosis [6]. Nitroprusside is a more effective arteriolar dilator than nitroglycerine, which generally produces more venous dilatation. Nitroglycerine may produce hypotension if the patient is relatively hypovolemic, creating a severe drop in preload with a corresponding fall in arterial blood pressure.

Several other agents are commonly employed to decrease afterload. Calcium channel blockers, such as nicardipine and clevidipine, are selective

arteriolar dilators and avoid marked decreases in preload, as they dilate only the arterial side of the circulation. Inotropic agents, such as dobutamine and milrinone, produce arteriolar vasodilatation and increase contractility. ACE inhibitors may be useful as well, but since they are generally given intermittently rather than as infusions, making fine adjustments is more difficult.

The loss of vascular tone, or vasoplegia, requiring pressor agents has been well recognized in patients with septic shock. Researchers at Columbia University studied vasopressin levels in patients with septic vasodilatory shock. They documented vasopressin deficiency as a contributing cause of the shock [7]. Vasoplegia has also been recognized in some cardiac surgical patients following cardiopulmonary bypass and also after placement of ventricular assist devices. The researchers at Columbia University studied vasopressin levels in post-bypass patients with vasodilatory shock requiring catecholamine pressors who were undergoing placement of a ventricular assist device. They documented low plasma vasopressin levels inappropriate for the degree of hypotension. The patients with vasopressin deficiency responded to intravenous administration of vasopressin [8]. Vasopressin is now one of the pharmacologic options employed in vasodilatory shock.

More recently, researchers of the ATHOS-3 Study found that intravenous angiotensin II was effective for treatment of vasodilatory shock. This represents another alternative therapeutic option to vasopressin and catecholamine vasopressors for vasoplegia [9]. Effective treatment of vasoplegia is important to ensure adequate perfusion pressure and prevent multiorgan system failure.

19.6 Contractility

Increasing ventricular myocardial contractility with inotropic agents is another important option to improve the ventricular function curve on which a patient's heart is operating [10]. Selection of the support agent will be determined by the patient's sensitivity to specific drugs and whether increasing myocardial oxygen demand will be met with adequate coronary blood flow. If the patient has minimal or no coronary artery disease, or has had bypass surgery for coronary artery disease and complete revascularization has been accomplished, a catecholamine such as dobutamine may work well. On the other hand, if a patient has residual areas of myocardial ischemia due to diffuse disease, a phosphodiesterase inhibitor such as milrinone, which is less likely to increase myocardial oxygen consumption, is advantageous. In the presence of shock, norepinephrine appears to be preferable to dopamine, as it is associated with fewer arrhythmias [11]. The calcium sensitizing agent levosimendan, used in Europe, appears to have a favorable hemodynamic profile and is particularly useful for the treatment of acute and advanced heart failure [12]. Management of pulmonary hypertension in the presence of right ventricular failure often involves combining several pharmacologic agents, including inotropes such as dobutamine and milrinone [13].

19.7 Position on the Ventricular Function Curve: Volume Responsiveness

Measuring filling pressures with central and PA catheters provides a quantitative measure of preload, but does not identify the patient's position on the Frank-Starling ventricular function curve. This position is important because it determines whether an infusion of volume will increase, have no effect, or reduce stroke volume and cardiac output. Stated another way, adding volume can affect sarcomere length and determine if the patient is on the rising portion of the ventricular function curve, on the plateau portion, or "over the top" onto the declining portion of the curve. In critically ill patients, an unwarranted infusion of volume may compromise the function of the respiratory, GI, and neurologic systems.

If the patient is relatively stable, the physician may have the luxury of infusing volume and awaiting the results to assess volume responsiveness. In the early postoperative period, volume

responsiveness can be more immediately estimated from pulsus paradoxus if the patient is on a mechanical ventilator. Marked variations in arterial pressure during the respiratory cycle generally indicate relative hypovolemia, which is volume responsive. Passive leg raising is a rapid and simple way to assess volume responsiveness at the bedside [14]. Raising both legs gives an automatic transient central infusion of 150–300 mL of volume, which can be instantly removed by lowering the legs. If passive leg raising increases arterial pressure, patients are likely to be on the rising portion of the Frank-Starling curve and will be volume responsive.

In the last several years, technology has been developed to provide continuous data on volume responsiveness. Arterial waveform analysis parameters such as stroke volume variation (SVV) and pulse pressure variation (PPV) can be used to monitor the patient's position on a ventricular function curve [15, 16]. An SVV of greater than 15% indicates a position on the ascending portion of the curve, which means that the patient will be volume responsive. In contrast, if the SVV is less than 10–15%, the patient's position on the ventricular function curve is near the plateau portion, and cardiac output will likely not increase with an infusion of volume.

Unfortunately, arterial waveform analysis technology cannot yet be used in the presence of arrhythmias or if the patient is on an intra-aortic balloon pump (IABP). Respirations must be completely controlled with a mechanical ventilator, and sedation and paralysis should be used if needed. Refinements in the technology to allow wider uses of arterial waveform analysis will be welcome, but in the most critically ill patients who are not having arrhythmias and are not on an IABP, the technology is an important advance.

19.8 Ventricular Compliance

The stiffness of a ventricle and its ability to relax in diastole are important determinants of a patient's ventricular function curve. The issue is that ventricular filling and, therefore cardiac output, are decreased when ventricular compliance is decreased. This parameter is particularly relevant for achieving optimal hemodynamics in patients with severe left ventricular hypertrophy (LVH) due to chronic severe hypertension or aortic stenosis. Patients with myocardial edema after a long period of cardio-pulmonary bypass also have reduced ventricular compliance. Bedside echocardiography is useful in the assessment of ventricular compliance and in guiding therapy [17].

Employing a higher preload in patients with decreased ventricular compliance may be particularly advantageous if it does not adversely affect pulmonary, renal and hepatic function. Pharmacologic interventions can have a favorable or a detrimental effect on ventricular compliance. Catecholamines tend to stiffen the ventricle or reduce ventricular compliance, so that increasing preload rather than adding or increasing the dose of a catecholamine is preferable. An additional approach is to employ lucitropic agents, such as levosimendan, which as mentioned has been used in Europe.

19.9 Ventricular Imaging

Bedside echocardiography and ultrasound technology have significantly advanced hemodynamic analysis in the ICU and is less invasive [18]. Ultrasound ventricular imaging provides important information on the degree of ventricular filling. With multiple readings, the configuration of the patient's ventricular function curve can be defined. Ultrasound imaging can be used to assess global systolic ventricular function, provide an estimate of ejection fraction, assess ventricular compliance, and differentiate between global and regional ventricular dysfunction. The latter may provide evidence of a malfunctioning bypass graft.

Importantly, bedside ultrasound can be used to identify cardiac tamponade, as well as dysfunctions in native, repaired, or replaced valves. Clearly, bedside echocardiography is a valuable component of post-cardiac surgical critical care monitoring and complements hemodynamic technology.

19.10 Oxygen Delivery and Balance

Adequate perfusion of the body and its individual organs depends on adequate oxygen delivery that meets oxygen demands. Oxygen delivery is dependent on arterial oxygen saturation, hemoglobin concentration in the blood, and cardiac output or cardiopulmonary bypass/VAD flow. Oxygen delivery in the operating room and the intensive care unit has been identified as an important risk factor for AKI after cardiac surgery [19, 20]. Especially in intensive care patients, issues of an imbalance of oxygen demand versus delivery can lead to inadequate oxygenation of tissues in patients who are febrile or shivering after surgery.

19.11 Whole Body Perfusion Monitoring

The detection and treatment of impaired whole body perfusion are essential to prevent irreversible organ damage and multiorgan system failure in critical care patients. In postoperative patients, maintaining optimal whole body perfusion facilitates a smooth recovery. Classical parameters to assess whole body perfusion include blood pressure, pulse, the temperature, color, and pulses in the extremities, urine output, and neurologic function. Pulmonary artery and central venous mixed venous oxygen saturation are valuable quantitative parameters. Another important index of whole body perfusion is serum lactate, particularly in the presence of sepsis [21].

Important monitoring advances include the continuous measurement of mixed venous oxygen saturation with a PA catheter and the measurement of central venous oxygen saturation with a catheter positioned in the SVC or right atrium. Normal values for true mixed venous oxygen saturation measured by a PA catheter (SvO_2) range from 60 to 80%. Central venous oxygen saturation measurements ($ScvO_2$) in critically ill patients tend to be slightly higher than true mixed venous oxygen, so the usual target is at least 70%. Reduction of central venous oxygen saturation has been shown to be a predictor of reintubation in difficult-to-wean patients [22].

Monitoring mixed venous or central venous oxygen saturation directs attention to the determinants of oxygen supply and demand, and can lead to important adjustments in management. Supply determinants include cardiac output, hemoglobin concentration, and arterial oxygen saturation, all of which have secondary determinants. Demand determinants in the ICU include fever, shivering, and activity. Cerebral monitoring systems are particularly useful for monitoring activity in the sedated patient. If the monitoring system indicates over-sedation, the sedative infusion can be decreased with a usual corresponding improvement in blood pressure, cardiac output, and mixed venous oxygen saturation. On the other hand, if the patient is found to be light, further sedation may result in more stable hemodynamics with fewer episodes of hypotension and hypertension, and may eliminate activity that increases metabolic demand. The result is better oxygen balance, which is reflected in an increase in mixed venous oxygen saturation.

19.12 Specific Organ Perfusion

Ultimately, the patient's prognosis and recovery will be determined by whether specific organ systems are adequately perfused. Among the most critical organ systems in the early postoperative period are the cardiovascular, respiratory, renal, GI, and neurologic systems Complications can be prevented or reduced in severity by identifying early organ dysfunction and making timely adjustments in therapy.

For years, physicians have used important indicators of myocardial injury, such as serum determinations of cardiac enzymes, bedside monitoring for arrhythmias, and ST segment changes. Serial standard electrocardiograms have also given early indications of myocardial injury or infarction. Similarly, measurements of blood gases, standard bedside chest films, and measurements of respiratory mechanics have provided important data regarding early pulmonary injury.

In contrast, until recently we have not had the means to detect acute kidney injury (AKI) soon after its occurrence. Elevations in serum creatinine, which have been the gold standard for AKI, may not be evident for up to 48 h after a damaging event, such as a myocardial infarction or a period of prolonged cardiopulmonary bypass. Fortunately, biomarkers for the early detection of AKI have been developed [23]. It is now possible to implement rapidly management strategies to prevent or decrease the severity of AKI. In the future, development of similar biomarker technology will make possible the early detection of injury to other vital organs.

19.13 Kidney Perfusion: Acute Kidney Injury and Acute Kidney Stress

The identification of cell cycle arrest biomarkers that signal the potential development of AKI is part of an evolution in the molecular diagnosis and understanding of AKI [24]. These cell cycle arrest biomarkers are released by kidney cells during injury or stress and have been recognized as potentially valuable markers of renal stress along a path which may lead to AKI [25]. The pre-injury phase that leads to AKI has been termed acute kidney stress (AKS). Focus on this phase addresses the challenge to detect situations where the kidney is in danger of sustaining injury [26].

Studies have documented that impaired hemodynamics in patients during and early after cardiac surgery are associated with AKI. The ADQI XIII Work Group described new treatment targets for renal hemodynamics to address the challenges of preventing and treating AKI [27].

Importantly, in adults, technology to monitor renal blood flow has yet to be developed. Currently, urine flow is used as a surrogate to monitor renal perfusion.

Hemodynamics clearly are an important determinant of renal blood flow. The use of cerebral oximetry to detect blood pressure excursions below the cerebral autoregulation threshold represents an innovative technology to alert physicians to hemodynamics that may result in AKI [28]. Such technology is now available for monitoring patients in the operating room and in intensive care units. However, obstructive lesions in the renal arterial vasculature and use of vasoconstrictive agents can impair renal blood flow in the presence of systemic blood pressure and cardiac output that are in the normal ranges for critical care patients.

As noted, a variety of renal biomarkers have now been identified and have the potential to enhance the understanding and diagnosis of AKI, particularly as biomarker monitoring is combined with monitoring changes in renal function. The 10th ADQI consensus conference summarized the potential use of biomarkers [23]. It seems appropriate that monitoring renal damage biomarker changes, such as cell cycle arrest biomarkers, which are released by kidney cells along a path which may lead to AKI [24], should be included in a diagnostic system for AKS. The renal biomarker NGAL can be a valuable clinical test to alert clinicians to AKI [29] and potentially AKS. However, its lack of specificity [30] and its loss discriminatory power with pre-existing renal disease [31] limit its use as an indicator of AKI and, accordingly of AKS.

Over the past several years, research studies have led to considerable progress in the prevention and treatment of AKI [32]. Computer decision support systems for in-hospital AKI have been developed [33]. Oxygen delivery has been identified as an important risk factor for AKI [19, 20]. Monitoring oxygen delivery in the operating room and in the ICU requires measurements of hemoglobin, arterial oxygen saturation and cardiopulmonary bypass flow or cardiac output.

Recent studies have led to preventive management strategies such as optimal fluid choice with avoidance of saline [34] and avoidance of nephrotoxic agents.

Adjustments in hemodynamics to prevent AKI can include elevation of the systemic blood pressure, optimization of central venous pressure to optimize the arterial-venous gradient across the kidney, increasing CPB flow or cardiac output via pharmacologic and/or mechanical support technology, and optimization of oxygen delivery.

Measures to prevent CSA-AKI have been summarized by Meersch and Zarbock [35].

19.14 Summary

The kidney and the heart individually, and interacting together, are key in determining whole body perfusion, and perfusion of individual organs. This interaction is of great importance in preventing and reversing multiorgan system failure. The definition of cardiorenal syndromes highlights the interaction between the kidney and the heart. Advances in monitoring and imaging technology now provide the critical care team with new targets to guide hemodynamic management. The key to treating low cardiac output is to adjust heart rate/rhythm, preload, afterload, and contractility to achieve optimal ventricular function. The pharmacologic treatment of vasodilatory shock, or vasoplegia, is now well established. Continuous monitoring of mixed venous oxygen saturation, an index of whole body perfusion, is now possible, and measurement of specific biomarkers for the early recognition of injuries to specific organs is becoming a reality. Research studies have led to considerable progress in the recognition, prevention and treatment of AKI. The overall result is that perfusion can be optimized, making it possible for critical care patients to have a smooth and more rapid recovery.

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20 Cardiac Consequences of Renal Artery Stenosis

Mohanad Hasan, Jose Tafur-Soto, and Hector Ventura

20.1 Introduction

Renal artery stenosis (RAS) is an important cause of secondary hypertension. RAS can be caused by athermanous plaque, vasculitis, congenital bands and fibromuscular dysplasia (FMD) (Fig. 20.1). In addition to threatening renal function, RAS presents an increased risk for cardiovascular decompensation syndromes such as refractory heart failure and flash pulmonary edema [1–3].

Atherosclerotic renal artery stenosis (ARAS) represent more than 90% of RAS. It affects mainly patients of advanced age and those with other risk factors for atherosclerotic disease (Diabetes, dyslipidemia, tobacco use) [4, 5]. ARAS may be unilateral or bilateral with involvement of the ostium and more proximal segments of the renal arteries.

FMD is a disease of medium size arteries affecting mainly young women. There is renal involvement about 60–75% [6] Balloon angioplasty has a significant impact on improving or curing many patients with isolated main renal artery FMD lesions [7, 8].

Understanding of the pathophysiology and clinical manifestation of RAS is crucial in optimizing care for patients with RAS. It is very important in each individual to understand if RAS is hemodynamically significant, and if it is, weather it is causing clinical problem like uncontrolled hypertension, fluid retention or renal insufficiency. On the other hand, RAS may only an innocent bystander. Importantly, not all patients with RAS will develop a clinical syndrome, and certainly, only a minority of patients with hypertension and/or heart failure have RAS.

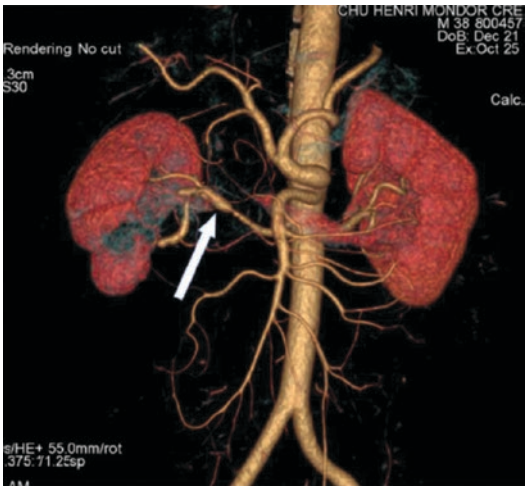

Fig. 20.1 CT angiography showing fibromuscular dysplasia of the right renal artery (arrow). **(All Figures obtained with permission)**

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20.2 Prevalence

It was difficult to evaluate prevalence of RAS in general population prior to newer, noninvasive diagnostic techniques. Most studies have evaluated RAS postmortem or in selective patients who underwent angiography. It is estimated that about two to four million patients in the United States may have renovascular disease [9]. An autopsy series showed RAS with ≥50% stenosis in 27% of patients above 50 years, and 53% of patients with prior history of diastolic hypertension [10]. CAD, Hypertension, diabetes, smoking and age are associated with increased prevalence of ARAS [11, 12]. In an autopsy study it was found that 8% of diabetic patients, and 10% of patients with both diabetes and hypertension had evidence of RAS [11].

The typical patient with ARAS frequently has atherosclerotic vascular disease involving other vascular beds like the coronaries, lower extremities and carotids. A study included 395 patients to determine the prevalence of atherosclerotic RAS in patients with atherosclerosis elsewhere found >50% RAS in 38% of subjects with abdominal aortic aneurysm and 39% of those with PAD. Another multicenter cohort study evaluated the association of RAS with age, gender and other potential risk factors among participants in the cardiovascular health study (CHS). RAS (≥60% stenosis) was found in 6.8%, 5.5% women and 9.1% of men (p = 0.053), RAS was found in 6.9% of white participants and 6.7% of African American participants (p = 0.993) [13]. Ischemic nephropathy secondary to ARAS has been reported to be a leading cause of end stage renal disease (ESRD) [14]. In one study, the prevalence of ARAS in patients 45 years of age or older starting renal replacement therapy was 41% of this was either bilateral or unilateral in a single kidney [15].

20.3 Pathophysiology

Neurohormonal activation from unilateral or bilateral renal hypoperfusion will result in renin release, renin is an early stimulator in renin angiotensin aldosterone system (RAAS) [16, 17]. This theory goes back to the 1930s, when Goldblatt et al. performed multiple studies investigating the effect of unilateral and bilateral RAS on blood pressure [18]. Goldblatt proved that the effect was due to a substance released by the kidneys causing vasoconstriction by clamping renal arteries in dogs. The substance was isolated and identified as proteolytic enzyme now known as renin.

When hypoperfusion occurs, the ischemic kidney releases renin from juxtaglomerular cells. Renin then stimulate the release of angiotensin I, which will be converted to angiotensin II by angiotensin converting enzyme (ACE) in the pulmonary endothelium. This will eventually lead to hypertension by vasoconstriction and pressure diuresis of the unaffected kidney "*pressure natriuresis*" that will prevent volume overload subsequently. This is the mechanism of hypertension and hyponatremia seen in unilateral RAS [19]. Angiotensin II will also stimulate the release of antidiuretic hormone from posterior pituitary gland, causing the release of aldosterone from adrenal cortex and subsequently more sodium and water retention by its effect on renal tubules. With bilateral (or unilateral with a single functioning kidney) the lack of such natriuresis will lead to significant fluid and sodium retention and congestive heart failure (CHF) [20].

Ischemic nephropathy in severe RAS with significant decrease in cortical oxygenation will eventually lead to excretory dysfunction. There are several mechanisms explaining how a hemodynamically significant lesion will ultimately result in interstitial fibrosis [21]. By one pathway, recurrent local ischemia causes tubulointerstitial injury and microvascular damage which will contribute to oxidative injury, increase production of fibro-genetic cytokines and inflammation that will eventually lead to atrophy and fibrosis. In moderate RAS cortical and medullary oxygenation are preserved by a compensatory decrease in oxygen consumption [22].

20.4 RAS and Cardiovascular Disease

RAS is becoming increasingly common due to the increase in the number of patients suffering from atherosclerosis. It is not uncommon to have renal artery stenosis with no symptoms espe-

cially in patients with other forms of vascular diseases. Patients with arterial atherosclerosis have 26–50% prevalence of concurrent atherosclerotic arterial renal artery stenosis ARAS [23], specifically, there is significant overlap between RAS and coronary artery disease CAD, peripheral arterial disease PAD, and carotid arterial disease. In one of the studies by Wollenweber et al., approximately 31% of patients with mild atherosclerotic narrowing (<50% occlusion) of renal artery had symptomatic arterial disease in the coronary, cerebrovascular, or peripheral vascular circulation and this proportion was even higher at 49% in patient with moderate to severe stenosis (>50%) [24]. RAS is also a predictor of poor cardiovascular prognosis, in a study included 3987 patients who underwent renal angiogram during a diagnostic cardiac catheterization, it was found that the presence of RAS was a strong independent predictor of mortality [25]. It was found in this study that 4 years survival was 89% compared to 70%, 68%, and 48% in patients with 50–75%, 75–95%, and >95% RAS, respectively. In another study with patients with RAS, it was found that 58% have clinical CAD (documented myocardial infarction, positive PCI, history of coronary artery bypass grafting, electrocardiogram changes, or angina) compared with 39% of patients without RAS ($p = 0.002$) [26].

The overlap with lower extremity PAD is also significant. In patients who had angiography as part of evaluation for a known PAD, >50% RAS was found in 38% of patients with abdominal aortic aneurysm [27]. Another prospective study [28] showed a 15-fold increase in mortality due to cardiovascular disease in patients with severe PAD and RAS. The prognostic impact of incidental RAS was studied in 550 patients who had angiography for PAD [29]. In 491 patients the renal arteries were visualized and RAS >50% stenosis was found in 26% of the patients. Mortality with RAS group was found to be 59% versus 28% in the non RAS group (od ratio 3.8, 95% confidence interval 2.5–5.7 and $p < 0.0001$).

Carotid artery disease is more common in patients with RAS [23]. A case control study of patients with history of cerebrovascular disease CVD compared patients with renovascular hypertension to patients with essential hypertension (EH) [30]. In this study, it was found that the plaques in patients with renovascular hypertension were more heavily calcified than those with EH. In another study a series of autopsies of patients with clinical evidence of stroke who died between 1980 and 1997 were examined [27], significant atherosclerotic RAS (>75%) was found in in 10.4% of patients. Patients with carotid artery disease were four times more likely to have RAS than patients without it (24.4% versus 5.9%, $p = 0.0001$).

20.5 Clinical Manifestations

Patients with hemodynamically significant RAS may present with renovascular hypertension, cardiac destabilization syndromes or ischemic nephropathy. Systemic vasoconstriction and fluid retention caused by RAS will eventually lead to worsening of coronary ischemia and CHF by fluid overload [1, 31]. An example of that is flash pulmonary edema which can be described as specific presentation of acute decompensated heart failure by fast fluid accumulation within the lungs as a result of acute increase in left ventricular end diastolic pressure.

RAS is a significant cause of secondary hypertension and patients with resistant hypertension should be evaluated for RAS. Studies that looked at treatment for resistant hypertension commonly revealed a high prevalence of previously unrecognized renovascular disease, especially in older patients groups, it also showed 12.7% of patients ≥50 years of age referred to a hypertension center had a secondary cause of hypertension [5, 32].

Ischemic nephropathy result from hemodynamically significant obstruction and decrease perfusion will eventually cause excretory dysfunction and ESRD if remain unrecognized. To define this disease, Breyer and Jacobson [33, 34], introduced the term “ischemic nephropathy”, that represent critical bilateral involvement or global renal ischemia. Studies suggested that 11–14% of ESRD is a result of ischemic nephropathy from ARAS [35]. Baboola et al. [36], observed that renal function decrease by 4 mL/min/year in a group of 51 patients with bilateral renovascular disease after 52 months of follow up. The cardio-

vascular complications of end stage renal disease include volume overload, vessel complication and arrhythmias.

20.6 Diagnosis

There are multiple diagnostic modalities available for the diagnosis of RAS. According to the American College of Cardiology/American Heart Association(ACC/AHA) Clinical practice guidelines, magnetic resonance angiography (MRA), computed tomographic angiography (CTA), and duplex ultrasonography all receive a class I indication (level of evidence B) for a screening test to establish RAS diagnosis [32]. When the clinical suspicion is high and the result of noninvasive test is inconclusive, catheter angiography is then recommended for screening. Each diagnostic test has its own advantages and disadvantages allowing physicians to have different approaches to different patients.

Duplex ultrasonography (DUS), is a noninvasive test that combines direct visualization of renal arteries with velocity measurements, with a sensitivity up to 84%, specificity of 97%, and positive predictive value of 94% for the detection of significant RAS [37]. This modality provide information about location and degree of stenosis in addition to kidney size measurements. DUS is the least expensive imaging modality and it doesn't require the use of intravenous iodinated contrast. Detection of stenosis depend on measurement of peak systolic velocity (PSV) with a sensitivity of 90% and specificity of 95% in detection RAS when the velocity is >180 cm/s, or by renal aortic velocity ratio (RAR) with a value more than 3.5, which has sensitivity and specificity compared to contrast angiography of 84% and 97% respectively [12]. The test is very useful in follow up after stent placement [38]. However, stent monitoring should take in consideration that PSV and renal/aortic velocity ratio (RAR) obtained by DUS are higher for any percentage of arterial narrowing within the stent. Therefore, it is not recommended to obtain baseline measurements post stenting. The main limitation of this modality include that it is time consuming and takes about 45–60 min, it can be affected by bowel gas that may lead to suboptimal study, it can be technically challenging in obese patients and it depend significantly on the operator. A study demonstrated about 10–20% rate of failure resulted from operator's lack of experience [39].

CTA is a diagnostic modality that has high spatial resolution and the possibility of three dimensional reconstructions that allows for identification of accessory renal arteries and visualization of adjacent anatomical structures [40]. CTA has several advantages compared to MRA including higher spatial resolution and ability to detect in stent re stenosis (ISR) [41, 42]. Compared to DUS the test is less operator dependent. It has sensitivity and specificity to detect significant RAS between 88–99% and 92–98% respectively [43, 44]. CTA disadvantages include the need for injection of 100–150 mL of iodinated contrast with a potential risk of contrast induced nephropathy (CIN) especially in patients with GFR < 60 [45, 46].

MRA enables visualization of renal arteries without the need for ionizing radiation. Compared to invasive angiography MRA has a sensitivity up to 97% and specificity up to 93% for the diagnosing RAS [47, 48]. MRA has its own limitations. (It's the most expensive modality and carries the risk of nephrogenic systemic fibrosis with gadolinium contrast in patients with GFR $\leq$ 30 mL/min/1.73 m^2). The test is problematic also in patient with claustrophobia or patients with metal implants. MRA cannot evaluate ISR as metallic stent generate artifact [41].

Arterial angiography is the gold standard for diagnosis of RAS, its usually recommended in which RAS is highly suspected and a noninvasive imaging cannot be obtained or peripheral access is already obtained for other procedure such as coronary artery angiogram. Limitations from invasive angiography include vascular access complication, CIN and contrast related allergy [49].

20.7 Medical Treatment

Medical treatment is the main approach in managing RAS. Controlling risk factors like smoking, dyslipidemia and hyperglycemia is

paramount. No randomized study has analyzed the effects of different regimens treating hypertension associated with RAS as such patients often have refractory hypertension and use multiple antihypertensive medication [50]. According to ACC/AHA guidelines, angiotensin receptor blockers (ARBS), calcium channel blockers, ACE inhibitors, and beta blockers are class I recommendation in treating secondary hypertension result from RAS [32]. The cardiovascular outcome in renal atherosclerotic lesion (CORAL) trial showed no difference in outcomes between medical treatment versus medical treatment plus renal artery stenting in patients with RAS and hypertension [51] highlighting the importance of medical therapy.

Traditionally, use of renin-angiotensin-aldosterone system RAAS antagonists (ACE inhibitors or ARBS) has been contraindicated because of the theoretical risk of worsening kidney function caused by decrease in the perfusion pressure to the kidney. However, many studies have shown better outcomes after using those medications [52]. An observational study found that 53% of patients included with renovascular disease were taking RAAS antagonists, and the study showed that those patients had remarkably lower risk of the primary outcome (myocardial infarction, stroke and death) (hazard ratio 0.70 and confidence interval 0.53–0.90) [53]. Using RAAS antagonist in RAS patients should come with close monitoring for the renal function, and care should be taken to prevent hypotension thus reducing perfusion pressure which may cause ischemic nephropathy [54]. RAAS antagonists were tolerated in 357 out of 378 patients (92%) when used prospectively and this was also seen in 54 of 69 patients (78.3%) with bilateral RAS (>60%) or occlusion [53].

The benefit from statins and antiplatelet therapy in general populations of patients with atherosclerosis support their use of both in patients with ARAS. Association between statins use and improve survival in patients with ARAS was reported in a large case series of patients with RAS who had stenting [55].

20.8 Renal Revascularization

Multiple studies have been carried out over the past decades to establish weather renal artery revascularization would add benefit to medical treatment. Renal artery revascularization can be achieved by surgical or endovascular approach, and it's an accepted option for patient with uncontrolled hypertension and hemodynamically significant RAS [42, 56–58] (Fig. 20.2).

Surgical revascularization was the only available option for revascularization prior to angioplasty, however a lot of concerns have been raised regarding safety of surgical approach. Some data indicated about 10% in hospital mortality after surgical revascularization in Medicare patients [59].

Angioplasty has largely replaced surgery given its lower rate of procedural complications [60]. The use of stents, improved the rate of restenosis compared with angioplasty alone. This was evaluated in a randomized prospective trial of patients with ostial ARAS [61], angioplasty with stent placement had less restenosis and need for re-intervention at 6 months. It's very crucial to identify patients who are most likely to benefit from revascularization. Angiographic visual estimation of the severity of stenosis is inaccurate, especially when RAS is moderate (50–90%). Physiologic assessment of the severity of stenosis such as FFR or pressure gradients should always be considered [42, 62]. In studies performed with renal vein sampling simultaneously to ipsilateral renal artery balloon gradual inflation it was found that a translesional systolic pressure gradient > 20 mmHg and a translational resting pressure ratio of 0.90 (pressure distal to stenosis/pressure proximal to the stenosis) correlate with a significant increase in concentration of renin in the ipsilateral renal vein [58, 63] (Figs. 20.3, 20.4, and 20.5).

20.9 Important Clinical Trials

Several clinical trials helped in our understanding of the role of renal artery angioplasty as compared to medical treatment alone. Dutch Renal

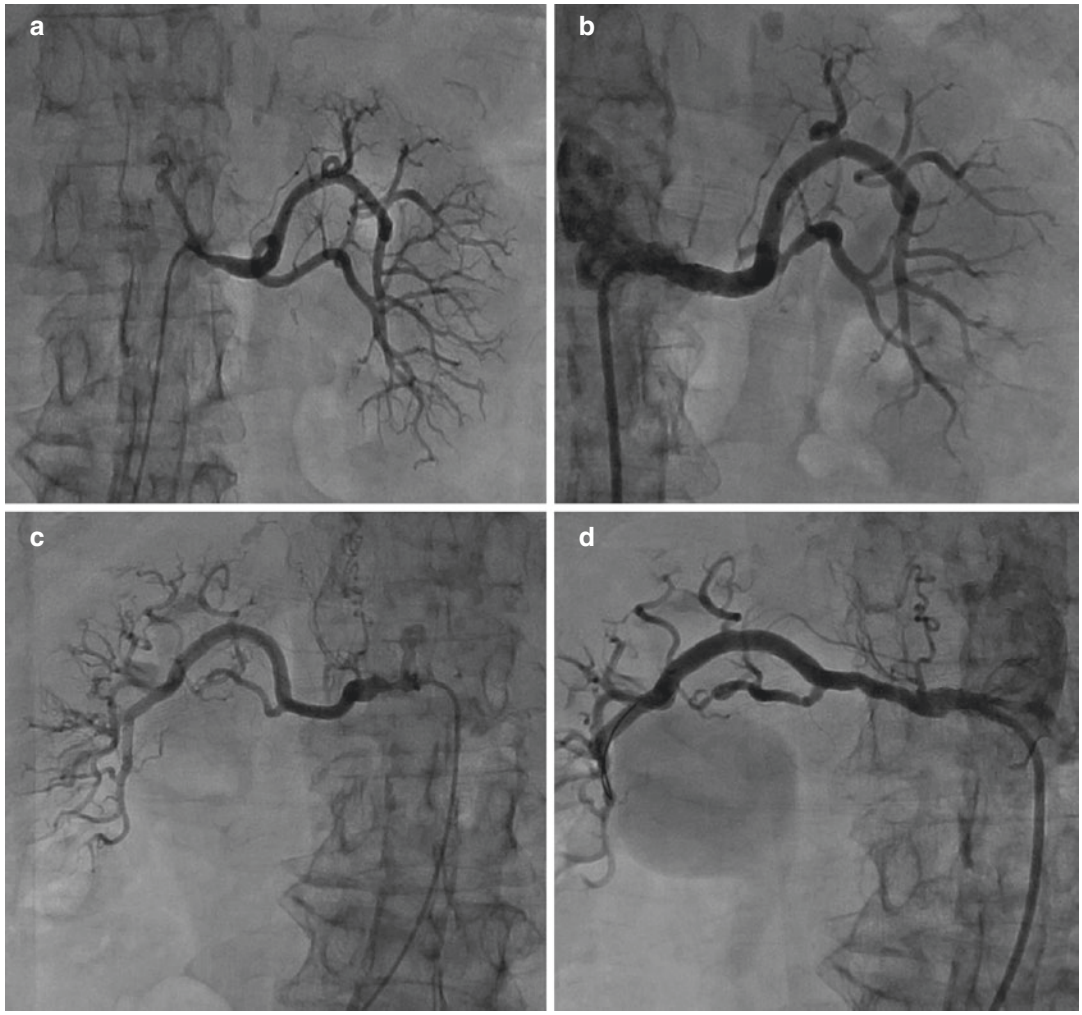

Fig. 20.2 Original images of an 84-year-old female with renovascular hypertension. She has severe focal >70% stenosis of the right (**a**) and left (**c**) renal arteries. Imaging after stenting of the right (**b**) and left (**d**) renal arteries showing no significant residual stenosis. Image courtesy of Tyrone Collins, MD (tcollins@ochsner.org). **(All Figures obtained with permission)**

Artery Stenosis Intervention Cooperative (DRASTIC) and Angioplasty and Stenting for Renal Artery lesion (ASTRAL) compared medical therapy to medical therapy and stenting for patients with hypertension and RAS. Stenting of Renal Artery (STAR) studied the effect of revascularization in progression of chronic kidney disease. All of these trials concluded no additional benefit from revascularization [64]. However, all of these trials have been widely criticized because of some major flaws in their study design [65]. The subjects in these trials did not have hemodynamic confirmation of the severity of stenosis, allowing revascularization procedures in lesions that were not significant. Additionally, there were higher than expected complications rates in the revascularization arms, suggesting a problem with the operators [66, 67].

It's worth mentioning the Cardiovascular Outcome in Renal Atherosclerotic lesions (CORAL). This multicenter, randomized trial with result published in 2014 [68]. The study included 947 patients and was designed to compare optimal medical treatment alone versus optimal medical

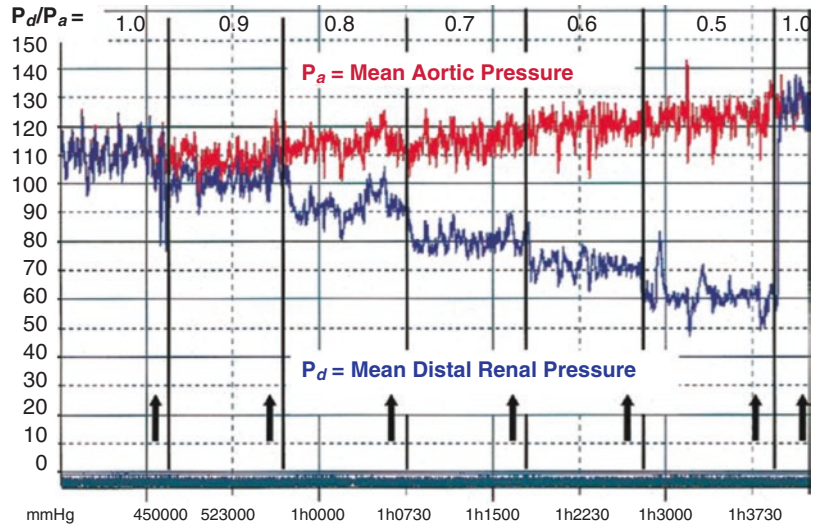

Fig. 20.3 Example of mean pressure tracings obtained simultaneously in the aorta and distal to the artificial renal stenoses induced by incremental balloon inflations. Each degree of stenosis severity was maintained for 10 min. The **arrows** indicate the timing of sampling in the aorta and in both renal veins. **(All Figures obtained with permission)**

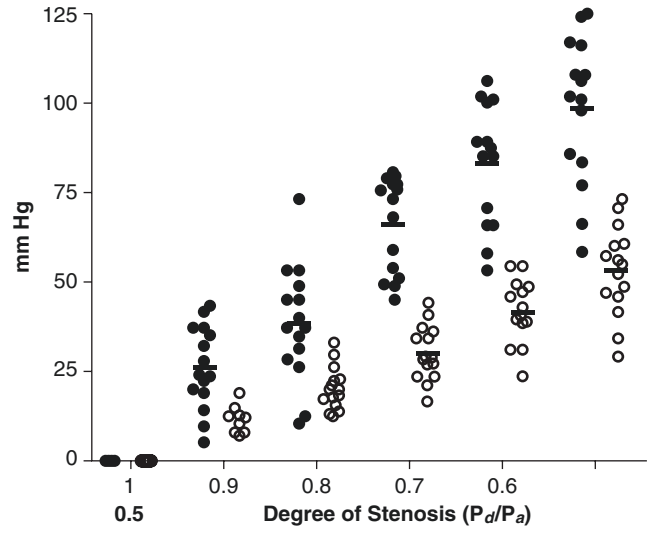

Fig. 20.4 Relationship between the individual values of mean aortic pressure (P_d)/mean pressure distal to the renal artery stenosis (P_a) ratios and the corresponding systolic pressure gradients (**closed circles**) and mean pressure gradients across the stenosis (**open circles**). **(All Figures obtained with permission)**

treatment with stenting. Optimal medical treatment in the study consisted of antiplatelet therapy as per guidelines, antihypertensive medications (candesartan ± hydrochlorothiazide, amlodipine-atorvastatin) with BP target of 140/90 (130/80 if DM or CKD) and dyslipidemia medication Atorvastatin-Amlodipine (Caduet), titrated to guideline targets. The primary outcome was composite endpoint of major cardiovascular and renal adverse events. Inclusion criteria were ARAS ≥ 60% with a systolic pressure gradient of 20 mmHg ARAS ≥80% with no gradient necessary in addition to systolic blood pressure of ≥155 mmHg on at least 2 antihypertensive medications. The results of this study showed that after a median follow up period of 43 months, the rate of the primary composite endpoint did not differ significantly between participants who underwent stenting in addition to receiving medical treatment and those who received medical treatment alone (35.1%and 35.8%, respectively; hazard ratio with stenting 0.94; 95% confidence interval 0.76–1.17; p = 0.58). The authors concluded that "renal artery stenting did not confer a significant benefit with respect to prevention of clinical event when added to comprehensive multi factorial medical therapy

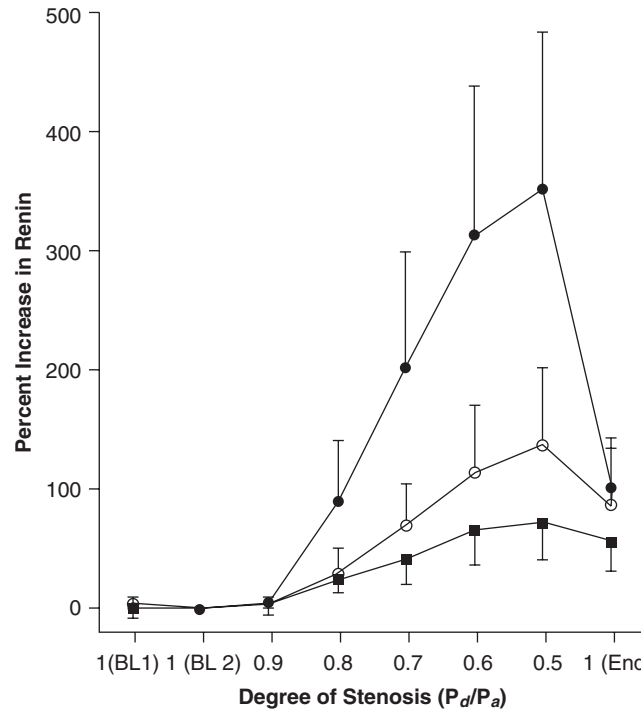

Fig. 20.5 Effects of a balloon-induced, unilateral, controlled, graded stenosis (expressed as P_d/P_a ratio) on plasma renin concentration in the aorta (**squares**), in the vein of the stenotic kidney (**closed circles**), and in the vein of the non-stenotic kidney (**open circles**). *BL1* baseline before stenting, *BL2* baseline after stenting; other abbreviations as in Fig. 20.4. **(All Figures obtained with permission)**

in people with ARAS and hypertension or chronic kidney disease". This study however did not study those patients who were not controlled despite maximal medical therapy or those who did not tolerated it.

20.10 Guidelines Summary

The American College of Cardiology (ACC)/American Heart Association (AHA) and European college of cardiology (ESC) have released guidelines for the management of patients with RAS, the guidelines are summarized in Tables 20.1, 20.2, and 20.3.

In patients with high clinical suspicion for RAS and inconclusive noninvasive test ACC/AHA recommend using invasive catheter angiography to establish the diagnosis [69]. Both guidelines are in agreement that captopril renal scintigraphy is not recommended as useful test for RAS (Class III) [69, 70]. According to SCAI [71] and based on invasive angiography mild RAS is <50% stenosis, moderate 50–70% stenosis and severe is >70% stenosis. And for patients with moderate RAS the lesion considered hemodynamically significant only when renal fractional flow reserve (FFR) is ≤0.8 or when

Table 20.1 ACC/AHA and ESC guidelines of 2013 for diagnosis of RAS recommend conducing diagnostic studies to evaluate RAS in patients with any of the following [69, 70]

1. New onset of severe hypertension in patients after age of 55.
2. New onset of severe hypertension in patients prior to age of 30.
3. Sudden worsening of previously well controlled hypertension.
4. Unexplained renal failure.
5. Flash pulmonary edema.
6. Worsening renal function after starting patient on ACE inhibitor or ARB.
7. Malignant hypertension (hypertension with end organ damage like acute kidney injury, aortic dissection, or neurological changes).
8. Resistant hypertension which was defined as failure of a blood pressure control despite full dozes of an appropriate free drug regimen including a diuretic.
9. Kidney size discrepancy of greater than 1.5 cm between the kidneys or atrophy kidney that unexplained by other conditions.

All tables created manually

Table 20.2 ACC/AHA and ESC guidelines of 2013 for selecting a diagnostic study to establish RAS the guidelines had a class I recommendation for the following [69, 70]

1. DUS is the first line test.
2. MRA for patients with creatinine clearance >30 mL/min.
3. CTA in patients with creatinine clearance >60 mL/min.

All tables created manually

Table 20.3 ACC/AHA and ESC guidelines of 2013 recommend percutaneous intervention in patients with hemodynamically significance RAS plus any of the following [69]

1. Ostial ARAS renal stent placement is recommended (class I).
2. Sudden onset of unexplained pulmonary edema (class I).
3. Malignant, resistant or accelerated hypertension or hypertension with unexplained unilateral small kidney and intolerance to medication (class IIa).
4. Unstable angina (IIa).

All tables created manually

patient has a resting mean pressure gradient > 10 mmHg or systolic hyperemic make a pressure gradient > 20 mmHg.

And finally but importantly we have to keep in mind patients who are not a good candidates for renal artery stenting, according to SCAI patients with complete blockage or long standing loss of blood flow are not a good [71, 72].

20.11 Conclusion

RAS is a common disease and usually encountered with other atherosclerotic vascular diseases as CAD, carotid and PAD. The diagnosis should be considered in patients with resistant hypertension or hypertension with renal insufficiency. RAS has a poor prognosis with most studies that looked at the natural history of ARAS showed progressive arterial obstruction and or decline in kidney function.

Detection of RAS can be achieved by number of diagnostic studies as DUS, and if a good quality ultrasound cannot be obtained then other diagnostic studies as CTA or MRI can be appropriate for the patient. Medical treatment with statins and antihypertensive medications is recommended for ARAS with close monitor for kidney function after starting medications. Renal artery revascularization is accepted option for patients with hemodynamically significant RAS associated with resistant or uncontrolled hypertension or cardiac destabilization syndromes.

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Obesity

21

Sohail Abdul Salim, Krishna Keri, and Mohit Agarwal

21.1 Introduction

Obesity has been a growing concern and World health Organization reports that around 3.4 million people die annually as result of obesity. Rates of obesity in last 20 years have doubled in the last 20 years and small pacific nation islands top the list followed by United States [1] (or Kuwait according to some authors). In the United States, according to Behavioral risk factor surveillance system data, West Virginia has the highest adult obesity rate at 37.7%, closely followed by Mississippi at 37.3%, and Colorado has the lowest at 22.3%. There are five southern states in which rates exceed 35% [2] and in 2016 Centre for Disease Control and Prevention lists these states on top of list for having high kidney disease mortality. Obesity ultimately causes structural and functional adaptations in both heart and kidneys, leading to a complex interplay involving cytokines and Renin Angiotensin system.

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Contemporaneous with and parallel to increasing prevalence of obesity, chronic kidney disease (CKD) rates have been increasing. Prevalence of CKD in obese subjects with Body Mass Index (BMI) >30 using national health and nutrition examination survey in the United States (NHANES) from 2011 to 2014, was 17.6% [3]. Several observational and experimental studies have reported association between obesity and kidney disease [4] and found obesity to be an independent risk factor of proteinuria and glomerulosclerosis. Obese subjects have a higher prevalence of type 2 diabetes mellitus, hypertension and dyslipidemia, all of which lead to metabolic dysregulation and metabolic syndrome, which hasten progression of cardiovascular and renal disease. Guo et al. evaluated trends in cardiovascular health metrics in obese adults from 1988 to 2014 in the United States and concluded that prevalence of all three cardiovascular risk factors greatly increased from 16.4% to 22.4%, largely due to worsening glycosylated hemoglobin levels [5]. Indubitably, cardiovascular and renal systems are physiologically involved in controlling blood pressure and volume status via regulatory mechanisms like renin angiotensin aldosterone system (RAAS), sympathetic nervous system (SNS), and nitrous oxide (NO) and malfunction of either heart or kidneys sets up a domino effect that ultimately affects both organ systems, known as cardio-renal syndrome (CRS).

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21.2 Obesity Related Dysfunction of Cardio-Renal Axis and Cardiac Adaptation

Multiple factors are involved in the dysregulation of this axis, which are demonstrated in Fig. 21.1. Even though there is increased systemic blood volume resulting in increased cardiac output, there is a relatively inappropriate increase in total peripheral vascular resistance, leading to obesity related hypertension. Increased peripheral vascular resistance with normal cardiac output characterizes essential hypertension.

Experimental studies have shown that leptin produced in white adipose tissue can increase sympathetic activity leading to vasoconstriction. Leptin levels have been found to be high in patients with obesity. Investigators from Athens school of medicine found higher leptin levels in individuals with fixed or masked hypertension, when compared with normotensive subjects [6]. Patients with metabolic syndrome and coronary artery disease epicardial adipose tissue have been found to secrete IL-6, MCP-1, IL-1β compared to subcutaneous adipose tissue, which are proinflammatory [7]. There is RAAS activation leading to increased sodium reabsorption at the proximal tubule by Angiotensin II and distal nephron by aldosterone, leading to hypertension. Above factors lead to compensatory eccentric left ventricular hypertrophy and consequent obesity cardiomyopathy ultimately cascading into cardio-renal syndrome.

Autopsy study of 12 obese patients showed that increase in heart weight and ventricular wall thickness were not due to fatty infiltration or increased epicardial fat [8]. Mononuclear cell infiltration of Sino-atrial node, fat infiltration of conduction system and lipomatous hypertrophy of interatrial septum and cardiomyocyte hypertrophy have been reported [9, 10]. Carotid artery intima media thickness and cardiovascular

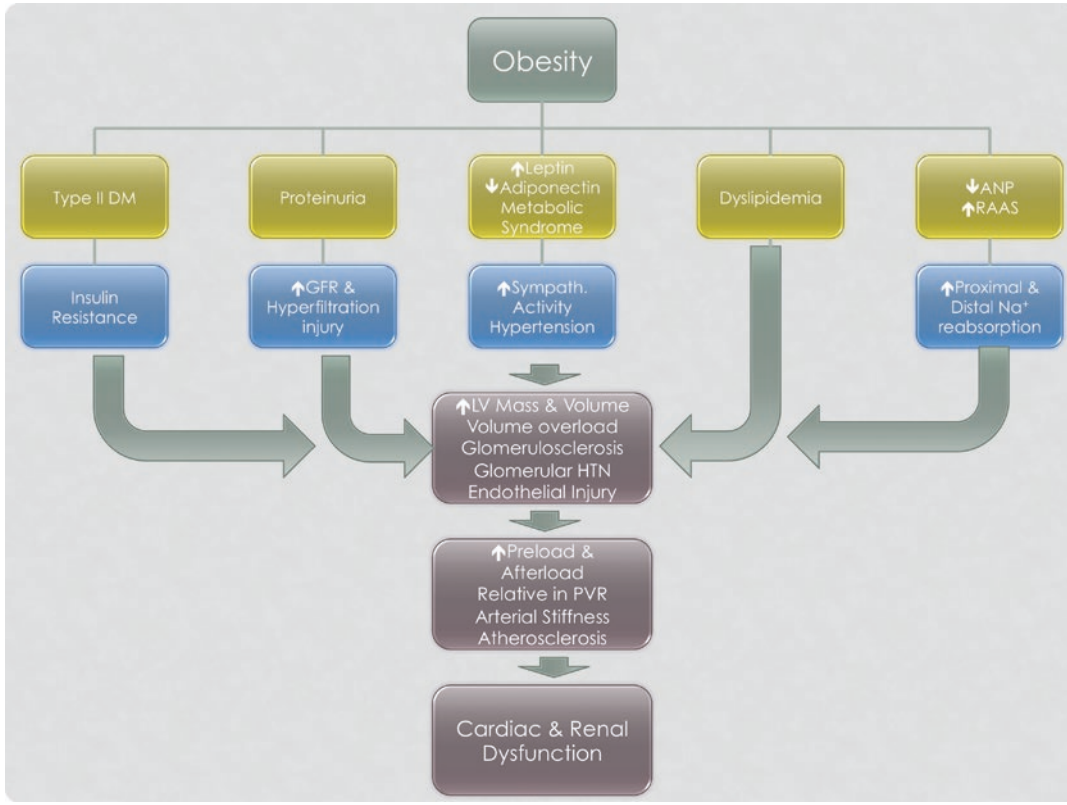

Fig. 21.1 Mechanisms of obesity related cardiac and renal dysfunction

mortality was increased in patients with obesity when compared to healthy non-obese subjects [11]. Left ventricular hypertrophy is a strong predictor of CKD progression [12] and Left ventricular mass index has been found to be higher in obese patients without metabolic abnormality than non-obese patients without metabolic abnormality [13].

Obesity causes structural changes in heart muscle, conduction system and blood vessels, all ultimately leading to higher cardiovascular mortality, congestive heart failure, arrhythmias, and sudden death. There was a higher incidence of sudden cardiac death reported in obese subjects of Framingham heart study [14] which might have been due to arrhythmias from structural changes of heart in this subgroup population. There is impaired baroreceptor sensitivity and poor response to inotropic and chronotropic variability of heart in obesity which leads to sympathetic overstimulation leading to increased catecholamine levels, contributing to obesity related hypertension [15].

21.3 Renal Adaptations to Obesity

It is undoubtedly clear that higher BMI predisposes to new onset kidney disease as we see from Framingham study which showed that an increase in each unit of BMI is associated with a 20% risk of developing kidney disease over a follow up period of 20 years [16]. This study mostly recruited Caucasians. Debour et al. evaluated subjects from Jackson Heart study cohort, which enrolled exclusively African Americans and found that metabolic syndrome severity exhibited sex-based differences for incident CKD, with increased risk in women when compared with men, even though higher severity of obesity was associated with higher prevalence of GFR in the lowest quartile at baseline in both males and females [17]. Another paper published using cohort data from Jackson heart study concluded that baseline BMI and waist circumference were not associated with incident CKD but metabolically active visceral adipose volume and dietary quality were key determinants of obesity related CKD [18].

There is increased renal blood flow with increased filtration per functioning nephron and hyperfiltration in obesity. Higher filtration fraction causes increased pressure in peritubular arterioles resulting in increased sodium reabsorption with low sodium delivered distally at macula densa, activating tubulo-glomerular feedback (TGF) and hyperfiltration. Insulin is a vasodilator that not only inhibits voltage-gated Ca^{2+} influx but also increases cellular Ca^{2+} efflux, which results in decreased intracellular Ca^{2+} consequently decreasing vascular resistance. Thus insulin resistance in obesity increases vascular resistance [19]. As mentioned above in this chapter, obesity induced activation of RAAS, SNS, impaired natriuresis, decreased Atrial natriuretic peptide and insulin resistance leads to obesity related hypertension and glomerulosclerosis.

Table 21.1 shows microscopic changes secondary to renal adaptation. Obesity related glomerulopathy involves adaptive or secondary focal segmental glomerulosclerosis (FSGS) (Fig. 21.2a) and glomerulomegaly (Fig. 21.2b). Kambham from Stanford University published biopsy of 71 patients with obesity related glomerulopathy (mean BMI of 41) comparing to 50 patients with idiopathic FSGS and noted lower

Table 21.1 Microscopic changes in kidney with obesity [20–23]

Light microscopy
• Glomerulomegaly
• Focal segmental glomerulosclerosis.
• Predominance of classic perihilar lesion of sclerosis.
• Segmental thickening of glomerular basement membrane
• Increased mesangial matrix and cellularity
• Less tubulointerstitial damage
• Extensive arteriosclerosis
Electron microscopy
• Mild foot process effacement
• Decreased podocyte density and number
• Hypertrophied podocytes with swollen cytoplasm in nonsclerosed glomerulus
• Wrinkling, focal thickening and segmental irregularities of GBM
• Double contouring of GBM
• Thickened Tubular basement membranes

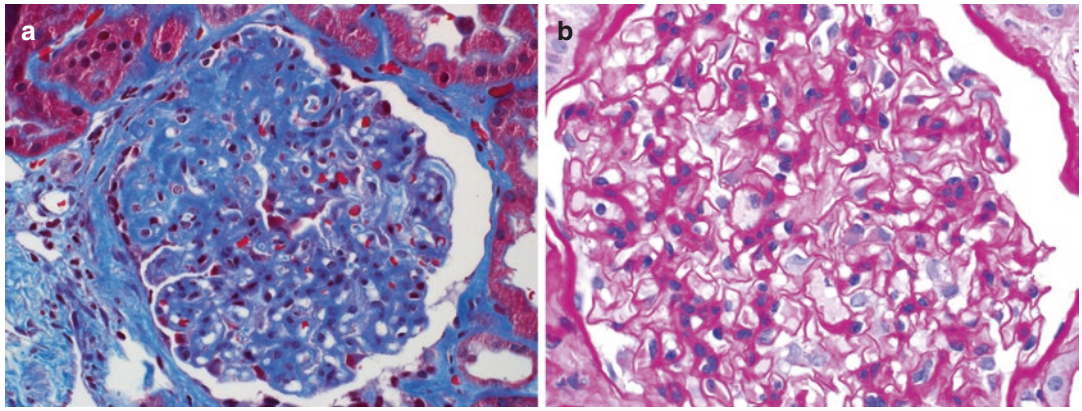

Fig. 21.2 (**a**) Focal segmental glomerulosclerosis in obesity related glomerulopathy (courtesy of Nidia Messias, Arkana Labs). (**b**) Enlarged glomerulus in obesity related glomerulopathy. (Courtesy of Nidia Messias, Arkana Labs)

incidence of proteinuria and nephrotic syndrome, fewer segmental sclerosis, higher glomerulomegaly with increased glomerular diameter in obesity, than in idiopathic FSGS. Although adaptive or secondary FSGS shows less foot process effacement and lesser grades of proteinuria compared to primary FSGS, all of the above changes result in podocyte depletion and interstitial fibrosis, ultimately leading to end-stage renal disease (ESRD) in up to one third of patients [24]. Notably, a review of more than 6000 biopsies from 1986 to 2000 showed increased incidence of obesity related glomerulopathy over time [20].

21.4 Role of Cytokines, Inflammatory Pathways, and Adipokines in Obesity

Chronic Inflammation in obesity stimulates expression of cytokines and inflammatory mediators such as leptin, IL-6, 8, 10, Transforming growth factor Beta, Tumour necrosis factor (TNF), C-Reactive protein (CRP), apelin, vascular endothelial growth factors, resistin, inducible nitrous Oxide (NO) Synthase, Type I and type 4 collagen production, ROS and decreased adiponectin all of which ultimately cascades into inflammation, cellular apoptosis, tubule-interstitial inflammation, fibrosis, and atherosclerosis. In obesity, insulin, leptin and resistin levels are increased but adiponectin levels are lower. Endothelial dysfunction in animal studies has been linked to high IL-6 and low adiponectin levels. Abdominal adipocytes secrete IL-6, which increases CRP, which explains increased levels of CRP in obesity and consequent fall with weight loss [25]. Leptin produced by white adipose tissue normally acts on hypothalamic neurons to produce satiety but there is leptin resistance in obese patients. Leptin increases sympathetic activity, decreases endogenous NO activity and increases Na+, K+-ATPase activity [26] causing obesity related hypertension with impaired natriuresis. Animal studies prove that chronic elevation in leptin causes fibrotic changes in interstitium, glomerulosclerosis and proteinuria in non-obese mice with metabolic syndrome who were fed a high fat diet [27]. Leptin is metabolized in proximal tubule by tubular uptake and endocytosis resulting in higher levels when this metabolism is decreased as in CKD. Leptin also produces myocyte hypertrophy, which might contribute to increase LVH in obese patients.

Contrasting to leptin, adiponectin, levels of which are low in obesity (especially in people with metabolic syndrome), promotes insulin sensitivity, decreases gluconeogenesis and glycogenolysis in liver, increases endogenous NO, decreases ROS and promotes skeletal muscle lipid peroxidation. High-circulating free fatty acid (FFA) and the elevated cellular uptake of fatty acid (FA), decrease secretion of adiponectin. Melanocortin and neuropeptide Y are

neurotransmitters, which mediate action of leptin with sympathetic centers in midbrain. Overweight or obese subjects with a loss-of-function mutation in the melanocortin 4 receptor showed a lower incidence of hypertension which reinforces the role of leptin in hypertension as leptin and melanocortins are interconnected [28]. James Hall from University of Mississippi Medical Center proved in animal studies that a functional melanocortin system is necessary for the CNS-mediated actions of leptin.

21.5 Role of Aldosterone and Resistin

An interesting article published in Hypertension hypothesized that Polyunsaturated fatty acids such as linoleic acid released by white adipose tissue stimulates aldosteronogenesis [29] in rats which might explain increased aldosterone levels in obesity and resultant proteinuria and effects of spironolactone use in proteinuria. Aldosterone in cultured human proximal tubular cells increase collagen III and IV expression promoting tubulointerstitial fibrosis and scarring of glomerulus [30] and cardiovascular fibrosis. Aldosterone also promotes generation of NADPH oxidase, which inhibits mitochondrial generation of phosphate i.e. decreased energy production in mitochondria. ATP is needed for propagation of insulin signal in podocytes, which is inhibited by high levels of aldosterone [31]. Physiological function of foot process of occluding slit pores preventing protein loss, is maintained by collaboration of nephrin, insulin and adiponectin. This might be another mechanism of albuminuria in obesity. Resistin is secreted in macrophages and levels increase with obesity and CKD. Resistin causes insulin resistance through its action on Toll like receptor-4 (TLR4) in animal models [32]. Insulin resistance with hyperinsulinemia promotes hypertension. Insulin resistance through impaired metabolism of FA and advanced glycated end products can be toxic to podocytes leading to glomerulomegaly, FSGS and eventually fibrosis.

Obesity can cause insulin resistance and increased fatty acids. High Leptin levels increase insulin sensitivity, but in obese patients where leptin levels are high there is relative leptin resistance leading to insulin resistance. Adiponectin deficiency or increased resistin in obesity can lead to impaired mitochondrial fatty acid oxidation and FA accumulation, which worsens insulin resistance. Filtration barrier for albumin at slit-pore of the glomerulus is maintained by energy generated from fatty acid oxidation. This might explain albuminuria in patients with obesity.

21.6 Obesity, Metabolic Status and Chronic Kidney Disease

There has been increasing rates of obesity, CKD and metabolic syndrome in past decade. There are multiple organizations defining metabolic syndrome with differing criteria but one of most commonly used criteria is NCEP ATP III (Table 21.2) which takes in to account waist circumference (WC), hypertension, High density lipoproteins, triglyceride levels and hyperglycemia. Presence of three or more components is diagnostic. World health organization criteria include insulin resistance and microalbuminuria. A single center Japanese study using 213 subjects showed that metabolic syndrome and albuminuria were independently associated with CKD progression [33].

Metanalysis using four studies published in 2016 showed a positive but weak association between higher risk of kidney disease progression and BMI [34]. Investigators from Loyola University investigated association between waist circumference or BMI and End stage renal disease (ESRD) using Participants from

Table 21.2 Diagnostic criteria for metabolic syndrome: NCEP ATP III criteria

Component	Criteria
Increased waist circumference	Men: ≥40 in. Women: ≥35 in.
Elevated triglycerides	≥150 mg/dL
Dyslipidemia (HDL-C)	Men: <40 mg/dL Women: <50 mg/dL
Hyperglycemia	≥100 mg/dL
Hypertension	≥130/85 mmHg

REGARDS (Reasons for Geographic and Racial Differences in Stroke) and found no significant association between BMI and ESRD incidence but higher WC, when adjusted for BMI significantly increased ESRD risk [35]. Panwar et al. used participants from REGARDS study and concluded that, higher BMI was associated with increased risk of ESRD in those with metabolic syndrome [36]. But risk of progression to ESRD was lower with higher BMI in absence of metabolic syndrome. This brings to light the importance of assessment of metabolic status in determining risk. That doesn't make metabolically healthy obesity a benign condition; nevertheless they have lower insulin resistance and better lipid profiles.

Investigators from South Korea studied metabolically healthy (Metabolic health was defined as a homeostasis model assessment of insulin resistance of <2.5 and no components of metabolic syndrome) overweight and obese patients, and found that they had higher rates of CKD compared to non-obese individuals. Another Korean study used Adult Treatment Panel-III criteria to define metabolic status and compared metabolically healthy non-obese with metabolically healthy obese group which showed higher risk of incident CKD in the obese group. Metabolically unhealthy non-obese individuals were at an increased risk of incident CKD than the metabolically healthy non-obese group although metabolically unhealthy obese individuals conferred highest risk [37]. Investigators from Korean Cohort Study for Outcome in Patients with Chronic Kidney Disease (KNOW-CKD) [13] did an observational study with 1940 participants, which concluded that obesity with metabolic abnormality was associated with 1.53-fold increased risk for worsening renal function compared to non-obesity without metabolic abnormality and that metabolic abnormality strengthens association of obesity with CKD progression. Over 5 years of follow up the risk of CKD progression was highest in subjects with three or more metabolic components of metabolic syndrome. To sum up, assiduous perusal of this topic shows that metabolic syndrome and obesity lead to worsening CKD over time and thus interventions are needed to limit progression to cardio-renal abnormalities.

21.7 Therapeutic Interventions

As mentioned in the above section, obesity and hypertension contribute to cardiorenal dysfunction via varied mechanisms. Therefore, the management of obesity related cardio renal syndrome revolves around the management of these comorbidities (Table 21.3).

21.7.1 Dietary Modification

Dietary approaches produce modest weight loss. Most diets with caloric restriction of 800–1200 kcal/day are considered low calorie diets (LCD). More extreme diets featuring less than 800 kcal/day are considered very low-calorie diets (VLCD). VLCDs do not produce better long-term outcomes compared to LCDs [38]. Diets that feature low calorie/low fat, low-carbohydrate/high-protein diets such as Mediterranean, Atkins, weight watchers', Ornish or zone diets can promote weight loss. Regardless of the type of diet, adherence to the diet must be noted as the most important factor that dictates weight loss outcomes [39]. Dietary approaches to stop hypertension (DASH) diet is a well-studied program that adopted a diet rich in fruits, vegetables and low-fat dairy products along with reduced saturated and total fat. Within 3 weeks, this diet caused a reduction of systolic and diastolic blood pressures by 11.4 mmHg and 5.5 mmHg respectively [40]. This study also noticed that a consumption of less than 100 mEq sodium further reduced the blood pressures by 2–3 mmHg.

Table 21.3 Approach for the management of obesity in patients with cardiorenal syndrome

1	Dietary modifications
2	Increase physical activity
3	Behavioral modification
4	Antiobesity agents
5	Bariatric surgery

21.7.2 Physical Activity

Exercise is a very important component in the management of obesity. It is very well known that adequate levels of physical activity reduce the risk of obesity [41, 42]. Clinical trials have shown that vigorous physical activity is associated with maintenance of reduced weight, lower hip circumference and fat percentage [43]. Thirty minutes of walking in most overweight individuals can lead to decreased weight, hip and abdominal circumference even if they do not adopt weight loss diets or life style changes, emphasizing the importance of exercise alone [44].

Moderate intensity activity as a walking for more than 30 min a day for 5–7 days of a week is beneficial in terms of cardiovascular outcomes and preventing weight gains. However, at least 60 min of moderate-intensity activity is required in the maintenance period [45]. A combination of aerobic and strength training is considered optimal compared to either of the strategies alone [46]. The addition of wearable devices that track physical activity do not appear to improve weight loss outcomes [47]. Prior to prescribing an exercise regimen, the health status and prior physical activity must be taken into consideration. Individual's naïve to intense physical must be warned regarding the musculoskeletal stresses. Patients with poor cardiovascular reserve must be cautioned against sudden initiation of intense physical activity.

21.7.3 Behavioral Modification

Most of the behavior modification techniques identify that the obese individuals have learned maladaptive patterns that influence the food intake and that these behaviors must be modified to cause weight loss. Therefore, behavioral therapies affect better eating habits by setting realistic goals, re-in force self-monitoring and provide social support [48–50]. Stimulus control is an important part of these programs that focuses on gaining control over the triggers that lead to overeating [51]. In addition to these nutritional education, meal planning with portion controlled plates have been recognized as important strategies [52]. Other techniques that are not proven in clinical trials but worth considering in the management of weight loss include cognitive restructuring, assertiveness training and stress reduction.

21.7.4 Antiobesity Agents

Along with diet and exercise, pharmacological agents can be considered as an additional tool to manage obesity. According to NHLBI guidelines (National Heart, Lung and Blood institute), individuals with BMI greater than 30 kg/m^2 and individuals with BMI of 27–29.9 kg/m^2 with additional co-morbidities such as diabetes mellitus, hypertension, hyperlipidemia or sleep apnea are appropriate candidates for pharmacological methods of weight loss [53].

Orlistat, an inhibitor of pancreatic lipase inhibitor is generally considered as a first-line agent due to beneficial effects on glycemia and lipid metabolism [54]. However, it is not tolerated very well due to its gastro-intestinal side effects. Abdominal cramps, mal-absorption of fat soluble vitamins, renal oxalate stones are its notable side effects.

A diabetic agent, Liraglutide which is a GLP-1 (glucagon like peptide) has been approved for longer terms due to favorable effects on glucose metabolism, weight loss and safe cardiovascular profile, although the cost and gastro-intestinal side effects may limit its use [55].

Lorcaserin, a serotonin agonist has efficacy similar to orlistat with better side-effect profile. This has been approved by USFDA as a weight loss agent in patients with BMI > 27 kg/m^2 [56] but has now been withdrawn from the market due to concerns as a safety clinical trial shows an increased occurrence of cancer.

Combination of bupropion-naltrexone is equi-efficacious to orlistat or lorcaserin. However, it has more adverse effect profile and contraindications [57, 58].

Sympathomimetic drugs such as phentermine, diethylpropion, benzphetamine may be considered for a short-term use only (up to 12 weeks) [59, 60]. Phenteramine/Topiramate combination has been approved for long-term weight loss but

phenteramine use alone is approved only for upto 12 weeks. All these agents can increase blood pressure and heart rate. They are contraindicated in patients with hypertension, hyperthyroidism, atherosclerosis and or in individuals with history of drug abuse. It must be noted that Sibutramine, a sympathomimetic agent was removed from USA, Canadian and European markets due to its adverse cardiovascular profile [61]. Therefore, sympathomimetics are best avoided in obese patients with cardio renal syndrome.

Clinical trials do not support the use of alternative agents such as green tea, Garcinia cambogia, HCG (human chorionic gonadotropin), which are marketed as weight loss agents [62–64]. We refer readers to systematic review and meta-analysis by Khera et al. that details the use of pharmacotherapy for weight loss [65].

21.8 Obstructive Sleep Apnea (OSA)

Prevalence of OSA increases with BMI [66]. Obstructive sleep apnea is associated with both cardiovascular and renal morbidity. Moreover, each of the OSA associated disorder such as hypertension and diabetes mellitus are also risk factors for Chronic Kidney Disease (CKD) [67, 68]. OSA has also been implicated in glomerular hyperfiltration and proteinuria [69]. Since the treatment of OSA helps with better blood pressure control, reduces renin angiotensin activation, and improves metabolic abnormalities associated with metabolic syndrome, it is conceivable that patient with cardiorenal syndrome may benefit from the same [70–72]. Modalities of therapy for OSA include continuous positive airway pressure (CPAP), bilevel positive airway pressure (BPAP) and autotitrating positive airway pressure (APAP) [73]. All the modalities have comparable outcomes [74].

21.9 Hypertension Pharmacotherapy

Ideally, drugs used to treat hypertension and heart failure in obese patients must also target pathogenetic pathways of obesity at a molecular level. However, there are not many trials evaluating the efficacy of drugs in obesity and cardio renal situations.

Renin angiotensin aldosterone (RAAS) blockade is a logical choice in obese patients with obesity and cardiorenal syndrome. Obesity related glomerulopathy (ORG) is a well-recognized entity that leads to glomerular hyperfiltration and proteinuria [20]. RAAS blockade can effectively reverse the pathophysiology that leads to decline in renal function in addition to decreasing cardiovascular mortality and hospitalization [24, 75]. Adipose tissue is known to have its own renin angiotensin system. Therefore, RAAS blockade also gives the additional advantage of improving insulin sensitivity and reducing leptin in obese individuals [76, 77].

Diuretics, including both loop and thiazides, must be considered for the management of hypertension and congestive heart failure. Loop diuretics are devoid of hyperlipidemic effects and can be more effective in treatment of hypervolemia in cardio renal patients and maintain efficacy even in patients with advance chronic kidney disease. Prolonged use of thiazides is associate with hyperlipidemia, hyperuricemia [78]. Although, thiazides are not absolutely contraindicated, loop diuretics should be considered as first line therapy in obese patients with coexisting metabolic syndrome.

Dihydropyridine (DHP) calcium channel blockers (CCB) such as amlodipine may increase glomerular hyperfiltration where as Non-DHP CCBs tend to be decrease hyperfiltration and proteinuria [79]. No prospective RCTs are available comparing these classes of drugs head to head in obese patients with cardio renal syndrome.

Sodium Glucose co-transporter-2 (SGLT-2) inhibitors are novel class of drugs that have hypoglycemic and hypotensive effects. Although intended to be used mainly in diabetic patients, this class of drugs have shown to improve cardiovascular mortality while decreasing glomerular hypertension [80]. More clinical trials are needed to establish the benefits of this class in obese cardio renal patients.

21.10 Bariatric Surgery

Lifestyle changes, behavioral and pharmacotherapy may prove ineffective in morbidly obese patients and may offer limited long term efficacy [81]. Individuals who are morbidly obese (>40 kg/m^2) or those with BMI > 35 kg/m^2 with obesity related comorbidities must be considered for weight loss or bariatric surgery. Swedish obese subjects trial demonstrated the efficacy of bariatric procedures over medical therapy in the long run. These procedures may also improve quality of life and life expectancy [82].

Bariatric surgeries can be classified as restrictive, malabsorbtive and combination restrictive and malabsorbtive. Restrictive procedures such as laparoscopic adjustable gastric banding (LAGB), sleeve gastrectomy and Vertical banded gastroplasty (VBG) limit the food intake by reducing the size of stomach. Jejunoileal bypass (JIB) and the biliopancreatic diversion (BPD) are malabsorptive procedures which decreases effectiveness of nutrient absorption by shortening the length of the functional small intestine, either through bypass of the small bowel absorptive surface area or diversion of the biliopancreatic secretions that facilitate absorption. Combination of restrictive and malabsorbtive procedure such as Roux-en-Y gastric bypass (RYGB) bypass a segment of small intestine and cause malabsorptive and metabolic changes that lead to weight loss. Due to its efficacy and metabolic benefits, RYGB is considered by some as "gold standard" [83]. Nevertheless, gastric sleeve surgery (also called vertical sleeve gastrectomy which removes 75–80% of the stomach) is now the most commonly performed bariatric procedure in the United States and also worldwide, as intestinal bypass results in the malabsorption of vitamins and nutrients, which can lead to deficiencies and can also cause dumping syndrome. Also this surgery is simpler and the recovery is shorter when compared with RYGB. Careful consideration and application of suitable procedure in a selected patient can treat obesity along with improving blood pressures, glycemic control [84]. These procedures can also improve albuminuria and stabilize chronic kidney disease [85].

21.11 Conclusion

Obesity causes progressive changes in renal and cardiovascular systems with extensive proinflammatory milieu causing release of cytokines, activation of RAAS, metabolic disturbances, impaired natriuresis, autonomic dysregulation, and cardiac and renal adaptations that lead to combined cardiac and renal dysfunction and promote CKD progression. A multidisciplinary approach consisting of behavioral, pharmacological and surgical therapies aiming to attenuate disease progression should be implemented. Strategic research exploring inflammatory mechanisms is warranted to wrest control of this debilitating disease.

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Class Effects of SGLT2 Inhibitors on Cardiorenal Outcomes

22

Aaron Y. Kluger

Abbreviations

ACEi	Angiotensin-converting-enzyme inhibitor
AE	Adverse event
ARB	Angiotensin-receptor blocker
CANVAS	CANagliflozin CardioVascular Assessment Study
CANVAS-R	CANVAS-Renal
CI	Confidence interval
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CrCl	Creatinine clearance
CREDENCE	Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation
CV	Cardiovascular
CVD	Cardiovascular disease
CVOT	Cardiovascular outcomes trial
DECLARE-TIMI 58	Dapagliflozin Effect on CardiovascuLAR Events
DPP4i	Dipeptidyl peptidase 4 inhibitor(s)
eGFR	Estimated glomerular filtration rate
EMPA-REG OUTCOME	Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients—Removing Excess Glucose
ESRD	End-stage renal disease
FDA	United States Food and Drug Administration
HF	Heart failure
HHF	Heart failure hospitalization
HR	Hazard ratio
MDRD	Modification of Diet in Renal Disease
MI	Myocardial infarction

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RAASi	Renin-angiotensin-aldosterone system inhibitor
RRR reduction	Relative risk
RRT therapy	Renal-replacement
SGLT2i	Sodium-glucose cotransporter 2 inhibitor(s)
T2DM mellitus	Type 2 diabetes
UACR	Urinary albumin-creatinine ratio

Type 2 diabetes mellitus (T2DM) is significantly associated with cardiovascular disease (CVD) and is a risk factor for heart failure (HF); diabetic patients are hospitalized for HF approximately four times more frequently than nondiabetic patients [1–5]. T2DM is a risk factor for chronic kidney disease (CKD) and end-stage renal disease (ESRD) [6, 7]. T2DM is also associated with non-healing lower extremity wounds, deep tissue osteomyelitis, metabolic bone disease, anemia, pancreatitis, and diabetic ketoacidosis [8–10]. Further, T2DM medications often have deleterious side effects. Thiazolidinediones are linked to edema, HF hospitalization (HHF) and cardiovascular (CV) death in certain patient subsets [11–13]. Oral sulfonylureas are associated with hypoglycemia, myocardial infarction (MI), stroke, and CV death, although a recent intervention trial found that sulfonylureas had similar rates of CV events compared to pioglitazone (1.5 per 100 patient-years for both groups, hazard ratio (HR) = 0.96, 95% confidence interval (CI) 0.74–1.26, p = 0.79) [14–16].

The 2008 United States Food and Drug Administration (FDA) antidiabetic drug guidance required cardiovascular outcome trials (CVOTs) for novel antihyperglycemic medications to demonstrate that new drugs would not increase the risk for MI, stroke, or CV death [17]. The FDA has approved four sodium-glucose cotransporter 2 inhibitors (SGLT2i) based on these guidelines: canagliflozin (Invokana), dapagliflozin (Farxiga), empagliflozin (Jardiance), and ertugliflozin (Steglatro). A fifth SGLT2i, sotagliflozin (Zynquista), is in late clinical development as of September 2019. Multiple expert consensus decisions attest to the potential of SGLT2i as a promising new class for the treatment of patients with T2DM and established CVD [18, 19].

Three SGLT2i (canagliflozin, empagliflozin, dapagliflozin) have been studied in CVOTs to date; canagliflozin has also been studied in an additional randomized clinical trial involving patients with diabetic kidney disease [20–23]. This review will explore the design and results of each of the four key SGLT2i trials and discuss the potential determinants for their CV, renal, and safety outcomes.

The relevant trials' original methodology and results papers were reviewed. The methodological details and outcomes of the trials will be reviewed below. As some p-values were not provided in all trials, they were calculated from the HR and 95% CI [24]. The relative risk reduction percentages were calculated from the HR. Continuous variables are presented as mean ± standard deviation or median [quartile 1, quartile 3], if skewed. Categorical variables are presented as frequency (%).

22.1 The EMPA-REG OUTCOME Trial

The first SGLT2i CVOT, the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients—Removing Excess Glucose randomized double-blind controlled trial (EMPA-REG OUTCOME) assigned 7020 patients with T2DM and CVD to 10 or 25 mg of empagliflozin or placebo daily over a 3.1 year mean and median follow-up period [20, 25]. Study patients were required to have estimated glomerular filtration rate (eGFR) >30 mL/min/1.73 m^2 (calculated using the Modification of Diet in Renal Disease (MDRD) equation); empagliflozin is indicated for T2DM patients with eGFR ≥45 mL/min/1.73 m^2 [26].

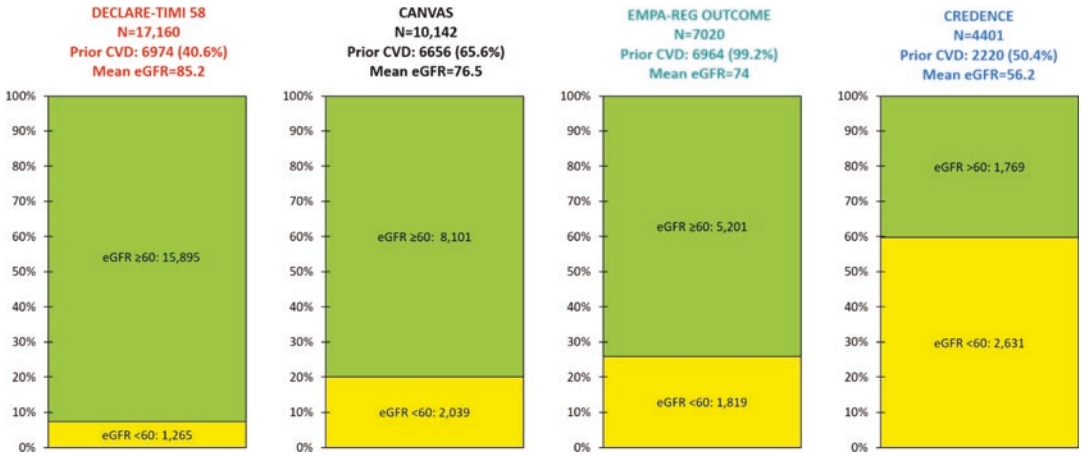


Fig. 22.1 Baseline estimated glomerular filtration rates (eGFRs) and prior cardiovascular disease (CVD) rates in the Dapagliflozin Effect on CardiovascuLAR Events (DECLARE-TIMI 58), CANagliflozin CardioVascular Assessment Study (CANVAS) Program, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients—Removing Excess Glucose (EMPA-REG OUTCOME), and Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trials. Prior CVD displayed as incidence (percentage)

Nearly all (6964 (99.2%)) EMPA-REG OUTCOME patients had established CVD, most commonly stable coronary artery disease (Fig. 22.1). The mean eGFR was 74 ± 21 mL/min/1.73 m^2, 1819 (25.9%) patients had eGFR <60 mL/min/1.73 m^2, and 5201 (74.1%) had eGFR >60 mL/min/1.73 m^2 [20, 27]. There were 4171 (59.4%) patients with urinary albumin-creatinine ratio (UACR) <30 mg/g, 2013 (28.7%) with UACR >30–300 mg/g, and 769 (11.0%) with UACR >300 mg/g. Although angiotensin-converting-enzyme inhibitor (ACEi) or angiotensin-receptor blocker (ARB) use was not required, they were used in 5666 (80.7%) patients.

The primary composite CV endpoint (CV death, nonfatal MI, or nonfatal stroke) occurred in 10.5% of empagliflozin patients compared to 12.1% of placebo patients (rate per 1000 patient-years = 37.4 vs. 43.9, respectively; HR = 0.86, 95% CI = 0.74–0.99, p = 0.04) (Fig. 22.2). With regard to secondary outcomes, HHF occurred in 2.7% of empagliflozin patients compared to 4.1% of placebo patients (rate per 1000 patient-years = 9.4 vs. 14.5, HR = 0.65, 95% CI = 0.50–0.85, p = 0.002). HHF or CV death (excluding fatal stroke) occurred in 5.7% of empagliflozin patients compared to 8.5% of placebo patients (rate per 1000 patient-years = 19.7 vs. 30.1, HR = 0.66, 95% CI = 0.55–0.79, p < 0.001). The composite renal outcome [doubling of serum creatinine level accompanied by an eGFR ≤45 mL/min/1.73 m^2, initiation of renal-replacement therapy (RRT), or renal death] occurred in 1.7% of empagliflozin patients compared to 3.1% of placebo patients (rate per 1000 patient-years = 6.3 vs. 11.5, HR = 0.54, 95% CI = 0.40–0.75, p < 0.001) (Fig. 22.3) [28].

22.2 The CANVAS Program

The second SGLT2i CVOT, the CANagliflozin CardioVascular Assessment Study (CANVAS) Program combined the CANVAS and CANVAS-Renal (CANVAS-R) study cohorts into a randomized double-blind controlled trial, assigning 10,142 T2DM patients to daily canagliflozin (100 mg with optional increase to 300 mg) or placebo over a 2.4 year median (188.2 week mean) follow-up period [21, 29]. Patients were required to be ≥30 years old with established CVD or ≥50 years with at least two CVD risk factors. Study patients were required to have

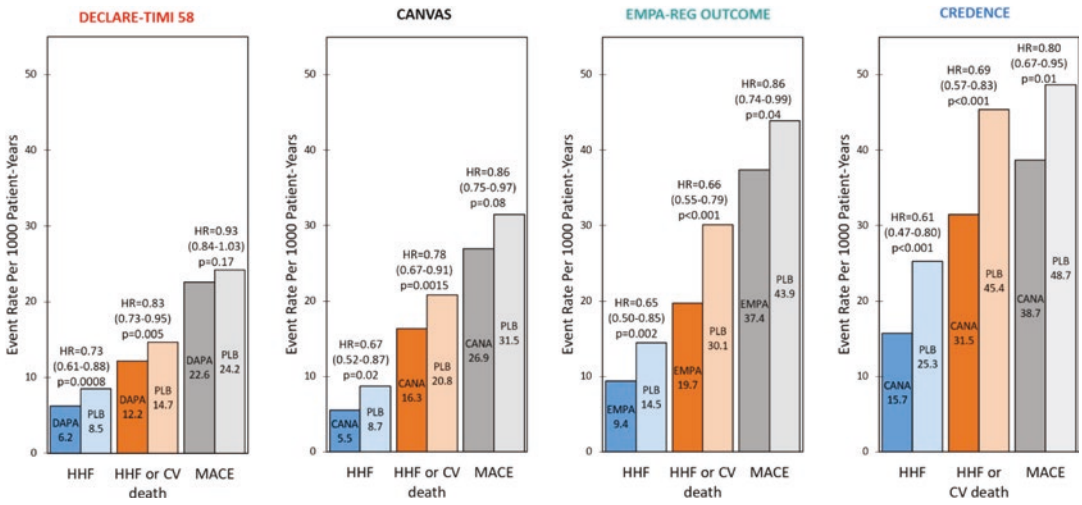


Fig. 22.2 Heart failure hospitalization (HHF), HHF and cardiovascular (CV) death, and major adverse cardiovascular event (MACE) event rates per 1000 patients in the Dapagliflozin Effect on CardiovascuLAR Events (DECLARE-TIMI 58), CANagliflozin CardioVascular Assessment Study (CANVAS) Program, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients—Removing Excess Glucose (EMPA-REG OUTCOME), and Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trials. Statistical outcomes displayed as hazard ratio, 95% confidence interval, p-value. *HR* hazard ratio, *DAPA* dapagliflozin, *CANA* canagliflozin, *EMPA* empagliflozin, *PLB* placebo

eGFR >30 mL/min/1.73 m^2 (calculated using the MDRD equation); canagliflozin is indicated for T2DM patients with eGFR ≥45 mL/min/1.73 m^2 and contraindicated for patients with eGFR <30 mL/min/1.73 m^2 [30].

A total of 6656 (65.6%) CANVAS Program patients had established CVD, most commonly stable coronary artery disease (Fig. 22.1). The mean eGFR was 76.5 ± 20.5 mL/min/1.73 m^2, 2039 (20.1%) patients had eGFR <60, and 8101 (79.9%) had eGFR >60 mL/min/1.73 m^2 [21, 31]. The median UACR was 12.3 [6.65, 42.1] mg/g; 7007 (69.8%) patients had UACR <30 mg/g, 2266 (22.6%) had UACR >30–300 mg/g, and 760 (7.6%) had UACR >300 mg/g. Although antihypertensive agent use was not required, patients receiving these drugs were required to have a documented systolic blood pressure higher than 140 mmHg. Renin-angiotensin-aldosterone system inhibitor (RAASi) use was not required; however, they were used in 8116 (80.0%) patients.

The primary composite CV endpoint (CV death, nonfatal MI, or nonfatal stroke) rate per 1000 patient-years was 26.9 for canagliflozin patients compared to 31.5 for placebo patients (HR = 0.86, 95% CI = 0.75–0.97, p = 0.08) (Fig. 22.2). With regard to secondary outcomes, the HHF rate per 1000 patient-years was 5.5 for canagliflozin patients compared to 8.7 for placebo patients (HR = 0.67, 95% CI = 0.52–0.87, p = 0.02). The HHF or CV death rate per 1000 patient-years was 16.3 for canagliflozin patients compared to 20.8 for placebo patients (HR = 0.78, 95% CI = 0.67–0.91, p = 0.0015). The composite renal outcome [40% reduction in eGFR sustained for at least two consecutive measures, need for RRT (chronic dialysis, sustained eGFR <15 mL/min/1.73 m^2, or kidney transplantation), or renal death] rate per 1000 patient-years was 5.5 in empagliflozin patients compared to 9.0 in placebo patients (HR = 0.6, 95% CI = 0.47–0.77, p < 0.001) (Fig. 22.3) [21].

22.3 The DECLARE-TIMI 58 Trial

The third and most recent SGLT2i CVOT, the Dapagliflozin Effect on CardiovascuLAR Events randomized double-blind controlled trial

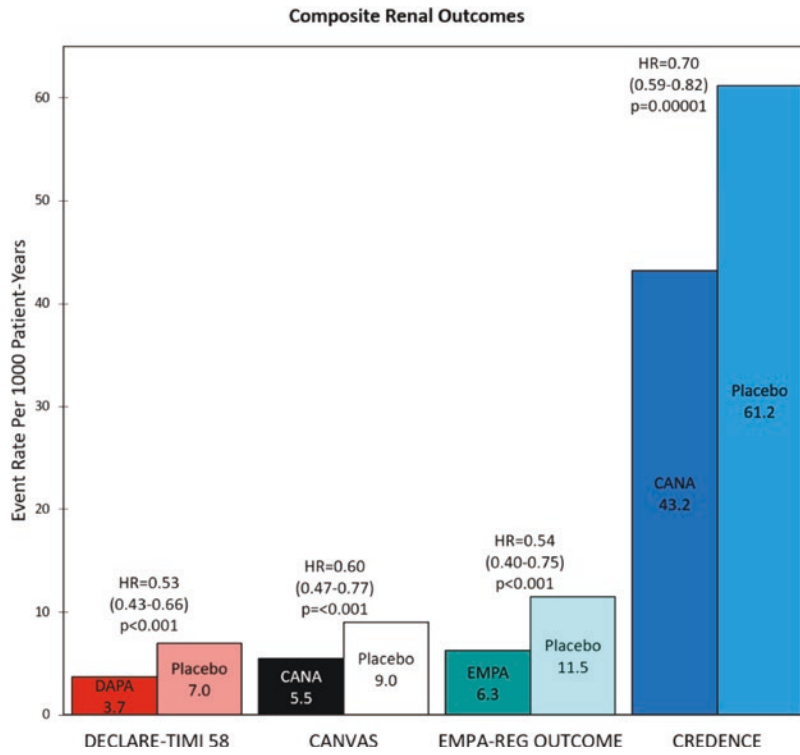


Fig. 22.3 Composite renal outcome rates in the Dapagliflozin Effect on CardiovascuLAR Events (DECLARE-TIMI 58), CANagliflozin CardioVascular Assessment Study (CANVAS) Program, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients—Removing Excess Glucose (EMPA-REG OUTCOME), and Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trials. Statistical outcomes displayed as hazard ratio, 95% confidence interval, p-value. Composite renal outcomes defined as follows: DECLARE-TIMI 58: ≥40% reduction in estimated glomerular filtration rate (eGFR) to <60, end-stage renal disease (ESRD) (dialysis ≥90 days, transplant or sustained eGFR <15), or renal/cardiovascular (CV) death; CANVAS: ≥40% reduction in eGFR, renal-replacement therapy (RRT) (transplant, chronic dialysis, or sustained eGFR <15), or renal death; EMPA-REG OUTCOME: doubling of serum creatinine (Cr) with eGFR ≤45, RRT, or renal death; CREDENCE: doubling of serum Cr, ESRD (eGFR <15, dialysis, or renal transplant), renal/CV death. *HR* hazard ratio, *DAPA* dapagliflozin, *CANA* canagliflozin, *EMPA* empagliflozin

(DECLARE-TIMI 58) assigned 17,160 T2DM patients to 10 mg of dapagliflozin daily or placebo over a median 4.2 [3.9, 4.4] year follow-up period [22]. Males ≥55 years or females ≥60 years with ≥1 CVD risk factor were included in the trial. Study patients were required to have creatinine clearance (CrCl) ≥60 mL/min with no specified minimum eGFR [32]. Dapagliflozin is indicated for T2DM patients with eGFR ≥45 mL/min/1.73 m^2 (initially eGFR ≥60 but updated to 45 in March 2019) and contraindicated for patients with eGFR <30 mL/min/1.73 m^2 [33, 34]. Investigators used the Cockcroft-Gault equation to calculate CrCl for the exclusion criteria and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation to calculate eGFR when reporting the composite renal outcomes.

In DECLARE-TIMI 58, 6974 (40.6%) patients had established CVD, most commonly stable coronary disease (Fig. 22.1). The mean eGFR was 85.2 mL/min/1.73 m^2, 1265 (7.4%) patients had eGFR <60, and 15895 (92.6%) had eGFR >60 mL/min/1.73 m^2. The median UACR was 13.1 [6.0, 43.6] mg/g; 11652 (67.9%) patients had UACR <30 mg/g, 4023 (23.4%) had UACR >30–300 mg/g, and 1169 (6.8%) had UACR >300 mg/g. Although ACEi/ARB

use was not required, they were used in 13,950 (81.3%) patients.

The primary composite CV endpoint (CV death, nonfatal MI, or nonfatal stroke) occurred in 8.8% of dapagliflozin patients compared to 9.4% of placebo patients (rate per 1000 patient-years = 22.6 vs. 24.2, HR = 0.93, 95% CI = 0.84–1.03, p = 0.17) (Fig. 22.2). With regard to secondary outcomes, HHF occurred in 2.5% of dapagliflozin patients compared to 3.3% of placebo patients (rate per 1000 patient-years = 6.2 vs. 8.5, HR = 0.73, 95% CI = 0.61–0.88, p = 0.0008). HHF or CV death occurred in 4.9% of dapagliflozin patients compared to 5.8% of placebo patients (rate per 1000 patient-years = 12.2 vs. 14.7, HR = 0.83, 95% CI = 0.73–0.95, p = 0.005). The composite renal outcome [≥40% reduction in eGFR to a threshold <60 mL/min/1.73 m^2, ESRD (dialysis ≥90 days, sustained eGFR <15 mL/min/1.73 m^2, or kidney transplantation), or renal/CV death] occurred in 1.5% of dapagliflozin patients compared to 2.8% of placebo patients (rate per 1000 patient-years = 3.7 vs. 7, HR = 0.53, 95% CI = 0.43–0.66, p < 0.001) (Fig. 22.3) [22].

22.4 The CREDENCE Trial

The Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation randomized double-blind controlled trial (CREDENCE) assigned 4401 patients with T2DM and CKD to 100 mg of canagliflozin or placebo daily over a 2.62 year median follow-up period [23]. Study patients were required to have eGFR between 30 and 90 mL/min/1.73 m^2 (calculated using the CKD-EPI equation) and investigators planned to include ~60% of patients with eGFR between 30 and 60 mL/min/1.73 m^2. Additionally, patients were required to have albuminuria, defined as UACR >300–5000 mg/g. Patients were not required to have prior CVD. Notably, the trial was stopped early as it met the pre-specified efficacy criteria for premature cessation.

In CREDENCE, 2220 (50.4%) patients had established CVD and ~16% had a baseline history of HF (Fig. 22.1). The mean eGFR was 56.2 ± 18.2 mL/min/1.73 m^2, 2631 (59.8%) patients had eGFR <60 mL/min/1.73 m^2, and 1769 (40.2%) had eGFR >60 mL/min/1.73 m^2. In striking contrast to the three CVOT trials, the median UACR was 927 [463, 1833] mg/g; 31 (0.7%) patients had UACR <30 mg/g, 496 (11.3%) had UACR >30–300 mg/g, 3371 (76.6%) had UACR >300–3000 mg/g, and 503 (11.4%) had UACR >3000 mg/g. Stable ACEi/ARB use was required for ≥4 weeks prior to randomization and RAASi were used in 4395 (99.9%) patients.

The primary composite renal endpoint [doubling of serum creatinine from baseline (sustained for at least 30 days), ESRD (dialysis, renal transplantation, or sustained eGFR <15 mL/min/1.73 m^2), or renal/CV death] occurred in 11.1% of canagliflozin patients compared to 15.4% of placebo patients (rate per 1000 patient-years = 43.2 vs. 61.2, respectively; HR = 0.70, 95% CI = 0.59–0.82, p = 0.00001) (Fig. 22.3). With regard to secondary outcomes, the composite CV outcome (CV death, nonfatal MI, or nonfatal stroke) occurred in 9.9% of canagliflozin patients compared to 12.2% of placebo patients (rate per 1000 patient-years = 38.7 vs. 48.7, HR = 0.80, 95% CI = 0.67–0.95, p = 0.01) (Fig. 22.2). HHF occurred in 4.0% of canagliflozin patients compared to 6.4% of placebo patients (rate per 1000 patient-years = 15.7 vs. 25.3, HR = 0.61, 95% CI = 0.47–0.80, p < 0.001). HHF or CV death occurred in 8.1% of canagliflozin patients compared to 11.5% of placebo patients (rate per 1000 patient-years = 31.5 vs. 45.4, HR = 0.69, 95% CI = 0.57–0.83, p < 0.001).

22.5 Cardiovascular and Renal Outcomes

When considering the four SGLT2i trials, overall relative risk reductions for HHF and CV death were externally consistent among the clinical trials (Fig. 22.4). The relative reductions in HHF were considerably greater than those for ischemic events including nonfatal MI and ischemic stroke. Additionally, the absolute risks of CV events appeared to be more related to baseline

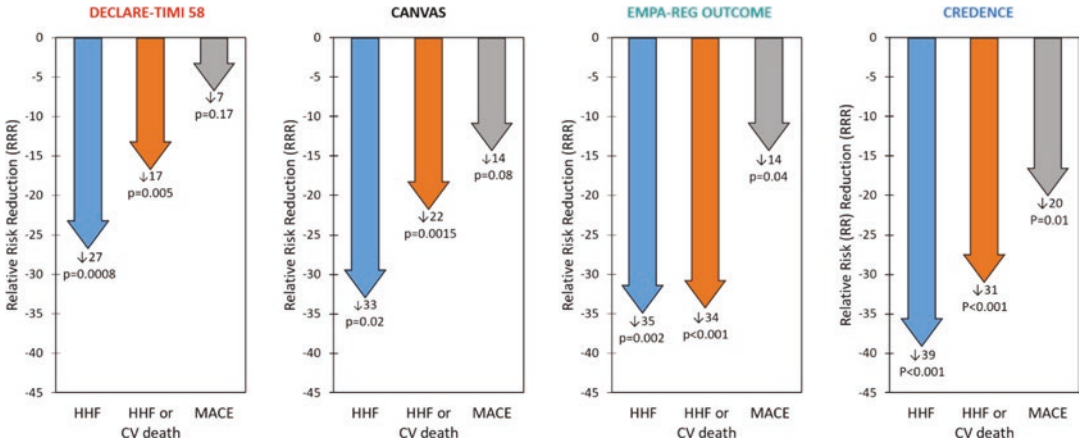


Fig. 22.4 Heart failure hospitalization (HHF), HHF and cardiovascular (CV) death, and major adverse cardiovascular event (MACE) relative risk reductions (RRRs) in the Dapagliflozin Effect on CardiovascuLAR Events (DECLARE-TIMI 58), CANagliflozin CardioVascular Assessment Study (CANVAS) Program, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients—Removing Excess Glucose (EMPA-REG OUTCOME), and Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trials. Statistical outcomes displayed as RRR, p-value. RRRs were calculated from hazard ratios

renal filtration than the baseline CVD rate (largely comprised of stable coronary artery disease in the patient histories). Finally, when the trial criteria was designed to enroll patients with significant diabetic nephropathy with albuminuria, not only was a compelling reduction in the primary renal composite outcome observed, but the highest rate of CV events was observed as well.

Of the four SGLT2i trials, CREDENCE had the highest CV event rates and DECLARE-TIMI 58 the lowest (Fig. 22.2). Relative risk reductions (RRRs) varied among the trials, but in general CREDENCE had the largest CV RRRs and DECLARE-TIMI 58 the smallest (Fig. 22.4). This is consistent with the superior baseline renal filtration function of DECLARE-TIMI 58 patients. CREDENCE had the highest composite renal event rates and DECLARE-TIMI 58 the lowest (Fig. 22.3). Despite these differences, the relative risk reductions in similar renal composite endpoints were externally consistent among the four trials (Fig. 22.5).

The differences in CV and renal outcomes between the three CVOTs (CANVAS, DECLARE-TIMI 58, EMPA-REG OUTCOME) have been described in a previous review [35]. This review argued that the different results of the trials were at least partially attributable to non-standard inclusion criteria, renal filtration function equations, and event definitions rather than inherent differences among the medications. The same may be true when comparing the three CVOTs to CREDENCE—its population had much higher baseline renal risk, and thus experienced more CV and renal outcomes. Specifically, CREDENCE had the lowest mean baseline eGFR (56.2 mL/min/1.73 m^2) compared to DECLARE-TIMI 58, CANVAS, and EMPA-REG OUTCOME (85.2 mL/min/1.73 m^2, 76.5 mL/min/1.73 m^2, and 74 mL/min/1.73 m^2, respectively) (Fig. 22.1). Most importantly, CREDENCE had the highest degree of albuminuria (median UACR = 927 [463, 1833] mg/g) compared to CANVAS (median UACR = 12.3 [6.65, 42.1] mg/g), DECLARE-TIMI 58 (median UACR = 13.1 [6.0, 43.6] mg/g), and EMPA-REG OUTCOME (median and quartiles 1 and 3 not supplied; 59.4% UACR <30, 28.6% UACR >30–300, 11.0% UACR >300 mg/g). Together, these trials establish the UACR as a risk predictor not only for renal events but also CV outcomes. Figure 22.6 positions the four trials according to baseline UACR and eGFR; CREDENCE had the highest renal risk and

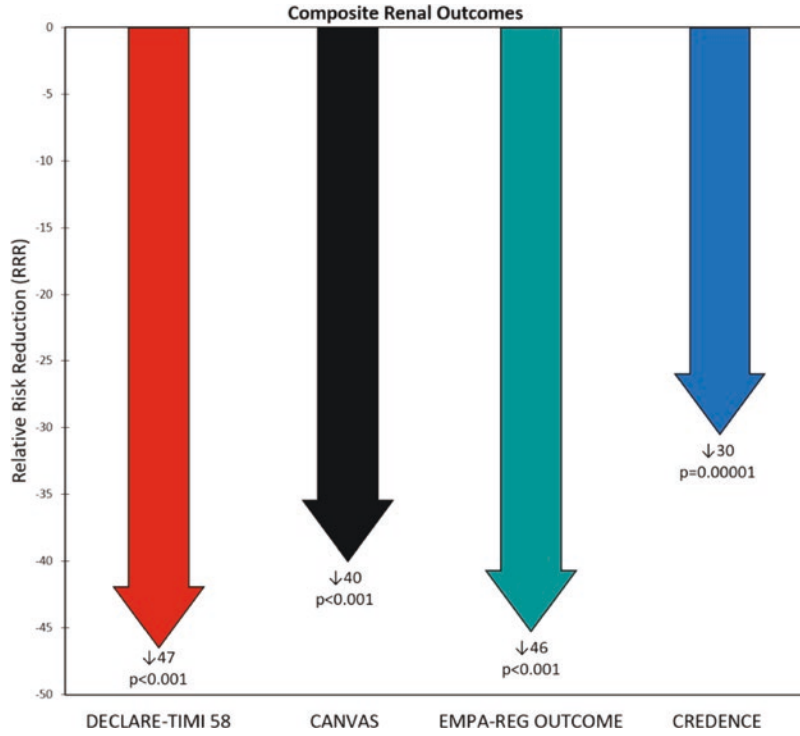
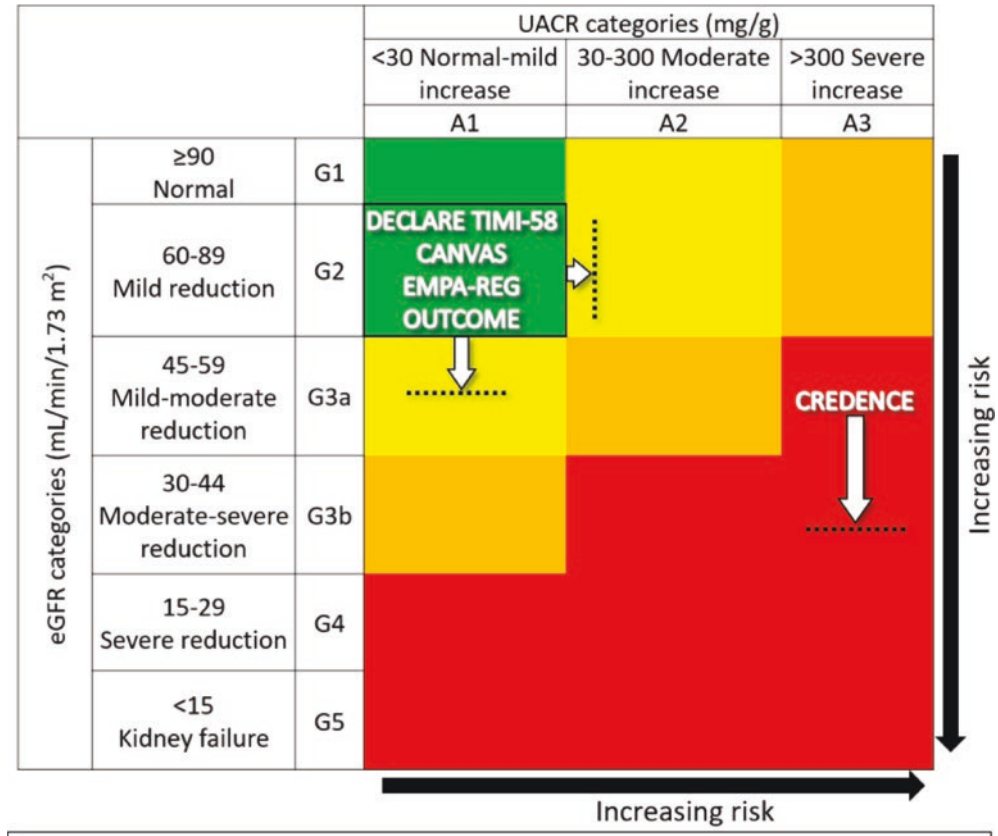


Fig. 22.5 Composite renal outcome relative risk reductions (RRRs) in the Dapagliflozin Effect on CardiovascuLAR Events (DECLARE-TIMI 58), CANagliflozin CardioVascular Assessment Study (CANVAS) Program, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients—Removing Excess Glucose (EMPA-REG OUTCOME), and Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trials. Statistical outcomes displayed as RRR, p-value. RRRs were calculated from hazard ratios. Composite renal outcomes defined as follows: DECLARE-TIMI 58: ≥40% reduction in estimated glomerular filtration rate (eGFR) to <60, end-stage renal disease (ESRD) (dialysis ≥90 days, transplant or sustained eGFR <15), or renal/cardiovascular (CV) death; CANVAS: ≥40% reduction in eGFR, renal-replacement therapy (RRT) (transplant, chronic dialysis, or sustained eGFR <15), or renal death; EMPA-REG OUTCOME: doubling of serum creatinine (Cr) with eGFR ≤45, RRT, or renal death; CREDENCE: doubling of serum Cr, ESRD (eGFR <15, dialysis, or renal transplant), renal/CV death

DECLARE-TIMI 58 the lowest. This "heat map" was derived from the Chronic Kidney Disease Prognosis Consortium and the results summarized are consistent with the higher absolute renal and CV events observed in the four trials [37].

Note that eGFR is more likely to identify CKD in older patients whereas UACR/albuminuria is more likely to identify it in younger patients [38]. Additionally, albuminuria is an important predictor of CKD progression. Some degree of the heterogeneity in cardiorenal outcomes between the trials may be accountable to population differences in these two biomarkers.

Baseline renal filtration function appears to play a major role in predicting cardiorenal outcomes, perhaps more so than prior CVD. Even though CREDENCE was not planned as a CVOT and thus only 50.4% of its population had prior CVD (compared to 40.6%, 65.6%, and 99.2% for DECLARE-TIMI 58, CANVAS, and EMPA-REG OUTCOME, respectively), CREDENCE still had, for example, a twofold increase in MACE compared to DECLARE-TIMI 58. This is supported by findings that SGLT2i decreased CV risk depending on baseline renal filtration function but not prior CVD status—lower function was associated with greater reductions in HHF [39].



DECLARE-TIMI 58
Baseline renal status: eGFR=85.2; UACR = 13.1 [6.0, 43.6]; n=17,160.
Composite renal outcome: ≥40% reduction in eGFR to <60, ESRD (dialysis ≥90 days, transplant or sustained eGFR<15), or renal/CV death

CANVAS
Baseline renal status: eGFR=76.5±20.5; UACR = 12.3 [6.65, 42.1]; n=10,142.
Composite renal outcome: ≥40% reduction in eGFR, RRT (transplant, chronic dialysis, or sustained eGFR<15), or renal death

EMPA-REG OUTCOME
Baseline renal status: eGFR=74±21; 59.4% UACR<30, 28.6% UACR >30-300, 11.0% UACR >300; n=7020.
Composite renal outcome: Doubling of serum Cr with eGFR ≤45, RRT, or renal death

CREDENCE
Baseline renal status: eGFR=56.2±18.2; UACR = 927 [463, 1833]; n=4401.
Composite renal outcome: Doubling of serum Cr, ESRD (eGFR <15, dialysis, or renal transplant), renal/CV death

Fig. 22.6 Baseline renal risk and composite renal outcome definitions in the Dapagliflozin Effect on CardiovascuLAR Events (DECLARE-TIMI 58), CANagliflozin CardioVascular Assessment Study (CANVAS) Program, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients—Removing Excess Glucose (EMPA-REG OUTCOME), and Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trials. Horizontal dotted lines and white arrows approximate trials averaged mean eGFRs −1 pooled standard deviation; vertical dotted lines and white arrows approximate trials' quartile 3 of UACR. Data displayed as mean eGFR ± standard deviation (where available); median UACR [quartile 1, quartile 3] or percent of study population with UACR <30, >30–300, and >300 (depending on trial). *eGFR* estimated glomerular filtration rate in mL/min/1.73 m^2, *UACR* urinary albumin-creatinine ratio in mg/g. (Adapted from reference [36])

22.6 Outcome Definitions

Variance in trial methodologies were considered as possible determinants for differences in results. Although the four trials had comparable CV event definitions due to FDA regulatory guidance, their composite renal outcome definitions varied according to sponsor choice (Table 22.1). For example, DECLARE-TIMI 58 and CREDENCE included CV death while CANVAS and EMPA-REG OUTCOME did not. There were also minor differences in the choice of renal filtration function estimation equation: DECLARE-TIMI 58 and CREDENCE used CKD-EPI to calculate eGFR while the other two trials used the MDRD equation. The CKD-EPI equation is slightly more accurate and precise and is more prognostic for mortality than MDRD [40–43]. These relatively subtle differences in event definitions and estimation of renal filtration function probably did not play an appreciable role in the trials' results or interpretation—the most significant factor still appears to be the position of the trials on the renal risk heat map (Fig. 22.6).

22.7 Other Notable Trial Results

Interestingly, the CREDENCE and EMPA-REG OUTCOME placebo groups had similar MACE incidence rates (48.7 per 1000 patient-years and 43.9 per 1000 patient-years, respectively), despite different baseline UACR and eGFR. This can may be attributed to the balance of baseline CVD vs. renal risk: CREDENCE had significantly higher renal risk but only 50.4% prior CVD whereas EMPA-REG had nearly 100% prior CVD.

The composite renal outcome RRR is another intriguing result when comparing the four trials. In a reversal of the trend seen with the other outcomes, CREDENCE had the smallest RRR and

Table 22.1 Renal drug guidelines, entry criteria, mean estimated glomerular filtration rate, and composite outcome definitions in the Dapagliflozin Effect on CardiovascuLAR Events (DECLARE-TIMI 58), CANagliflozin CardioVascular Assessment Study (CANVAS) Program, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients—Removing Excess Glucose (EMPA-REG OUTCOME), and Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trials

	FDA indicated guidelines	Study renal entry criteria			Results	
Trial	Minimum recommended eGFR	eGFR minimum	eGFR equation	Additional renal criteria	Mean eGFR	Composite renal outcome
DECLARE-TIMI 58	45	N/A	CKD-EPI	CrCl 60 mL/min (Cockcroft-Gault equation)	85.2	≥40% reduction in eGFR to <60, ESRD (dialysis ≥90 days, transplant or sustained eGFR <15), or renal/CV death
CANVAS	45	30	MDRD	N/A	76.5	≥40% reduction in eGFR, RRT (transplant, chronic dialysis, or sustained eGFR <15), or renal death
EMPA-REG OUTCOME	45	30	MDRD	N/A	74	Doubling of serum Cr with eGFR ≤45, RRT, or renal death
CREDENCE	45	30	CKD-EPI	UACR 300–5000	56.2	Doubling of serum Cr, ESRD (eGFR <15, dialysis, or renal transplant), renal/CV death

All eGFRs are in mL/min/1.73 m^2

eGFR estimated glomerular filtration rate, *MDRD* Modification of Diet in Renal Disease, *CKD-EPI* Chronic Kidney Disease Epidemiology Collaboration, *RRT* renal-replacement therapy, *ESRD* end-stage renal disease, *CV* cardiovascular, *CrCl* creatinine clearance, *Cr* creatinine, *UACR* urinary albumin-creatinine ratio in mg/g

DECLARE-TIMI 58 the largest (Fig. 22.5). One hypothesis is that this effect may reflect differences in renal functional reserve (RFR) among the trial participants [44]. RFR is defined as peak eGFR (induced via stress response) minus baseline eGFR and may result from recruiting inactive nephrons or increasing single nephron filtration [45, 46]. RFR has an inverse relationship with CKD stage, decreasing as CKD progresses [47]. Reducing renal hyperfiltration injury in patients with less severe CKD and thus more RFR (i.e., those in the three CVOTs) may yield more robust risk reduction or preventable fraction than in patients with advanced CKD and thus less RFR (i.e., those in CREDENCE). This hypothesis of varying opportunity for prevention of renal filtration function loss needs to be tested formally.

22.8 RAASi Use

Other sources of confounding were considered for differences among the trials. All four trials had substantial RAASi use: approximately 80% in the three CVOTs and 99.9% in CREDENCE. Thus, differential rates of RAASi would probably not explain the contrasts between the trials. Notably, the high rates of RAASi use indicate that the patients were well-treated at baseline. This should ease skepticism about the real-world therapeutic opportunity for SGLT2i, as any benefits due to the SGLT2i can be viewed as being additional to those from RAASi therapy.

22.9 Safety

The efficacy results were balanced with the safety data. The four trials demonstrated several general safety trends (Tables 22.2 and 22.3). SGLT2i were found to be significantly safer than placebo regarding adverse events (AEs) and serious AEs. However, they were generally associated with increased risk of diabetic ketoacidosis and amputation and decreased risk of acute kidney injury. There were no clear trends regarding fractures or urinary tract infections. SGLT2i were significantly associated with increased risk of genital infections; however, this is expected due to the glucosuria promoted by the drugs. Some research results found that SGLT2i are associated with increased risk of Fournier's gangrene [48, 49]. However, DECLARE-TIMI 58—the only trial of the four prospectively to study this AE—reported that Fournier's gangrene occurred in 18 (0.2%) of dapagliflozin patients vs. 24 (0.3%) of placebo patients.

22.10 Future Potential Benefits of SGLT2i

SGLT2i have demonstrated a host of positive effects of interest for future research. In animal models of T2DM female mice, empagliflozin ameliorated kidney injury by promoting glycosuria, and possibly by reducing systemic and renal artery stiffness; canagliflozin attenuated the progression of atherosclerosis, reducing hyperlipidemia, hyperglycemia, and inflammation by lowering the expression of some inflammatory molecules [50, 51]. Of note, the hyperexpressed SGLT1 in cardiomyocytes may represent a potential pharmacological target for cardioprotection [52]. In human studies of T2DM patients, both dapagliflozin and canagliflozin demonstrated beneficial effects on left ventricular diastolic functional parameters [53, 54]. With regard to SGLT2i versus other antihyperglycemic agents, SGLT2i were associated with a reduced risk of HHF compared to dipeptidyl peptidase 4 inhibitors (DPP4i) and canagliflozin was associated with a reduced risk of HHF and a similar risk of MI or stroke compared to DPP4i, glucagon-like peptide-1 agonists, and sulfonylureas [55, 56]. Finally, the EMPA-REG OUTCOME results may be applicable to T2DM patients with a broader CV risk profile, including patients at low risk of CVD [57].

22.11 Class Effects

Giugliano and colleagues studied the three SGLT2i CVOTs and suggested a class effect with regard to HF risk reduction [58]. After review-

Table 22.2 Adverse events in the Dapagliflozin Effect on CardiovascuLAR Events (DECLARE-TIMI 58), CANagliflozin CardioVascular Assessment Study (CANVAS) Program, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients—Removing Excess Glucose (EMPA-REG OUTCOME), and Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trials

	DECLARE-TIMI 58					CANVAS				EMPA-REG OUTCOME				CREDENCE					
	DAPA n (%)	Placebo n (%)	Risk[a]	HR (95% CI)	p-value	CANA event rate	Placebo event rate	Risk[a]	p-value	Pooled EMPA n (%)	Placebo n (%)	Risk[a]	p-value	CANA n (%)	Placebo n (%)	CANA event rate	Placebo event rate	Risk[a]	HR (95% CI)
Male genital infection[b]	76 (0.9)	9 (0.1)	+	8.36 (4.19–16.68)	<0.001	34.9	10.8	+	<0.001	166 (5.0)	25 (1.5)	+	<0.001	28 (0.2)	3 (0.0)	8.4	0.9	+	9.30 (2.83–30.60)
Female genital infection[b]						68.8	17.5	+	<0.001	135 (10.0)	17 (2.6)	+	<0.001	22 (0.3)	10 (0.0)	12.6	6.1	+	2.10 (1.00–4.45)
Any AE	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	4230 (90.2)	2139 (91.7)	-	<0.001	1784 (8.1)	1860 (0.8)	351.4	379.3	-	0.87 (0.82–0.93)
Serious AE	2925 (34.1)	3100 (36.2)	-	0.91 (0.87–0.96)	<0.001	104.3	120	-	0.04	1789 (38.2)	988 (42.3)	-	<0.001	737 (3.3)	806 (0.4)	145.2	164.4	-	0.87 (0.79–0.97)
AE leading to discontinuation	693 (8.1)	592 (6.9)	+	1.15 (1.03–1.28)	0.01	35.5	32.8	+	0.07	813 (17.3)	453 (19.4)	-	<0.001	N/A	N/A	N/A	N/A	N/A	N/A
Hypoglycemia	58 (0.7)	83 (1.0)	-	0.68 (0.49–0.95)	0.02	50	46.4	+	0.20	1303 (27.8)	650 (27.9)	-	N/A	225 (1.0)	240 (0.1)	44.3	48.9	-	0.92 (0.77–1.11)
UTI	127 (1.5)	133 (1.6)	-	0.93 (0.73–1.18)	0.54	40	37	+	0.38	842 (18.0)	423 (18.1)	-	N/A	245 (1.1)	221 (0.1)	48.3	45.1	+	1.08 (0.90–1.29)
Fracture	457 (5.3)	440 (5.1)	+	1.04 (0.91–1.18)	0.59	15.4	11.9	+	0.02	179 (3.8)	91 (3.9)	-	N/A	67 (0.3)	68 (0.0)	11.8	12.1	-	0.98 (0.70–1.37)
Hyperkalemia	N/A	N/A	N/A	N/A	N/A	6.9	4.4	+	0.10	N/A	N/A	N/A	N/A	151	181	29.7	36.9	-	0.80
Amputation	123 (1.4)	113 (1.3)	+	1.09 (0.84–1.40)	0.53	6.3	3.4	+	<0.001	N/A	N/A	N/A	N/A	70 (0.3)	63 (0.0)	12.3	11.2	+	1.11 (0.79–1.56)
AKI	125 (1.5)	175 (2.0)	-	0.69 (0.55–0.87)	0.002	3	4.1	-	0.33	45 (1.0)	37 (1.6)	-	<0.05	86 (0.4)	98 (0.0)	16.9	20	-	0.85 (0.64–1.13)
Breast cancer	36 (0.4)	35 (0.4)	0	1.02 (0.64–1.63)	0.92	3.1	2.6	+	0.65	N/A	N/A	N/A	N/A	8 (0.1)	3 (0.0)	4.1	1.6	+	2.59 (0.69–9.76)
Bladder cancer	26 (0.3)	45 (0.5)	-	0.57 (0.35–0.93)	0.02	1	1.1	-	0.74	N/A	N/A	N/A	N/A	10 (0.0)	9 (0.0)	1.7	1.6	+	1.10 (0.45–2.72)
DKA	27 (0.3)	12 (0.1)	+	2.18 (1.10–4.30)	0.02	0.6	0.3	+	0.14	4 (0.1)	1 (<0.1)	+	N/A	11 (0.0)	1 (0.0)	2.2	0.2	+	10.80 (1.39–83.65)

DAPA dapagliflozin, *CANA* canagliflozin, *EMPA* empagliflozin, *HR* hazard ratio, *CI* confidence interval, *AE* adverse event, *N/A* not available, *UTI* urinary tract infection, *AKI* acute kidney injury, *DKA* diabetic ketoacidosis

[a]Indicates increased ("+"), decreased ("−"), or no difference in ("0") risk associated with study drug compared to placebo. Blue color indicates statistical significance at the $\alpha = 0.05$ level

[b]DECLARE-TIMI 58 did not differentiate genital infection by sex

ing the CVOTs and CREDENCE, this class effect can be expanded to include CV and renal outcomes in general. Note that there is no universal definition of class effect; the closest approximation is the term "class labeling" used by the FDA, which "assumes that all products within a class are closely related in chemical structure, pharmacology, therapeutic activity, and adverse reactions." [59]. With this in mind, there is sufficient evidence of a class effect. The SGLT2i have similar molecular structures. Also, though much of their pharmacological methods of action are unknown, one plausible explanation is off-target inhibition of the sodium-proton antiporter/exchanger—a membrane-bound family of channels present in both the heart and kidneys [60, 61]. The four trials are internally consistent, with no particular subgroup benefitting over another and no treatment interactions within any of the trials. The trials are externally consistent with each other, showing reliable cardiorenal benefit (according to baseline risk) and comparable adverse effects. Lastly, the SGLT2i studied have similar known mechanisms of action resulting in losses of glucose and sodium in the urine and reductions in blood pressure and body weight [59]. This proposed pharmacologic class effect would apply more to HHF, CV death, and renal composite events than to the MACE composite outcome, which was not significantly reduced in DECLARE-TIMI 58. Additionally, this class effect is limited to the three SGLT2i reviewed in this paper: canagliflozin, dapagliflozin, and empagliflozin. It remains to be seen if it will extend to ertugliflozin, sotagliflozin, and/or other similar agents.

Table 22.3 Risk associated with study drug compared to placebo for adverse events in the Dapagliflozin Effect on CardiovascuLAR Events (DECLARE-TIMI 58), CANagliflozin CardioVascular Assessment Study (CANVAS) Program, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients—Removing Excess Glucose (EMPA-REG OUTCOME), and Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trials

	DECLARE-TIMI 58	CANVAS	EMPA-REG OUTCOME	CREDENCE
Male genital infection[a]	+	+	+	+
Female genital infection[a]		+	+	+
Any AE	N/A	N/A	-	-
Serious AE	-	-	-	-
AE causing discontinuation	+	+	-	N/A
Hypoglycemia	-	+	-	-
UTI	-	+	-	+
Fracture	+	+	-	-
Hyperkalemia	N/A	+	N/A	-
Amputation	+	+	N/A	+
AKI	-	-	-	-
Breast cancer	0	+	N/A	+
Bladder cancer	-	-	N/A	+
DKA	+	+	+	+

Blue color indicates statistical significance at the $\alpha = 0.05$ level
"+" = increased risk, "−" = decreased risk, "0" = no difference in risk
AE adverse event, *N/A* not available, *UTI* urinary tract infection, *AKI* acute kidney injury, *DKA* diabetic ketoacidosis
[a]DECLARE-TIMI 58 did not differentiate genital infection by sex

22.12 Conclusions

Dapagliflozin, empagliflozin, and canagliflozin have internally and externally consistent class effects on cardiorenal outcomes and similar safety profiles. Baseline renal filtration function and degree of albuminuria are the most significant indicators of risk for both CV and renal events. Thus, these two factors also anticipate the greatest clinical benefit for SGLT2i.

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23 Management of Diabetes Mellitus in Acute and Chronic Cardiorenal Syndromes

Allison J. Hahr and Mark E. Molitch

23.1 Introduction

Approximately 422 million adults worldwide have diabetes mellitus (DM), affecting about 8.5% of adults. The prevalence globally has almost doubled since 1980 when an estimated 4.7% of adults had diabetes [1]. About 30 million Americans have diabetes, which represents about 9.4% of the population in the United States. Of these 30 million, about 1.25 million have type 1 diabetes [2].

The management of diabetes in patients with cardiorenal syndrome presents its own challenges. The roles the heart and kidney play in individuals with diabetes is well-known. Cardiovascular disease (CVD) is highly prevalent in individuals with diabetes and is the leading cause of morbidity and mortality [3]. The presence of chronic kidney disease (CKD) further increases overall cardiovascular risk in those with diabetes [4]. It is therefore of vital importance that cardiovascular risk factors be controlled as best as possible, as this can slow the progression of CVD. Risk factors should be evaluated in all individuals with diabetes at least on an annual basis and includes assessment of blood pressure, smoking status, family history of coronary artery disease, lipids, and kidney status, looking for the presence of CKD and albuminuria [3].

Even without the presence of known CVD or cardiac disease, individuals with diabetes need to be monitored carefully for the development of nephropathy. Diabetes is the most common cause of kidney failure in the United States, and it is also one of the most common causes worldwide. Diabetic kidney disease (DKD) is chronic kidney disease related to diabetes and is defined most often by the presence of albuminuria and/or a low estimated glomerular filtration rate (eGFR); it affects about 20–40% of all individuals who have diabetes [5]. In addition to glycemic control, high blood pressure will also contribute to the development of DKD [6].

There is improvement in the proportion of individuals in the United States who are achieving the goals for Hemoglobin A1c (A1c), LDL cholesterol, and blood pressure, with a decline in the mean A1c from 7.6% (60 mmol/mol) to 7.2% (55 mmol/mol) as estimated by the National Health and Nutrition Examination Survey (NHANES) from 1999 to 2002 to 2007–2010 [7]. Accordingly, subsequent decreases in microvascular complications and improvements in cardiovascular disease have been noted with this improvement in glycemic control [7]. Despite these noted improvements, however, it is

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estimated that nearly 50% of individuals with diabetes do not meet glycemic, cholesterol and/or blood pressure targets [7]. This emphasizes the need for continued monitoring and attention to all cardiovascular risk factors including kidney disease. Once CKD has been identified, it is important to be aware of how to safely use the various anti-hyperglycemic medications in the presence of CKD. In addition, the glycemic target should be individualized for each patient with the emphasis on avoiding hypoglycemia but also controlling hyperglycemia.

23.2 Screening for Diabetes

Individuals with type 2 diabetes often go undiagnosed for several years. It is estimated that in the U.S., about 25% of individuals with diabetes go undiagnosed [8]. Given this high number, patients with cardiorenal syndrome should be screened annually for diabetes.

Criteria for the diagnosis of diabetes includes a fasting glucose ≥126 mg/dL (7.0 mmol/L), 2 h glucose of ≥200 mg/dL (11.1 mmol/L) after a 75 g glucose load, A1c ≥6.5% (48 mmol/mol) or a random plasma glucose of ≥200 mg/dL (11.1 mmol/L) in an individual with symptoms of hyperglycemia. It is recommended that an abnormal result be confirmed with a repeat test, unless there is obvious hyperglycemia present [8]. As of 2010, the American Diabetes Association included the use of A1c for diagnosis due to its ease of use. In addition, it is not affected by recent changes in glucose levels due to new illness and stress. However, it may be more costly, not always available, and inaccurate in some individuals, such as those with hemoglobinopathies, conditions leading to high red blood cell turnover including anemia and recent blood transfusions, or acute onset of hyperglycemia (such as new diagnosis type 1 diabetes). It is also less sensitive than using plasma glucose measurements. The 2 h glucose tolerance test is a more sensitive test but it is more time consuming and inconvenient for the patient [8]. The choice of which screening test to use should be weighed individually for each patient.

23.3 Screening for CKD

Individuals with cardiorenal syndrome already have been identified to have CKD. In these individuals, the development of CKD can be from a number of causes, one of which may be diabetes. Referral to a nephrologist should be considered if the cause is uncertain (e.g. lack of retinopathy, nephrotic range proteinuria without GFR impairment, rapid progression) and also for management of complications related to advancing kidney disease. In general, patients with diabetes should be screened on an annual basis for the development of CKD by measurement of urinary albumin and serum creatinine.

A screening urine albumin to creatinine ratio (ACR) can be measured on a spot urine or timed urine collection such as over 4 or 24 h. Measurement is much easier on a spot collection, and a timed collection does not increase accuracy [9, 10]. Elevated urine albumin excretion is defined as more than 30 mg per gram creatinine or 30 mg per 24 h. An abnormal reading should be confirmed on at least two of three additional urine tests over a 3–6 month period [5]. Other causes of elevated urine protein should be considered such as infection, strenuous exercise, fever, severe hyperglycemia, hypertension, heart failure and hematuria (including menstruation). The serum creatinine should be used to estimate glomerular filtration rate (GFR) and thus, the level of CKD. The two equations that can be used to calculate GFR are the Modification of Diet in Renal Disease (MDRD) and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) [11, 12]; the CKD-EPI is preferred [10]. These equations do not use weight but they do use African-American race as an additional modifier; an online calculator for these equations is available on the website for the National Kidney Foundation (www.kidney.org).

23.4 Medications in Diabetic Nephropathy

In the presence of impaired GFR, it's important to know how to safely use diabetes medications. Glycemic control in CKD adds another level of

complexity that requires consideration for which diabetes medications can be used and how kidney disease affects their metabolism. Patients with nephropathy are at higher risk of hypoglycemia due to decreased clearance of insulin as well as other medications used to treat diabetes. In addition, individuals with fluctuating renal function need even more monitoring as their diabetes medications may need frequent adjustment.

There are multiple different classes of medications available for glycemic control. Please refer to Table 23.1 for dosing adjustments for diabetes medications in the presence of CKD.

23.4.1 Insulin

The kidney is responsible for about 30–80% of insulin clearance; reduced kidney function is associated with a prolonged insulin half-life and a reduction in insulin requirements as GFR decreases [13]. All currently available types of insulin preparations can be used in patients with CKD, and there is no specific advised reduction in dosing. The insulin type, dose, and administration should be individualized to achieve goal glycemic levels while limiting hypoglycemia. An inpatient study comparing typical weight-based doses (0.5 units/kg body weight) to halving of the insulin doses to 0.25 units/kg body weight, using glargine plus prandial glulisine in patients with an eGFR <45 mL/min/1.73 m^2, found comparable levels of glycemic control but much less hypoglycemia [14]. In general, patients on insulin need extra careful monitoring to reduce the risk of hypoglycemia. All insulin mentioned below is subcutaneous with the exception of inhaled insulin.

23.4.1.1 Long-Acting Insulins

The long-acting insulin analogs are U-100 glargine, U-300 glargine, detemir, U-100 degludec, and U-200 degludec; these are all used as basal insulins. Glargine is soluble at an acidic pH but less soluble when at a physiologic pH, so subcutaneous injection leads to precipitation and slower absorption. It has an onset of action of 2–4 h after injection, duration of 20–24 h and is usually dosed once daily; it does not have a clear

Table 23.1 Dose adjustment for insulin compounds and oral medications for diabetes in chronic kidney disease

Medication class	CKD stages 3 and 4 and predialysis 5
Insulins	No advised dose adjustment[a]
First-generation sulfonylureas	
Acetohexamide	Avoid use
Chlorpropamide	GFR 50–80 mL/min/1.73 m^2: reduce dose 50% GFR <50 mL/min/1.73 m^2: avoid
Tolazamide	Avoid use
Tolbutamide	Avoid use
Second-generation sulfonylureas	
Glipizide	No dose adjustment
Glimepiride	Start conservatively at 1 mg daily
Glyburide	Avoid use
Gliclazide	No dose adjustment
Glinides	
Repaglinide	No dose adjustment
Nateglinide	Start conservatively at 60 mg with meals. Do not use if eGFR <60 ml/min/1.73 m^2
Biguanides	
Metformin	Maximum dose 1000 mg/day for eGFR <45 ml/min/1.73 m^2 and discontinue for eGFR <30 ml/min/1.73 m^2
Thiazolidinediones	
Pioglitazone	No dose adjustment
Rosiglitazone	No dose adjustment
Alpha-glucosidase inhibitors	
Acarbose	Avoid if GFR <26 mL/min/1.73 m^2
Miglitol	Avoid use
DPP-4 inhibitor	
Sitagliptin	GFR >50 mL/min/1.73 m^2: 100 mg daily GFR 30–50 mL/min/1.73 m^2: 50 mg daily GFR <30 mL/min/1.73 m^2: 25 mg daily
Saxagliptin	GFR >50 mL/min/1.73 m^2: 5 mg daily GFR ≤50 mL/min/1.73 m^2: 2.5 mg daily
Alogliptin	GFR 50 ml/min/1.73 m^2; 25 mg daily GFR 30–50 ml/min/1.73 m^2; 12.5 mg daily GFR <30 ml/min/1.73 m^2; 6.25 mg daily
Linagliptin	No restrictions
GLP-1 agonists	
Exenatide	Not recommended if GFR <30 mL/min/1.73 m^2
Liraglutide	No dose adjustment
Semaglutide	No dose adjustment

(continued)

Table 23.1 (continued)

Medication class	CKD stages 3 and 4 and predialysis 5
Dulaglutide	No dose adjustment
Lixisenatide	Not recommended if eGFR <15 ml/min/1.73 m^2
Amylin analog	
Pramlintide	No dose adjustment
SGLT2 Inhibitors	
Canagliflozin	eGFR 45 to <60 ml/min/1.73 m^2: max dose 100 mg once daily eGFR <30 ml/min/1.73 m^2: avoid use
Dapagliflozin	eGFR <45 ml/min/1.73 m^2: avoid use
Empagliflozin	eGFR <45 ml/min/1.73 m^2: avoid use
Ertugliflozin	eGFR <60 ml/min/1.73 m^2: avoid use

CKD chronic kidney disease, *NPH* neutral protamine Hagedorn, *GFR* glomerular filtration rate
[a]Adjust dose based on patient response

peak after injection [15, 16]. Detemir binds to albumin after injection which gives detemir its prolonged action, extending its half-life in the circulation. Detemir has an onset of action at 1–3 h, with a small peak at 6–8 h and duration of action of 18–22 h [17–19]. Detemir is dosed twice daily to give adequate basal coverage in type 1 diabetes; in type 2 diabetes, once daily dosing may suffice. Degludec is an additional long-acting insulin with a half-life of about 25 h. It has a minimal peak and low variability in concentration day-to-day. U-300 glargine and degludec (both U-100 and U-200) have prolonged half-lives so that once daily injection is virtually always sufficient. The longer durations of action of U-300 glargine and degludec are due to a prolongation of their absorption from the subcutaneous injection sites and not related to a decrease in renal clearance. Thus, despite the longer duration of action, their pharmacokinetics are not changed with advancing CKD [20, 21]. No specific dose changes are needed with a reduced GFR with these basal insulins other than the general dose reduction needed for all insulins.

23.4.1.2 Intermediate-Acting Insulin

Isophane insulin, or NPH (neutral protamine Hagedorn) is the only currently available intermediate-acting insulin; it is the result of adding protamine to regular insulin. NPH has an onset of action at 2–4 h, peak concentration at 4–10 h, and duration up to 10–18 h; it is used as a basal insulin when given as a twice daily injection. NPH can be mixed in a syringe with short- or rapid-acting insulins [22, 23]. Its use can be limited by its highly variable absorption, making the long-acting insulins preferable. However, its cost is much lower compared to insulin analogs.

23.4.1.3 Short-Acting Insulin

Regular crystalline insulin has an onset of action at about 30–60 min, peak action at 2–3 h and duration of action of 5–8 h. Regular insulin should ideally be given 30 min prior to a meal. Its cost is also much less compared to insulin analogs.

23.4.1.4 Rapid-Acting Insulins

The rapid-acting insulin analogs aspart, lispro, and glulisine are the quickest acting of all the insulins; they have a faster onset of action compared to regular insulin and a shorter duration of action. They are ideal for quick correction of blood sugars or use as prandial insulin. The average onset of action is at about 15 min, peak action at about 60 min and an average duration up to 4 h. In general, these insulins can be used interchangeably. They are injected up to 15 min before eating and are used in "basal-bolus therapy," also known as multiple daily injections (MDI). There are now a fast-acting insulin aspart (Fiasp® in the U.S.) and a fast-acting insulin lispro (LyumjevR in the U.S.) available which have a faster onset and offset compared to the other insulin analogs. They are given directly before eating but can be dosed up to 20 min after starting a meal. All of these insulin preparations can be used in insulin pumps.

Patients with stage 4–5 CKD and those on dialysis may have delayed gastric emptying. In these individuals, giving rapid-acting insulin after the meal may be helpful for matching the insulin peak with the time of the postprandial blood glucose peak. Patients with advanced cardiorenal syndrome may have poor appetites. For these individuals, it may be necessary to inject

rapid-acting insulin after eating in order to match the insulin dose in proportion to the amount of food eaten.

23.4.1.5 Premixed Insulins

Premixed insulin contains a fixed percentage of an intermediate-acting and a rapid- or short-acting insulin. Because they contain a combination of two insulin types, they have two separate peaks and two durations of actions. One example is "70/30" which consists of 70% NPH and 30% regular insulin. These preparations offer convenience for the patient with twice daily dosing but offer less flexibility and more restrictions in titration of the insulin. Premixed insulin must be taken at fixed times and the patient must have consistent meals. 70/30 insulin is sometimes helpful in patients getting 12-h cycled tube feeds.

23.4.1.6 Varying Insulin Concentrations

Insulin is typically U-100, which is defined as 100 units of insulin per 1 mL. All insulin mentioned previously is U-100 unless stated otherwise. Multiple different concentrations of insulin are now available. U-500, defined as 500 units of insulin per 1 mL, is only available as regular insulin. The high concentration of U-500 insulin alters the properties of regular insulin making its pharmacokinetics different. It has a similar onset of action to regular insulin, near 30 min, but the peak is at 4–8 h and duration is 14–15 h. It can be given up to 30 min prior to meals and is typically given two to three times daily, without the use of any separate basal insulin [24]. It is generally used in patients who are severely insulin resistant and can be given as a subcutaneous injection or in a pump. There are also higher concentrations of insulin available including U-300 glargine, U-200 degludec, and U-200 lispro. These are useful in patients who have elevated insulin resistance and/or for patients who use large amounts of insulin daily since the same amount of insulin can be delivered in a smaller volume. It is also helpful for those on high doses since an insulin pen can then last longer (for example, a pen may contain 600 units rather than the standard 300 units).

23.4.1.7 Inhaled Insulin

Inhaled insulin was approved for use in the U.S. in 2015. It is a rapid-acting insulin that can be used as a prandial insulin in adults with type 1 and type 2 diabetes. The onset of action is at about 12–15 min, peak at 50 min, and duration of action of 2.5–3 h. It carries a risk of pulmonary complications and should be avoided in individuals with chronic lung disease [25]. It has not been studied in renal impairment, and it is recommended to adjust dosing as with any insulin use in patients with nephropathy.

23.4.2 Oral Medications

There are six classes of oral medications and two classes of non-insulin injectable medications approved for treatment of type 2 diabetes (one of the injections, pramlintide, is also approved for type 1 diabetes). The non-insulin injectable medications will be discussed separately (see below).

23.4.2.1 Metformin (Biguanides)

Metformin increases insulin sensitivity and decreases hepatic gluconeogenesis; it does not cause hypoglycemia when used alone, and it can lead to weight loss in some patients. It reduces A1c on average by 1.0–2.0% [26]. The most common side effects are diarrhea, bloating and abdominal cramping. Vitamin B12 deficiency can occur with long-term use [27].

Metformin is cleared renally and therefore levels may increase in the presence of CKD and that can place patients at risk of developing lactic acidosis. The overall incidence of lactic acidosis with metformin use, however, is quite rare. A Cochrane database review of 347 prospective trials and observational cohort studies showed no cases of fatal or non-fatal lactic acidosis in 70,490 patient-years of metformin users or in 55,451 patient-years of users of other anti-hyperglycemic agents [28]. The Food and Drug Administration (FDA) guidelines that formerly recommended a creatinine cutoff for metformin use were revised so that metformin should not be used in patients with an eGFR <30 mL/min/1.73 m^2 [29]. It is suggested to not start metformin if the eGFR is

between 30 and 45 mL/min/1.73 m^2. If, while during use, the eGFR decreases to below 45 mL/min/1.73 m^2, review the risks and benefits of continuing metformin [29]. Additionally, it seems reasonable to reduce the maximum metformin dose to no more than 1000 mg/day with an eGFR <45 mL/min/1.73 m^2 and to hold metformin in unstable conditions such as hypoxia, hypotension and after administration of iodinated contrast until it is certain that there is no sustained loss of GFR [30, 31].

23.4.2.2 Sulfonylureas

Sulfonylureas bind to the sulfonylurea receptor on the beta-cells of the pancreas and increase insulin secretion. They lower A1c on average by 1.5–2% and can cause hypoglycemia, particularly with chlorpropamide or glyburide [26]. First-generation sulfonylureas include acetohexamide, chlorpropamide, tolazamide, and tolbutamide. The second-generation sulfonylureas include glipizide, glimepiride, glyburide, and gliclazide (the latter is not available in the U.S.).

Sulfonylureas and their metabolites are renally cleared, leading to an increased risk of hypoglycemia as GFR declines. First-generation sulfonylureas should not be used in CKD due to a high risk of hypoglycemia. With an eGFR <60 ml/min/1.73 m^2, hypoglycemia is greatly increased with glyburide and also with glimepiride, due to the presence of two active glimepiride metabolites cleared in part by the kidney [32, 33]. Glyburide should be avoided with an eGFR <60 ml/min/1.73 m^2. Glimepiride should be used with caution if the eGFR is <60 ml/min/1.73 m^2 and not be used with an eGFR <30 ml/min/1.73 m^2 [32, 33]. Glipizide and gliclazide do not have active metabolites and are not renally excreted so dose adjustment is not needed; however, some caution should still be used [34].

23.4.2.3 Glinides

Nateglinide and repaglinide, like sulfonylureas, increase insulin secretion by closing a sulfonylurea receptor/ATP-dependent potassium channel on the beta-cells of the pancreas. It is necessary for glucose to be present for the glinides to work, and they result in quick insulin release of short duration. Because of this, the meglitinides ideally are given before a meal. They have a shorter half-life compared to the sulfonylureas and can also cause hypoglycemia.

The active metabolite of nateglinide does accumulate in CKD; nateglinide should not be used with an eGFR <60 ml/min/1.73 m^2. The active metabolite is cleared by hemodialysis, however, so nateglinide can be used in those on dialysis. Conversely, repaglinide appears to be safe to use in individuals with CKD. It seems reasonable to exercise caution in those with more severe renal dysfunction, such as an eGFR <30 ml/min/1.73 m^2, and start at the lowest dose (0.5 mg) with slow titration up [34–37].

23.4.2.4 Thiazolidinediones

Thiazolidinediones (pioglitazone, rosiglitazone) increase insulin sensitivity by acting as agonists of peroxisome proliferator-activated receptor γ (PPARγ). They do not cause hypoglycemia, and they lower A1c by an estimated 0.5–1.4% [26]. Fluid retention is a major limiting side effect and they should not be used in advanced heart failure or other edema-forming conditions. This also makes their use in CKD limiting, particularly patients with nephrotic syndrome. They have been linked with increased fracture rates and bone loss; thus use in patients with underlying bone disease, such as renal osteodystrophy, needs to be taken into consideration although it's not known if use of thiazolidinediones worsens renal osteodystrophy. In 2010, the FDA restricted use of rosiglitazone based on studies linking it to increased ischemic heart disease. Upon further review, these restrictions were lifted in 2014 since subsequent analyses did not support this finding. An association between pioglitazone and bladder cancer was raised but further analysis and investigation into the data shows that this association is not clearly supported [38]. A pooled multi-population analysis also showed no association between thiazolidinediones and bladder cancer [39].

Thiazolidinediones are metabolized by the liver and can be used in CKD, so no dose adjust-

ment is needed [34, 40]. There are some retrospective cohort studies showing both cardiovascular and kidney outcome benefits with use of thiazolidinediones in patients with CKD [41, 42].

23.4.2.5 Alpha-Glucosidase Inhibitors

The alpha-glucosidase inhibitors acarbose and miglitol decrease the breakdown of oligo- and disaccharides in the small intestine, slowing digestion of carbohydrates and delaying absorption of glucose after food intake. The most common side effects are bloating, flatulence, and abdominal cramping. They usually lower A1c by 0.5–0.8% and usually do not lead to any changes in weight [26].

Acarbose is minimally absorbed with <2% of the drug and active metabolites present in the urine. With reduced renal function, serum levels of acarbose and metabolites are significantly elevated. Although no adverse effects have been noted, its use in patients with a GFR <26 mL/min/1.73 m^2 is not recommended [34]. Miglitol has greater systemic absorption with >95% renal excretion. It is recommended that use of miglitol be avoided with a low GFR [34].

23.4.2.6 Dipeptidyl Peptidase-4 Inhibitors

The dipeptidyl peptidase 4 (DPP-4) inhibitors include sitagliptin, saxagliptin, linagliptin, and alogliptin and decrease the breakdown of incretin hormones such as glucagon-like peptide 1 (GLP-1) and glucose-insulinotropic peptide (GIP). GLP-1 is secreted by the gastrointestinal tract in response to food. It promotes insulin secretion from the pancreas, decreases glucagon release and slows gastric emptying. The DPP-4 inhibitors are weight-neutral, do not cause hypoglycaemia, and decrease A1c by 0.5–0.8% [26].

The DDP-4 inhibitors can all be used in CKD but most need a dose adjustment. Only a small amount of linagliptin is cleared renally so no dose adjustment is needed with a reduced GFR [43]. Sitagliptin, saxagliptin and alogliptin all need dose adjustment [44]; please refer to Table 23.1 for details.

23.4.2.7 Sodium-Glucose Co-transporter 2 (SGLT2) Inhibitors

The SGLT2 inhibitors, empagliflozin, canagliflozin, dapagliflozin and ertugliflozin, reduce glucose absorption in the proximal tubule of the kidney, leading to an increase in glucose excretion in the urine and a reduction in A1c of about 0.9–1.0% [45]. They can also lead to weight loss of up to 5 kg in 1 year and do not cause hypoglycemia. Genital yeast infections occur in about 10% of women and 1–2% of uncircumsized men and urinary tract infections have been shown to be increased in some studies; older patients may experience symptoms due to volume contraction [45, 46]. In addition, there is association with "euglycemic" diabetic ketoacidosis (DKA), primarily in those with type 1 diabetes (in whom they are used "off-label") but also rarely in patients with type 2 diabetes [46]. The DKA may in part be related to elevated glucagon levels and volume depletion. While using SGLT2 inhibitors, patients should be educated to monitor for signs and symptoms of DKA, including nausea or vomiting, and if any occur (even with normal blood sugars), they should undergo evaluation for ketones in the urine or serum [46].

The EMPA-REG study demonstrated significant benefits in reduction of cardiovascular outcomes and mortality, slower worsening of kidney disease, and fewer renal events such as need to initiate renal-replacement therapy with empagliflozin use [47–49]. In 2017, the results of the CANVAS program studies demonstrated reduced cardiovascular events in canagliflozin users compared to placebo [50]. Renal outcomes, as defined by decline in GFR, requirement for renal replacement therapy, or renal death, was decreased in subjects given canagliflozin as compared to placebo in the CANVAS study [51]. However, this study also showed use of canagliflozin led to a greater risk of amputations and fractures [50]. Subsequent analyses of the EMPA-REG study did not show an increased risk of amputations associated with empagliflozin use [52]. Similar cardiovascular and renal benefits were seen with dapagliflozin in the DECLARE-TIMI 58 trial [53]; the same types of

benefits were seen with ertugliflozin in the VERTIS trial but only the benefit for hospitalization for heart failure was statistically significant [54]. The CREDENCE study was a prospective, randomized study carried out in subjects with overt kidney disease that showed that canagliflozin use resulted in cardiovascular and renal benefits were quite significant down to an eGFR of 30 ml/min/1.73 m^2 [55]. The CVD-REAL study showed reduced risk of death and hospitalization for heart failure in those newly started on empagliflozin, canagliflozin, or dapagliflozin compared to other diabetes medications, suggesting the benefit may be an SGLT2 inhibitor class effect [56]. The EASEL study was a population-based cohort study looking at patients newly started on diabetes medications and compared those on SGLT2 inhibitors (empagliflozin, canagliflozin, and dapagliflozin) to those started on other glucose-lowering medications including DPP-4 inhibitors, insulin, and sulfonylureas. Those on SGLT2 inhibitors showed reduced risk of major adverse cardiovascular events, all-cause mortality and hospitalization for heart failure. There was also a higher risk of below-the-knee amputations, mostly in those receiving canagliflozin but there were a higher proportion of patients taking canagliflozin over empagliflozin and dapagliflozin [57]. It is not yet clear if the increased amputation risk is a class effect or specific to a single SGLT2 inhibitor [58].

In August 2018, the FDA issued a warning regarding the rare risk of necrotizing fasciitis of the perineum, or Fournier's gangrene, with the use of SGLT2 inhibitors based on 12 reported cases, in both men and women, over about 5 years [59, 60].

The efficacy in glucose lowering decreases as the GFR goes below 60 ml/min/1.73 m^2. Due to an increase in adverse events related to intravascular volume contraction, no more than 100 mg once daily of canagliflozin should be used in patients with an eGFR of 45 to <60 ml/min/1.73 m^2. Despite the reduced efficacy of canagliflozin in reducing glucose levels at eGFR levels less than 60 ml/min/1.73m^2, it is very much indicated in patients down to an eGFR of 30 ml/min/1.73m^2 because of the marked benefits in reducing cardiovascular outcomes and delaying the progression of kidney disease. Dapagliflozin and empagliflozin can be used down to an eGFR of 45 ml/min/1.73 m^2. Interestingly, despite a very significant loss of the ability to lower blood glucose levels, these drugs maintain their blood pressure lowering and weight lowering effects, cardiovascular benefits and kidney benefits even with GFR levels below 60 ml/min/1.73 m^2 [61–64]. It has been hypothesized that the BP and weight reductions likely involve mechanisms other than urinary glucose excretion, including diuretic effects, increased sodium sensitivity, reduced arterial stiffness and direct vascular effects [64]. Furthermore, the CVD benefits in the EMPA-REG study were seen even when the eGFR's were down to 30 ml/min/1.73 m^2 [49].

23.4.2.8 Other Oral Medications

Bromocriptine (dopamine receptor agonist) has not been adequately studied in CKD.

Colesevelam (bile acid sequestrant) shows no difference in efficacy or safety in those with an eGFR <50 ml/min/1.73 m^2 but data are limited, as it has not been adequately studied in more advanced CKD.

23.4.3 Other Subcutaneous Medications

23.4.3.1 GLP-1 Receptor Agonists

The GLP-1 receptor agonists exenatide (regular and extended-release), liraglutide, dulaglutide, lixisenatide and semaglutide are injectable medications that mimic gut hormones called incretins, leading to insulin release, decreased glucagon secretion and delayed gastric emptying. They are FDA approved for use with metformin and/or sulfonylureas, and some are also approved for use with basal insulin. They contribute to central satiety, leading to a reduction in appetite and often weight loss. The average expected decrease in A1c is 0.5–1.0% [26]. Their use has been associated with pancreatitis but epidemiologic studies have not shown any higher frequency of pancreatitis as compared to other patients with diabetes using other agents [65, 66]. Nausea is a common

side effect that can limit their use. In addition, liraglutide has been associated with the development of thyroid C-cell tumors in animal studies and thus should not be given to patients with or at risk for medullary thyroid cancer although no cases in humans have been reported. Exenatide is given twice daily and liraglutide and lixisenatide are given once daily; exenatide extended-release, semaglutide and dulaglutide are dosed once weekly. There are also fixed dose combinations with insulin available such as degludec/liraglutide and insulin glargine/lixisenatide. An oral preparation of semaglutide, RybelsusR is also now available.

The LEADER, SUSTAIN-6, and REWIND studies showed significant reductions in cardiovascular mortality with liraglutide, semaglutide, and dulaglutide, respectively [67–69]; CVD benefit was not seen with extended-release exenatide or lixisenatide [70, 71].

Clearance of exenatide decreases with declines in GFR [72]. The FDA reported cases of acute renal failure associated with exenatide use and recommends it be used with caution in those with a GFR of 30–50 ml/min/1.73 m^2 and not be used if the GFR is <30 ml/min/1.73 m^2 [73]. Liraglutide is not metabolized primarily by the kidney [74]; no dose adjustment is indicated in those with renal impairment, including ESRD, although data in this population are limited [75]. There are also reports of acute kidney injury so it should be used with caution if the GFR is <30 ml/min/1.73 m^2 [76]. No dosage restrictions are needed for dulaglutide or semaglutide with decreasing GFR. Lixisenatide should not be used if the GFR is GFR is <15 ml/min/1.73 m^2 due to lack of experience; in those with an eGFR <60 ml/min/1.73 m^2, patients should be monitored closely [77, 78].

23.4.3.2 Amylin Analog

Amylin is co-secreted along with insulin by the beta-cells of the pancreas and levels have been found to be low in patients with diabetes. Pramlintide is an injectable amylin analog taken with meals as an adjunct to insulin therapy in type 1 and type 2 diabetes. It reduces A1c by 0.5–1.0% [26]. No dose adjustment appears necessary for mild to moderate CKD; it has not been studied in ESRD.

23.5 Glycemic Control

23.5.1 Glycemic Goal Targeting an A1c ~7.0%

Glycemic control is essential to delay the development of CVD and nephropathy. In general, the recommended target A1c for diabetes control in adults (not pregnant) by the ADA has been ≤7% [79]. The ADA also suggested a higher target (<8%) for certain populations, such as those with a prior history of severe hypoglycemia, shorter life expectancy, advanced complications, and extensive comorbidities [79]. A stricter goal of <6.5% can also be appropriate for certain populations [79]. The American Association of Clinical Endocrinologists (AACE) recommends a goal A1c of ≤6.5% in healthy patients who are at low risk for hypoglycemia but also acknowledges the goals need to be individualized [80]. The 2007 Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines for Diabetes and CKD endorse a target A1c of <7.0% [81] but their updated 2012 guidelines instead recommend an A1c of ~7.0% [11].

In type 1 diabetes, a number of studies show the development of microalbuminuria is associated with poorer glycemic control. In the DCCT, intensive therapy in patients with type 1 diabetes (mean A1c 9.1% vs. 7.2%) reduced the occurrence of microalbuminuria and risk reduction in progression to clinical albuminuria [82–84]. Furthermore, the long-term follow-up of the DCCT cohort in the Epidemiology of Diabetes Interventions and Complications (EDIC) study showed that that prior intensive group has a substantial reduction in the proportion of patients developing Stage 3 CKD (eGFR <60 ml/min/1.73 m^2) (DCCT/EDIC Research Group) [85]. In patients with type 2 diabetes, the Kumamoto study, UKPDS and Veterans Affairs Cooperative studies showed reduction of new onset nephropathy and progression of

nephropathy with intensive glycemic control [86–88].

The ACCORD study showed higher risk of hypoglycemia and mortality in patients with type 2 diabetes treated with intensive glucose control (mean A1c 6.4% vs. 7.5%), without any risk reduction on CVD. The increased mortality could not be attributed to hypoglycemia [89]. In the ADVANCE trial, more intensive glycemic control (A1c 6.5% vs. 7.3%) showed no reduction in CVD. However, the intensive group had a 21% reduction in nephropathy [90]. The VADT study (intensive group with A1c 6.9% vs. 8.4%) also showed no benefit on CVD risk with stricter glucose control [79, 91]. In neither the ACCORD nor the ADVANCE studies was there a benefit of reduced adverse cardiovascular outcomes with very tight glucose control. Thus, the target A1c is now generally recommended to be <7.0% rather than 6.5%. It should be pointed out, however, that such a further reduction in A1c was associated with improved kidney outcomes [92].

The data clearly show that lowering A1c leads to benefit in regards to CKD. Benefits in A1c reduction are also seen on rates of retinopathy and neuropathy. However, the effect of lowering A1c is much less in regards to macrovascular disease. Overall, it is reasonable that a target A1c ~7.0% offers an optimal risk to benefit ratio rather than a target that is much lower.

The Controversies Conference on Diabetic Kidney Disease (DKD) held by KDIGO addressed a number of issues surrounding DKD, including appropriate glycemic control targets [93]. There are insufficient data and trials regarding the ideal glucose target in patients with CKD stage 3 or worse. ESRD patients with diabetes benefit from maintaining their A1c between 7% and 8%, as A1c levels above 8% or below 7% carry increased risks of all-cause and cardiovascular death.

23.5.2 A1c and Glucose Targets

The A1c should be measured on average twice yearly in those with stable glucose control and at goal; it should be measured every 3 months if the goal is not being met or if treatment has been adjusted. Preprandial capillary glucose levels should ideally be 80–130 mg/dL (4.4–7.2 mmol/L), and postprandial capillary glucose levels 1–2 h after the meal, if measured, should be <180 mg/dL (10.0 mmol/L) [79]. However, less strict targets should be considered for patients with CVD or advanced microvascular complications because of the adverse effects of hypoglycemia [79]. Patients with advanced CKD are at greater risk for hypoglycemia in general and higher goals may be appropriate in such patients to avoid hypoglycemia [94]. Hypoglycemia is more common as GFR declines. In addition to impairment of renal gluconeogenesis from lower kidney mass [95], patients with progressing nephropathy have decreased clearance of insulin and oral diabetes medications as previously noted. In addition, anorexia and weight loss related to uremia can contribute to hypoglycemia due to an increase in sensitivity to insulin.

23.5.3 Accuracy of A1c

The measurement of A1c can be inaccurate in some patients with CKD. Contributing factors include anemia from reduced lifespan of the red blood cell, hemolysis and iron deficiency but falsely increased levels can occur from carbamylation of hemoglobin and the presence of acidosis. Fructosamine and glycated albumin are alternative measures available to estimate glycemic control. Fructosamine reflects the glycation of multiple serum proteins whereas glycated albumin reflects glycation of only albumin; both provide an estimate of control over the past 2 weeks. It is unclear if they offer superior measures of glucose control compared to A1c in patients with CKD. Studies suggest glycated albumin is superior to A1c in dialysis patients since A1c tends to underestimate glycemic control in those with ESRD, but there is a lack of standardization across laboratories [96–98]. A 2018 study showed that glycated albumin was better compared to A1c in assessing control as evidenced by a week's worth of glucose levels measured by continuous glucose monitoring [99].

However, it's not clear that glycated albumin is the answer since questions related to accuracy, inter-laboratory variability and how to use it remain; for dialysis patients, multiple daily blood glucose measurements should remain the standard by which glycemic control is assessed [100].

23.5.4 Strategy for Glycemic Control in Type 1 and type 2 Diabetes

The ideal medication regimen is based on the specific needs of the patient and physician experience. Each regimen is to be individualized and adjusted, especially as renal function fluctuates. An individual with type 1 diabetes must have insulin, and there are multiple ways insulin can be administered, but treatment differs greatly from type 2 diabetes. A greater range of therapies can be applied to those with type 2 diabetes and can combine oral agents with subcutaneous injections.

23.5.4.1 Type 1 DM

The ideal insulin regimen in type 1 diabetes reproduces physiologic insulin secretion by the pancreas, most often accomplished by the use of a long-acting basal insulin and multiple daily injections of a short- or rapid-acting insulin [101]. Before the availability of insulin analogs, a combination of twice-daily NPH and regular insulin was used. Typically, the two are given together before breakfast and before dinner. Because both types of insulin serve to treat fasting and postprandial glucose levels, it can be difficult to achieve target glycemic control using this regimen. Such fixed insulin combinations require that patients maintain similar mealtimes and similar intake at meals from day-to-day, and they do not mimic normal physiologic insulin secretion [101]. The main advantages of using NPH and regular insulins are their lower cost and need for only two daily injections.

Glargine insulin does not have a distinct peak, is superior to twice-daily NPH in reducing fasting glucose levels with less hypoglycemia, and results in more stable fasting glucose values. Reductions in A1c have been reported in studies comparing glargine and NPH [101]. Compared with NPH, glargine and detemir have been shown to have less intra- and inter-individual variability with greater predictability and reproducibility. Few studies have compared detemir with glargine in a clinical practice setting. The two newer longer-acting basal insulins, insulin glargine U-300 and insulin degludec have even less intra- and inter-individual variability and less hypoglycemia compared to insulin glargine U-100 and detemir.

In multiple studies, use of the rapid-acting insulins lispro, aspart or glulisine compared to regular insulin showed improved post-prandial glucose control, less hypoglycemia and in some studies, a lowering of the A1c [101]. The closest approximation of physiologic insulin secretion is through use of an insulin pump that delivers a continuous subcutaneous infusion of insulin (CSII). A rapid-acting analog is infused via the pump and serves as the basal, bolus and correction insulin. Insulin pumps can be used at all stages of CKD. Insulin pumps do require vigilance on the part of the patient, and their use should be overseen by endocrinologists and certified diabetes educators. Adjustment of insulin doses based upon pre- and postmeal glucose levels obtained via multiple finger-stick capillary glucose measurements or the newer continuous glucose monitoring devices is critical for both multiple daily injection regimens and insulin pumps [102].

There are multiple options for patients with type 1 diabetes. As a basal insulin, once-daily glargine U-100 or degludec would be an optimal first-choice agent, followed by twice-daily detemir, then NPH, with any of the rapid-acting insulin analogs then used for mealtime insulin supplemental doses. In some patients, the use of glargine U-300 and degludec may provide more even glycemic control with less hypoglycemia. For some, an insulin pump offers the best option for tight glycemic control. As noted previously, doses usually need to be reduced as the GFR falls, and careful home glucose monitoring is needed.

23.5.4.2 Type 2 DM

Multiple options and combinations of therapies are available for patients with type 2 diabetes. In patients who are newly diagnosed, if the diabetes is mild, in addition to lifestyle changes, beginning with an oral medication is an ideal starting point due to ease of use. If kidney function allows, metformin is an ideal first choice given the lack of associated hypoglycemia and that it may lead to weight loss but the dose may need to be reduced depending upon the level of kidney function (see above). It can cause gastrointestinal symptoms, and the dose should be titrated up slowly. The starting dose is usually 500 mg once daily and can be increased to 2000 mg daily over a period of weeks if tolerated. An extended-release form is also available. Dosing in CKD is discussed previously. The SGLT2 inhibitors are now recommended as the second oral agent to be added because of their proven renal and cardiovascular benefits [103]. The GLP-1 receptor agonists can be added to oral agents but they should not be used concurrently with DPP 4 inhibitors. Liraglutide, semaglutide and dulaglutide are now recommended as a second agent in patients with known CVD because of their proven ability to reduce CVD outcomes [103]. The injections may not be desirable, but the potential for reduction in hyperglycemia, weight loss and option for weekly dosing are additional appealing attributes. They can also be used as single agents. The DPP 4 inhibitors can be safely used at the appropriate dose in CKD, with the advantage that they do not cause hypoglycemia; the reduction in A1c is generally modest so they are ideal for individuals with mildly uncontrolled diabetes. Thiazolidinediones can be considered, though fluid retention, weight gain and a small lowering of the A1c make them a less optimal choice. The second-generation sulfonylureas are also a reasonable choice as they are inexpensive and are effective, but they do cause hypoglycemia. In CKD, glipizide or gliclazide is preferable. It is not unusual for some patients to be on multiple agents concurrently, but at some point as diabetes progresses, insulin may need to be considered.

In type 2 diabetes and obesity, there is a defect in insulin action leading to insulin resistance combined with progressive pancreatic beta-cell failure. In patients with uncontrolled A1c levels, high levels of insulin resistance or progressive beta-cell failure, insulin should be started. There is no clear consensus on which regimen to use in which patient. The insulin regimen needs to be customized to the patient and time of day when hyperglycemia is occurring. Often times, insulin is started by adding a long-acting basal insulin such as glargine, determir, degludec or NPH once daily. NPH carries a greater risk of hypoglycemia, especially if dosed at night. A starting dose of 10–15 units is often used, with further escalation based on blood sugars. Subsequently, no more frequently than every 3 days, the insulin dose can be increased by 1–2 units until the fasting goal is reached while, at the same time, avoiding hypoglycemia [101]. Some patients may achieve goal glucose control with the combination of basal insulin and oral agents. Basal insulin may also be combined with the GLP-1 receptor agonists. If goal glycemic control cannot be obtained with basal insulin, then a rapid-acting insulin should be started particularly if hyperglycemia is present during the day but fasting blood sugars are at target. Prandial insulin can be added initially to the largest meal of the day but often, prandial insulin is needed for each meal. The dose is guided by the carbohydrate content of the meal as well as the premeal glucose level [101]. In individuals affected only by hyperglycemia during the day, prandial insulin may be all that is needed.

23.5.4.3 Patients on Dialysis

There are a few oral and injectable diabetes medications that can be used safely in patients on dialysis, particularly if the diabetes is fairly mild which include repaglinide, pioglitazone, linagliptin, liraglutide, dulaglutide, and semaglutide. Most others, however, will need insulin for glycemic control. As mentioned previously, patients with stage 4–5 kidney disease and on dialysis can have delayed gastric emptying so it may be helpful to give rapid-acting insulin after meals, similar to patients with gastroparesis. Patients receiving hemodialysis (HD) can have different clearance rates of insulin that may be affected by

the timing of dialysis. Glycemic responses during HD can be variable and unpredictable, requiring frequent adjustment. Patients on peritoneal dialysis (PD) have exposure to large amounts of glucose in the dialysate that can lead to uncontrolled hyperglycemia. In patients receiving continuous PD, a standard basal/bolus regimen is best. However, those receiving overnight cycled PD, coverage of the increased glucose load may best be accomplished using a fixed mixture insulin combination, such as 70/30 or 75/25 insulin, given at the start of PD. The nephrologist prescribing the PD will often change the glucose concentration of the dialysate because of the need for more or less fluid removal and such changes need to be communicated to the endocrinologist so that the insulin doses can be adjusted accordingly.

23.6 Cardiovascular Disease and Risk Factors

The combination of diabetes and CKD is particularly powerful in regards to CVD risk, necessitating aggressive control of risk factors. In addition to hypertension, several factors contributing to the development of cardiovascular disease are present in individuals with diabetes and CKD and include dyslipidemia and obesity.

23.6.1 Blood Pressure Control

High blood pressure is extremely common in patients with diabetes, CVD and kidney disease; it contributes to the increased risk of progressive nephropathy and CVD. Hypertension is the next most common cause of nephropathy after diabetes, and it accelerates the progression of nephropathy.

Blood pressure should be checked at every clinic visit. The ADA recommends target BP of <140/80 mmHg but to consider a lower target, such as 130/80 mmHg, if there is high risk of CVD [3, 9]. The KDOQI realize the need for individual targets instead of a single target for all patients; they recommend a BP <130/80 mmHg for those with diabetes and albuminuria [104]. The Systolic Blood Pressure Intervention Trial (SPRINT) evaluated 9361 patients, without diabetes, and randomized them to Systolic BP (SBP) targets of <140 vs. <120 mmHg. The study showed a 25% reduction in major adverse cardiac events and a 27% reduction in all-cause mortality with the more intensive treatment [105]. There were significant increases in rates of hypotension, syncope, electrolyte abnormalities and acute kidney injury or failure in the more intensively treated group. A meta-analysis that incorporated SPRINT and 122 additional studies supported a SBP target <130 mmHg [106]. Notably, SPRINT did not include patients with diabetes. Evidence from the ACCORD study showed no cardiovascular benefit of lowering the systolic blood pressure target in patients with diabetes to an even lower value: <120 mmHg [107], as there was no reduction in the rate of major cardiovascular events, although the risk of stroke was reduced. However, a post-hoc report of SPRINT-eligible ACCORD-BP patients suggested that the SBP goal of 120 mmHg also applied to diabetic patients [108]. The ONTARGET trial followed 25,620 subjects, of which 38% had diabetes, and randomized them to ramipril, telmisartan or both. Benefit was again seen in regards to risk of stroke, however CV death was increased when subjects with a baseline systolic blood pressure of <130 mmHg experienced lowering of the BP [109]. The 2017 guidelines from the American College of Cardiology (ACC)/American Heart Association (AHA) define normal BP as <120/<80 mmHg and hypertension as a BP of 130/80 mmHg. Their recommended BP target for adults is <130/80 mmHg, including individuals with diabetes due to the increased risk for CVD [110]. Overall, there are multiple treatment approaches and goals. Intensity of BP lowering may also need to be individualized but it seems prudent to consider the more stringent BP target, especially in those with diabetes at highest CVD risk, if there are no clear disadvantages. Note that the BP target for CKD and for CVD may be different [93].

Either ACE inhibitors or ARBs are advised as initial choices for when treatment is indicated since these medications have renal protective benefits in addition to control of blood pressure. Multiple studies show benefit of blood pressure control with use of ACE inhibitors on slowing the progression of microalbuminuria and slowing reduction in GFR in type 1 diabetes [111, 112]. Benefit of ACE inhibitors and/or ARBs in regards to blood pressure control and slowing progression of nephropathy in type 2 diabetes has also been seen [81]. Monitoring of renal function and for hyperkalemia is necessary. Often, multiple medications may be needed to control hypertension especially as nephropathy advances.

23.6.2 Dyslipidemia

Dyslipidemias are one of many contributing factors involved in the development of CVD in all patients, with or without diabetes. The ADA recommends a lipid panel be checked at the time of diagnosis of diabetes and then at least every 5 years in those who are younger than 40 years old. More frequent monitoring is needed in certain populations based on age and duration of diabetes; those on statins need more regular monitoring [3]. The ADA recommends lifestyle therapy (weight loss, increased activity, and nutrition therapy) in addition to moderate- to high-intensity statin therapy based on age and presence of atherosclerotic CVD [3]. The 2018 guidelines from the ACC/AHA recommend the use of at least a moderate- to high-intensity statin in individuals with diabetes 40–75 years old with an LDL-cholesterol of 70–189 mg/dL (high-intensity is recommended if the 10-year ASCVD risk score is ≥20% or if there are additional risk factors) [113].

23.6.3 Nutrition and Dietary Protein

Nutrition plays an important role in individuals with diabetic nephropathy. A balance of several dietary factors including intake of sodium, potassium, phosphorus, and protein must be followed as well as monitoring intake of carbohydrates and unhealthy fats; patients benefit from working with a dietitian. Specifically in diabetic nephropathy, the recommended amount of daily protein intake by the KDOQI is 0.8 g per kilogram body weight in individuals with diabetes and CKD stages 1–4 [81]. The ADA also recommends an intake of 0.8 g of protein per kg body weight in patients with non-dialysis DKD [5].

Medical nutrition therapy is advisable for general diabetes care, and it is helpful to work with an experienced dietician to reach dietary goals. Reduction in weight in patients who are overweight or obese and regular exercise are generally recommended. Behavioral modification and lifestyle changes are important to control weight, improve nutrition, and modify dietary intake.

23.7 Referral to Specialized Care

In addition to following with cardiologists and nephrologists, patients with cardiorenal syndrome who have diabetes can benefit from following with an endocrinologist to optimize glycemic control. Along these lines, the expert care of a certified diabetes educator is also helpful, especially in those interested in insulin pump therapy, continuous glucose monitors and advancements in sensors and blood glucose monitoring systems recently available for following glucose levels at home. In order to address monitoring for microvascular complications, regular follow-up with an ophthalmologist is necessary and potentially also a podiatrist. As mentioned, medical nutrition therapy is advisable for general diabetes care. Utilization of a specialist in obesity or weight-management may also be needed.

23.8 Conclusion

The management of patients with diabetes and acute and chronic cardiorenal syndromes requires attention to several aspects of care.

Importantly, glycemic control should be optimized for the patient, with the goal to reach the target control to reduce complications while knowing which medication can be used safely. Treatment of diabetes in cardiorenal syndrome necessitates a multifactorial approach through the use of a diabetologist, cardiologist, nephrologist, and diabetes educator.

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Pharmacoepidemiology in Cardiorenal Medicine

24

Kristen M. Tecson and Scott S. Shafiei

24.1 Introduction

Cardiorenal syndrome (CRS) describes the phenomenon of joint dysfunction of the heart and kidneys and occurs when the acute or chronic dysfunction of one organ subsequently triggers acute or chronic dysfunction in the other [1]. For example, chronic kidney disease (CKD) contributes to pressure and volume overload, which subsequently cause cardiomyopathy and lead to heart failure (HF) [2]. The incidence and prevalence of both HF and CKD are increasing due largely to the aging, comorbid population. In fact, approximately 8 million Americans are expected to have HF by 2030 and 1 of every 9 deaths is currently associated with HF [3]. Further, in 2017, 30 million American adults were estimated to have CKD [4]. The majority of patients with CKD die from cardiovascular complications; however, regulating blood pressure through drug therapy can stall the progression of CKD and prevent the development of heart disease.

In this chapter, we provide an overview of pharmacological therapies and adaptations employed for patients with CRS, as well as common themes contributing to the drugs' underutilization. We elect to focus on common medication practices in the setting of HF for individuals with CKD.

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24.2 Therapies and Adaptations

Therapies utilized for the management of HF may include angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), beta adrenergic receptor blockers, mineralocorticoid receptor antagonists (MRAs), diuretics, statins, digoxin, and sodium-glucose transport protein 2 (SGLT2) inhibitors. Many of these classes (or particular drugs within the class) have dosing guidelines specifically based on the degree of renal impairment (Table 24.1).

24.2.1 Angiotensin Converting Enzyme Inhibitors

ACE inhibitors protect against cardiovascular disease (CVD) and delay CKD progression. Their mechanism of action involves preventing the conversion of angiotensin I to angiotensin II, a chemical that causes muscles surrounding blood vessels to contract, by competitively inhibiting ACE. As a result of decreased angiotensin II, there is vascular relaxation, natriuresis, and a reduction in systemic blood pressure. Further, decreased arterial and venous pressure reduces

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Table 24.1

Pharmaceutical drug	General drug dosing recommendations	Renal impairment drug dosing recommendations
	(Manufacturer's labeling unless otherwise indicated)	
Angiotensin-Converting Enzyme Inhibitors	*Indicated for treatment of HTN, prevention of CV events including HF, limiting progression of type 1 diabetic nephropathy, and reduction in CV events in patients after MI with LVD or HF; also indicated for treatment of HF* [5]	*Individualize dosing schedules for each HD session to avoid intradialytic hypotension; in general reduce dose by 50–75 % in ESRD* [5]
Benazepril	HTN: 5–10 mg daily, titrate up to 40 mg daily [6]	CrCl >30 mL/min: no adjustment CrCl <30 mL/min: 5 mg daily, titrate up to 40 mg daily HD/PD: 25–50 % of usual dose; supplemental dose not necessary [7]
Captopril	Diabetic Nephropathy: 25 mg TID HTN: 12.5–25 mg BID or TID, titrate up to 50 mg TID [6] HFrEF: 6.25–25 mg TID, titrate up to 50 mg TID [8] LVD after MI: single dose of 6.25 mg, then start at 12.5 mg TID, titrate up to 50 mg TID [9]	Reduce initial daily dose and titrate slowly with smaller increments CrCl >50 mL/min: no adjustment CrCl 10–50 mL/min: 75% of normal dose every 12–18 h CrCl <10 mL/min: 50% of normal dose every 24 h HD: administer after HD on HD days PD: same as CrCl 10–50 mL/min as above [7]
Enalapril	HTN: 5 mg daily, titrate up to 40 mg daily [6] HFrEF: 2.5 mg BID, titrate up to 10–20 mg BID [10]	CrCl >30 mL/min: no adjustment CrCl <30 mL/min: 2.5 mg daily, titrate up to 40 mg/day HD: 2.5 mg after HD on HD days, adjust dose on nondialysis days for goal blood pressure PD: administer 25% of usual dose [7]
Lisinopril	HTN: 5–10 mg daily, titrate up to 40 mg daily [6] HFrEF: 2.5–5 mg daily, titrate up to 40 mg daily [8] Reduction of Mortality in Acute MI: 2.5–5 mg daily within 24 h of presentation, titrate slowly up to 10 mg, then slowly up to 40 mg daily [9]	CrCl >30 mL/min: no adjustment CrCl 10–30 mL/min: 2.5–5 mg daily (half of usual dose), titrate up to 40 mg daily CrCl <10 mL/min: 2.5 mg daily, titrate up to 40 mg daily HD: 2.5 mg daily with dosing after HD, titrate up to 40 mg daily CRRT: administer 50–75% of usual dose [7]
Ramipril	HTN: 2.5 mg daily, titrate up to 20 mg daily (or 10 mg BID) [6] LVD after MI: 1.25–2.5 mg BID, titrate up to 5 mg BID Reduction in risk of MI, stroke, and death from CV causes: 2.5 mg daily, titrate slowly up to 10 mg daily	CrCl >40 mL/min: no adjustment CrCl <40 mL/min: administer 25% of usual dose
Angiotensin II Receptor Blockers	*Indicated for treatment of HTN, to limit the progression of type 2 diabetic nephropathy, and to reduce CV events in patients after MI with LVD or HF; indicated for HF in those intolerant to ACE inhibitors* [5]	*Levels of ARBs do not change significantly during HD* [5]
Candesartan	HTN: 2–8 mg daily, titrate up to 32 mg daily (or 16 mg BID) [6] HFrEF: 4–8 mg daily, titrate up to 32 mg daily [8]	No adjustment necessary; however, note if CrCl <30 mL/min, AUC and Cmax approximately doubled after repeated dosing
Irbesartan	Diabetic Nephropathy: 300 mg daily HTN: 150 mg daily, titrate up to 300 mg daily [6]	No adjustment necessary unless patient is volume depleted (75 mg daily) HD: non-dialyzable

(continued)

Table 24.1 (continued)

Pharmaceutical drug	General drug dosing recommendations	Renal impairment drug dosing recommendations
Losartan	Diabetic Nephropathy: 50 mg daily, up to 100 mg daily HTN: 25–50 mg daily, up to 100 mg daily [6] HFrEF (off-label): 25–50 mg daily, up to 150 mg daily [11]	No adjustment necessary unless patient is volume depleted HD: non-dialyzable
Olmesartan	HTN: 20 mg daily, titrate up to 40 mg daily [6]	CrCl >40 mL/min: no adjustment CrCl <40 mL/min: no initial dosage adjustment, but note AUC is increased threefold if CrCl <20 mL/min [12]
Telmisartan	CV Risk Reduction: 80 mg daily HTN: 20–40 mg daily, titrate up to 80 mg daily [6]	No adjustment necessary, but HD patients more susceptible to orthostatic hypotension
Valsartan	HTN: 80–160 mg daily, titrate up to 320 mg daily [6] HFrEF: 40–80 mg BID, titrate up to 160 mg daily [8] LVD after MI: 20 mg BID, then increase to 40 mg BID, titrate up to 160 mg BID	CrCl >30 mL/min: no adjustment CrCl <30 mL/min: use with caution; no adjustments provided HD: non-dialyzable
Mineralocorticoid Receptor Antagonists		
Eplerenone	HTN: 50 mg daily, titrate up to 50 mg BID (if concurrent use with moderate CYP3A4 inhibitors, then cut dose in half) [6] LVD after MI: 25 mg daily, titrate up to 50 mg daily [8]	CrCl >50 mL/min: no adjustment necessary CrCl 30–50 mL/min or sCr >2 mg/dL in males or >1.8 mg/dL in female: use not recommended due to risk of hyperkalemia CrCl <30 mL/min: use contraindicated HD: non-dialyzable
Spironolactone	Edema: 25–100 mg daily, titrate up to 200 mg daily HTN: 25–50 mg daily, titrate up to 100 mg daily (or 50 mg BID) [6] HFrEF: 12.5–25 mg daily, titrate up to 50 mg daily [8] Hyperaldosteronism: 100–400 mg until surgical correction	Monitor for hyperkalemia; no specific dosage adjustments for HTN; however, for HFrEF: CrCl >50 mL/min: no adjustment CrCl 30–50 mL/min: 25 mg every other day CrCl <30 mL/min: not recommended [8]
Beta Blockers	*Generally not recommended for HTN unless specific comorbidities (ischemic CM, HFrEF, arrhythmia)*	*No specific dose adjustments for patients with chronic kidney disease (unless noted)* [5]
Atenolol	Acute MI: 50–100 mg total dose daily [9] Angina Pectoris: 50 daily, titrate up to 100–200 mg daily HTN: 50 mg daily, titrate up to 100 mg daily	CrCl >35 mL/min: no adjustment CrCl 15–35 mL/min: 50 mg daily maximum CrCl <15 mL/min: 25 mg daily maximum HD: moderately dialyzable; administer dose post-HD or administer 25–50 mg supplemental dose PD: elimination is not enhanced; supplemental dose not necessary
Bisoprolol	HTN: 2.5–5 mg daily, titrate up to 10 mg daily [6] HFrEF (off-label): 1.25 mg daily, gradually titrate up to 10 mg daily [11]	CrCl >40 mL/min: no adjustment CrCl <40 mL/min: 1.25–2.5 mg, increase cautiously HD: non-dialyzable

(continued)

Table 24.1 (continued)

Pharmaceutical drug	General drug dosing recommendations	Renal impairment drug dosing recommendations
Carvedilol	HTN: 6.25 mg twice daily, titrate dose up to 25 mg twice daily [6] HFrEF: 3.125 mg twice daily, gradually titrate up to 25–50 mg twice daily [8, 11] LVD after MI: 3.125–6.25 mg twice daily, titrate up to 25–50 mg twice daily [8] *Note: if converting twice daily immediate release to daily extended release, multiply total dose of immediate release used daily by 1.6*	No dosage adjustment necessary HD: non-dialyzable
Metoprolol	Angina Pectoris: 50 mg (tartrate) twice daily, titrate up to 200 mg twice daily HTN: 50 mg (tartrate) twice daily, titrate up to 200 mg twice daily [6] HFrEF: 12.5–25 mg (succinate) daily, gradually titrate up to 200 mg daily [8, 11] MI: 12.5–25 mg (tartrate) every 6–12 h, titrate up to 100 mg twice daily [9] *Note: if converting twice daily (tartrate) to daily (succinate), add up total dose of tartrate used daily*	No dosage adjustment necessary
Statins	*Proven to aid in cardiovascular event protection* [5]	
Atorvastatin	Hyperlipidemia and Mixed Dyslipidemia: 10–20 mg daily, titrate up to 80 mg daily Homozygous Familial Hypercholesterolemia: 10 mg daily, titrate up to 80 mg daily Primary prevention of ASCVD [13, 14] If LDL-C >190 mg/dL and age 20–75 years, then 40–80 mg daily If LDL-C 70–189 mg/dL, age 40–75 years, and estimated ASCVD risk >7.5%, then 10–80 mg daily If DM, age 40–75 years, and estimated ASCVD risk <7.5%, then 10–20 mg daily If DM, age 40–75 years, and estimated ASCVD risk >7.5%, then 40–80 mg daily Secondary Prevention of ASCVD [13, 14] If clinical ASCVD or post-CABG and age <75 years, then 40–80 mg daily If clinical ASCVD or post-CABG and age >75 years, then 10–80 mg daily	No dosage adjustment necessary HD: due to high protein binding, not expected to be significantly cleared
Lovastatin	Hyperlipidemia: 20 mg daily, titrate up to 80 mg daily Primary prevention of ASCVD [13, 14] If LDL-C >190 mg/dL and age 20–75 years, then use a high-intensity statin If LDL-C 70–189 mg/dL, age 40–75 years, and estimated ASCVD risk >7.5%, then 40 mg daily or use a high-intensity statin If DM, age 40–75 years, and estimated ASCVD risk <7.5%, then 40 mg daily If DM, age 40–75 years, and estimated ASCVD risk >7.5%, then use a high-intensity statin Secondary Prevention of ASCVD [13, 14] If clinical ASCVD or post-CABG and age <75 years, then use a high-intensity statin If clinical ASCVD or post-CABG and age >75 years, then 40 mg daily or use a high-intensity statin	CrCl <30 mL/min: use with caution, especially if dose >20 mg/day

(continued)

Table 24.1 (continued)

Pharmaceutical drug	General drug dosing recommendations	Renal impairment drug dosing recommendations
Pravastatin	Hyperlipidemia: 40 mg daily, titrate up to 80 mg daily Primary prevention of ASCVD [13, 14] If LDL-C >190 mg/dL and age 20–75 years, then use a high-intensity statin If LDL-C 70–189 mg/dL, age 40–75 years, and estimated ASCVD risk >7.5%, then 40–80 mg daily or use a high-intensity statin If DM, age 40–75 years, and estimated ASCVD risk <7.5%, then 40–80 mg daily If DM, age 40–75 years, and estimated ASCVD risk >7.5%, then use a high-intensity statin Secondary Prevention of ASCVD [13, 14] If clinical ASCVD or post-CABG and age <75 years, then use a high-intensity statin If clinical ASCVD or post-CABG and age >75 years, then 40–80 mg daily or use a high-intensity statin	No dosage adjustment for mild to moderate impairment; start at 10 mg daily if severe impairment [5]
Rosuvastatin	Hyperlipidemia and Mixed Dyslipidemia: 10–20 mg daily, titrate up to 40 mg daily Homozygous Familial Hypercholesterolemia: 20 mg daily, titrate up to 40 mg daily Primary prevention of ASCVD [13, 14] If LDL-C >190 mg/dL and age 20–75 years, then 20–40 mg daily If LDL-C 70–189 mg/dL, age 40–75 years, and estimated ASCVD risk >7.5%, then 5–40 mg daily If DM, age 40–75 years, and estimated ASCVD risk <7.5%, then 5–10 mg daily If DM, age 40–75 years, and estimated ASCVD risk >7.5%, then 20–40 mg daily Secondary Prevention of ASCVD [13, 14] If clinical ASCVD or post-CABG and age <75 years, then 20–40 mg daily If clinical ASCVD or post-CABG and age >75 years, then 5–40 mg daily	CrCl >30 mL/min: no adjustment CrCl <30 mL/min: 5 mg daily, titrate up to 10 mg daily
Simvastatin	Hyperlipidemia: 10–20 mg daily, titrate up to 40 mg daily Homozygous Familial Hypercholesterolemia: 40 mg daily Primary prevention of ASCVD [13, 14] If LDL-C >190 mg/dL and age 20–75 years, then use a high-intensity statin If LDL-C 70–189 mg/dL, age 40–75 years, and estimated ASCVD risk >7.5%, then 20–40 mg daily or use a high-intensity statin If DM, age 40–75 years, and estimated ASCVD risk <7.5%, then 20–40 mg daily If DM, age 40–75 years, and estimated ASCVD risk >7.5%, then use a high-intensity statin Secondary Prevention of ASCVD [13, 14] If clinical ASCVD or post-CABG and age <75 years, then use a high-intensity statin If clinical ASCVD or post-CABG and age >75 years, then 20–40 mg daily or use a high-intensity statin	No dosage adjustment for mild to moderate impairment; start at 5 mg daily if severe impairment [5]

(continued)

Table 24.1 (continued)

Pharmaceutical drug	General drug dosing recommendations	Renal impairment drug dosing recommendations
Sodium-Glucose Transport Protein 2 Inhibitors		
Canagliflozin [15]	100 mg daily before first meal of the day Can be increased to 300 mg if 100 mg daily is tolerated and if eGFR is 60 mL/min/1.73 m^2 or greater and additional glycemic control is required	100 mg daily for 30 ≤ eGFR <60 mL/min/1.73 m^2 Contraindicated for individuals on dialysis and/or with severe renal impairment
Dapagliflozin [16]	5 mg daily in the morning with or without food Can be increased to 10 mg daily for patients tolerating the 5 mg dose who require additional glycemic control	Use is not recommended if eGFR is below 45 mL/min/1.73 m^2. Contraindicated if eGFR <30 mL/min/1.73 m^2
Empagliflozin [17]	10 mg daily in the morning Can be increased to 25 mg	Do not initiate if eGFR is below 45 mL/min/1.73 m^2; stop use if eGFR falls below 45 mL/min/1.73 m^2

ASCVD atherosclerotic cardiovascular disease, *CABG* coronary artery bypass grafting, *CAD* coronary artery disease, *CV* cardiovascular, *DM* diabetes mellitus, *HF* heart failure, *HFrEF* heart failure reduced ejection fraction, *HTN* hypertension, *LDL-C* low-density lipoprotein cholesterol, *LVD* left ventricular dysfunction, *MI* myocardial infarction, *AUC* area under the curve, *Cmax* maximum concentration of drug, *CrCl* creatinine clearance, *CRRT* continues renal replacement therapy, *HD* hemodialysis, *PD* peritoneal dialysis, *sCr* serum creatinine

preload and afterload, which improves HF [18]. Additionally, ACE inhibitors lower pulmonary capillary wedge pressure and directly work in the treatment of acute HF [19]. A meta-analysis of 92 randomized controlled trials studying 14 ACE inhibitors in a total of 12,954 participants with baseline blood pressure of 157/101 mmHg estimated an average trough blood pressure lowering effect of −8 mmHg for systolic and −5 mmHg for diastolic blood pressure [20]. Further, recommended starting doses (1/8 to 1/4 of the maximum dose) confer a 60–70% trough lowering effect, while a dose of 1/2 the maximum recommended daily dose yields 90% of the maximum's lowering effect; doses above the maximum do not significantly lower blood pressure beyond that of the maximum dose [20]. According to the 2017 Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults, the class I blood pressure treatment goal for adults with hypertension and CKD is <130/80 mmHg [21]. The guidelines further state a class IIa recommendation that in adults with hypertension and CKD (stage 3 or higher or stage 1 or 2 with albuminuria [≥300 mg/day, or ≥300 mg/g albumin-to-creatinine ratio or the equivalent in the first morning void]), treatment with an ACE inhibitor is reasonable to slow CKD progression, and a class IIb recommendation that in adults with hypertension and CKD (stage 3 or higher or stage 1 or 2 with albuminuria [≥300 mg/day, or ≥300 mg/g albumin-to-creatinine ratio in the first morning void]) (S9.3-7, S9.3-8), treatment with an ARB may be reasonable if an ACE inhibitor is not tolerated [21]. In 2009, the class of ACE inhibitors was the fourth most utilized drug class in the United States, with approximately 163 million prescriptions [22].

24.2.2 Angiotensin Receptor Blockers

ARBs lower blood pressure by preventing angiotensin II from binding to angiotensin II receptors on the muscles surrounding blood vessels, which allows the blood vessels to remain dilated. A meta-analysis of 46 randomized controlled trials in which 13,451 patients had a baseline blood pressure of 156/101 mmHg estimated that the trough

lowering efficacy for this class (at maximum recommended dose) is −8 mmHg for systolic and −5 mmHg for diastolic blood pressure [23]. Further, recommended starting doses (1/8 to 1/4 of the maximum dose) confer a 60–70% trough lowering effect, while a dose of 1/2 the maximum recommended daily dose yields 80% of the maximum's lowering effect; doses above the maximum do not lower blood pressure beyond that of the maximum dose [23]. The same analysis failed to find a difference in efficacy between the nine different ARBs [23]. A retrospective analysis of 6 years of data from Veterans Affairs records found that the most frequently used drug in this class was irbesartan (55%), followed by losartan (22%), candesartan (15%), and valsartan (8%); this data also revealed no difference in efficacy across the drugs studied in terms of mortality risk reduction in patients with chronic HF [24]. Early trials, such as the CHARM-Alternative, established that ARBs are effective for patients intolerant to ACE inhibitors [25]. Others, such as VAL-HeFT, advocate for ARBs in addition to an established HF therapy regimen, with resultant reductions in HF hospitalizations [26]. In many studies, use of either ACE inhibitors or ARBs is considered as a single treatment. For example, an analysis of nearly 7085 respondents of the National Health and Nutrition Examination Study (NHANES) with CKD from 1999 to 2014 revealed that 34.9% used an ACE inhibitor or ARB [27]. The rates of use increased over time from 25.5% to 40.1%, with large initial gains; however, the rates largely plateaued after 2003 [27]. Similarly, the rate of ACE inhibitor or ARB use among Veterans Affairs patients with CKD stages 3–5 was 44% in 2018 [28].

24.2.3 Beta Adrenergic Receptor Blockers

Another class of blood pressure lowering medication used in the treatment for CRS is that of beta blockers. Beta blockers, or beta adrenergic blocking agents, attenuate the effects of epinephrine, which in turn cause the heart to beat slower and with less force. Interrupting this activation of the sympathetic nervous system helps to prevent the progression of CVD and CKD [29]. In a study of nearly 700 non-dialysis patients with CKD (estimated glomerular filtration rate <60 mL/min/1.73 m^2) and early HF, initiation of beta blocker therapy was associated with a lower risk of death or HF hospitalization, even after adjusting for clinical factors (hazard ratio: 0.67, 95% confidence interval: 0.51–0.88) [30]. Carvedilol, in particular, has been shown to have favorable effects on renal function in patients with heart and kidney disease [31]. Unlike ACE inhibitors and ARBs, beta blockers are a heterogeneous class in that the drugs have different properties and metabolisms [32]. In fact, the ACCF/AHA 2013 Guidelines for the treatment of HF issued a class I recommendation in favor of one of three specific beta blockers (bisoprolol, carvedilol, sustained-release metoprolol succinate) which have been shown to reduce morbidity and mortality [33]. Only 20–30% of patients with CKD are prescribed a beta blocker [34].

24.2.4 Mineralocorticoid Receptor Antagonists

Aldosterone impacts sodium absorption and potassium excretion by acting on the collecting duct of nephrons and affects blood pressure through sodium regulation via extracellular fluid volume [35]. Steroidal MRAs work by blocking the epithelial and nonepithelial actions of aldosterone [36] and are utilized as diuretics to manage hypertension and HF with reduced ejection fraction [37]. MRAs are effective as monotherapy, but also confer benefit when used in combination with ACE inhibitors [38]. In a study of 812 patients with ejection fraction ≤40%, 553 (68%) had tried an MRA at some point; however, 184 (33%) discontinued therapy [39].

Members of this drug class, eplerenone and spironolactone, are associated with dose-dependent increases in serum potassium [40]. Eplerenone is more selective for the aldosterone receptor than is spironolactone (conferring the potential for fewer side effects); however, its efficacy does not exceed that of spironolactone [41, 42]. A retrospective cohort study of more

than 230,000 records in the PharMetrics Plus US claims database from 2009 to 2014 revealed that MRA use in the CKD population was low (1.2%), but that its use was higher for individuals with CKD and additional comorbidities; for example, 6.5% of those with CKD and HF used an MRA [43]. MRA use in that evaluation was largely driven by spironolactone (96%), and 16% of those who used an MRA had ESRD, even though steroidal MRA use is contraindicated [43].

24.2.5 Diuretics

Diuretics, most commonly loop diuretics, are prescribed to approximately 87% of patients with acute decompensated HF because they effectively and immediately relieve the symptoms of fluid retention and pulmonary congestion [44]. The method of action involves inhibiting the Na-K-2Cl co-transporter, which then causes natriuresis [45]. Because of their effect on neurohormonal activation and hemodynamics, loop diuretics are associated with the development of AKI; however, they are generally necessary in CKD to control extracellular fluid volume expansion [1, 46]. In a study of non-dialysis-dependent individuals with CKD, approximately 46% were treated with diuretics [47]. The risk of mortality for HF patients does not differ based on the choice of the three guideline-recommended loop diuretics (bumetanide, furosemide, and torsemide) [48].

There are three primary thiazide diuretics used for HF; hydrochlorothiazide and chlorthalidone manage edema in chronic HF and renal dysfunction, and indapamide treats salt and fluid retention in chronic HF [49]. These diuretics block the Na/Cl channel in the distal tube, which decreases the availability of sodium to cross the luminal membrane, and subsequently decreases the passage of sodium and water to the interstitium by decreasing the action of the sodium-potassium pump [50]. Of note, these drugs have a lower natriuretic effect and are typically used in conjunction with loop diuretics in cases of diuretic resistance [51].

Of note, HF patients have a decreased response to diuretics when compared to healthy patients due to decreased diuretic delivery to the kidney given reduced renal blood flow and increased sodium reabsorption due to hypoperfusion-induced activation of the renin-angiotensin-aldosterone system. Further, absorption of diuretics in the gastrointestinal tract is delayed given the presence of significant interstitial edema [52, 53]. Therefore a certain dose of diuretic will be unable to achieve its maximum peak concentration and its expected amount of diuresis. For this reason, intravenous diuretics are preferred given their ability to bypass the gastrointestinal tract and achieve maximum peak concentration quickly.

24.2.6 Statins

Statins are cholesterol lowering drugs prescribed for the primary and secondary prevention of CVD. Interestingly, statins may be effective in preventing CVD progression through additional anti-inflammatory, antioxidant, endothelial-protective and plaque-stabilizing properties [54].

Palmer and colleagues' review revealed that statin use prevented major cardiovascular events and lowered mortality in select patients with CKD [55]. A separate analysis concluded that high-efficacy statin therapy was associated with a significant decrease in the risk of stroke for patients with CKD [56]. While statins are contraindicated in patients with active liver disease and in patients with transaminase levels more than three times the upper limit of normal, it is important to note that statins do not have increased myopathy risk in CKD; hence, there is no need to routinely measure creatinine kinase levels unless patients develop myopathy [57]. While all statins significantly reduce the risk of CVD and mortality, the risk-benefit profile is not equivalent across the choice of drug [58]. Statins are also heterogeneous in that the dose of one drug is not equivalent to the same dose in another; for example, doses between 20 and 40 mg are considered low-intensity for fluvastatin and high-intensity for rosuvastatin

[59]. An analysis of NHANES data revealed that only 36% of individuals with CKD were taking a statin between 2011 and 2014, which is far under the 65% of these individuals who were recommended to do so based on American College of Cardiology and American Heart Association guidelines from 2013 [60]. Further, those without additional comorbidities were less likely to take a statin than those with additional comorbidities [60].

24.2.7 Digoxin

Although contemporary guideline-directed medical therapies include beta blockers and mineralocorticoid receptor agents, the management of HF may also benefit from incorporating digoxin. Digoxin is the most widely used cardiac glycoside and is effective by increasing the contraction force of the heart, decreasing conduction through the atrioventricular node, and decreasing the heart rate [61]. Malik and colleagues created a matched cohort of 698 hospitalized dyads from the Medicare-linked OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) registry and found that digoxin discontinuation in favor of guideline-directed medical therapies was associated with higher risks of HF readmission (hazard ratio [HR]: 1.21; 95% confidence interval [CI]: 1.05–1.39; p = 0.007), all-cause readmission (HR: 1.16; 95% CI: 1.04–1.31; p = 0.010), and the combined endpoint of HF readmission or all-cause mortality (HR: 1.20; 95% CI: 1.07–1.34; p = 0.002) across 4 years of follow up [62]. While beneficial, digoxin does have drug interactions and a narrow therapeutic range, which increases the risk of toxicity and may require additional therapeutic drug monitoring for patients [63]. For patients with congestive HF, the recommended therapeutic range is 0.5–0.9 nmol/L [64]. Approximately 18% of patients with incident (systolic) HF received digoxin in a retrospective review out of Kaiser Permanente from 2006 to 2008; digoxin users were less likely to have proteinuria than non-users (33.3% vs 38.5%, p = 0.02) [65].

24.2.8 Sodium-Glucose Transport Protein 2 Inhibitors

The newest class of drug to treat HF is that of sodium-glucose transport protein 2 (SGLT2) inhibitors, which has received an extended indication from the original intended use for the treatment of diabetes mellitus [66]. SGLT2 inhibitors decrease the kidneys' reabsorption of glucose, allowing for increased urinary glucose excretion, thereby reducing the level of plasma glucose independently of insulin [67]. Real world data from electronic health records revealed a 37% reduction in cardiovascular events for SGLT2 inhibitor users compared to those using dipeptidyl peptidase 4 inhibitors [68]. Further, SGLT2 inhibitors also significantly reduce the risk of adverse renal events. In the CVD-REAL 3 trial, patients taking an SGLT2 inhibitor were 51% less likely to have a 50% decline in estimated glomerular filtration rate or onset of end stage renal disease than were patients taking another glucose-lowering drug (3 events per 10,000 patient-years versus 6.3 events per 10,000 patient-years) [69]. Based on an analysis of four major cardiovascular outcomes trials for SGLT2 inhibitors, there is evidence of a class effect [70].

24.3 Medication Usage Limitations

Although these drugs have been associated with decreased cardiovascular morbidity and mortality, they remain underutilized. Several factors prevent patients from receiving optimal drug therapy, some of which may be attributable to pill burden, poor communication and affordability, and risk of side effects (which is of particular concern for patients with concomitant kidney dysfunction) [71].

24.3.1 Pill Burden

Most patients with HF and CKD have additional comorbidities requiring further drug therapy. As medication regimens become more complex, time

consuming, and costly, the likelihood of adherence decreases. For example, meal instructions may differ across medications and could cause confusion and/or inconvenience. A high pill burden has been documented in several chronic diseases. One study found that the median daily pill burden among dialysis patients was 19 [72]; another corroborated that 26% of patients with stage 5 CKD were taking ≥20 pills per day [73].

24.3.2 Poor Communication and Affordability

Mediocre counseling on the risks and benefits of medications may contribute to non-adherence [74]. Similarly, prescribers may be unaware of the cost of the drug or the burden that the cost imposes on the patient. In a national survey of Medicare beneficiaries aged 65 and older, 27% of patients who were non-adherent due to perceived inefficacy had not spoken with their physician about it [75]. Further, 39% of participants who reported cost-related non-adherence had not disclosed the issue to their physician; conversely, 38% of respondents who experienced cost-related non-adherence reported switching to a lower priced drug, an action that was significantly influenced by having a discussion with their physician about alternatives [70]. In a study of more than 90,000 patients who initiated a statin, those who received a generic drug were more likely to be adherent (77% vs. 71%) and had an 8% reduction in the composite risk of hospitalization for heart attack, stroke, or death [76]. However, while generic alternatives are widely available and generally improve adherence, the variability in pricing at the retail pharmacy level is still quite high [77].

24.3.3 Side Effects

While these drugs are generally well-tolerated, some individuals experience side effects. Some symptoms, such as dry cough and angioedema, are associated with increased kinins while taking ACE inhibitors. Other symptoms such as fatigue, headache, dizziness, and syncope are attributable to reduced angiotensin II and resultant hypotension. The prevalence of cough in ACE inhibitor users is estimated to range between 5% and 20%, with approximately 1.5–7.5% severe enough to terminate drug use [78, 79]. The likelihood of withdrawal of medication due to cough is about twofold higher in Asian-Americans than the general United States population [80]. African-Americans are at an increased risk of angioedema; an 8-year study showed that African-Americans constituted 5.9% of individuals prescribed an ACE inhibitor who did not experience angioedema, compared to the 19.6% of individuals prescribed an ACE inhibitor who developed angioedema [81].

ACE inhibition is also associated with decreased red blood cell production, which can result in anemia, and is most likely to do so in individuals with CKD [74]. N-acetyl-seryl-aspartyl-lysyl-proline, a stem cell regulator, is degraded by ACE, and is partially excreted in the urine [82]. Hence, it accumulates in the presence of ACE inhibition and reduced renal function [83].

While statins are the gold standard lipid lowering therapy, non-adherence and/or discontinuation is common due to patients' true or perceived adverse side effects. The most common complaints of statin users are muscle aches, pains, and/or weakness, all of which typically present within 4–6 weeks of initiation or dose increase [84]. The most severe muscle-related concern is that of rhabdomyolysis, a deterioration of skeletal muscle, affecting as many as 3.4 patients per 100,000 patients treated per year [85]. Approximately 20% of statin-eligible individuals have some degree of intolerance and up to 75% become non-adherent within two years of initiation; however, only about 3% are completely intolerant [86]. In fact, as high as 88% of patients who undergo a statin rechallenge do so successfully [87]. Statin use is also causally linked with a modest increase in the development of diabetes mellitus, affecting approximately 1 per 1000 patient-years [77].

Due to excess glucose excreted in the urine, patients, particularly women and uncircumcised

men, taking an SGLT2 inhibitor are at increased risk for genital infections; a pooled analysis revealed a 3.3-fold increase in such risk compared to non-SGLT2 inhibitor users [88]. Between 2013 and 2019, the FDA also noted 55 instances of Fournier gangrene among SGLT2 inhibitor users [89]. An additional infrequent adverse event is diabetic ketoacidosis, which was shown to occur in 1.002 per 1000 users by Hamblin and colleagues [90].

Paradoxically, serum creatinine may rise as intraglomerular pressure, and subsequently, albuminuria decrease. However, in a trial of antihypertensive therapy for patients with type 2 diabetes mellitus, researchers concluded that even a 30% rise in serum creatinine (coinciding with lower blood pressure) should not necessitate the reduction of antihypertensive medication, as the rates of adverse events did not differ significantly [91]. Despite this, renal insufficiency was listed as the primary reason for not receiving an ACE inhibitor or ARB in 42% of hypertensive patients not on guideline-directed medical therapy [92]. Additionally, a study of HF patients with suboptimal medical management listed contraindications for patients who had not tried an MRA due to renal dysfunction; however, 66 (72%) of these patients had an estimated glomerular filtration rate >30 mL/min, indicating that physicians may be overly conservative when prescribing or withholding medications for patients with moderately reduced kidney function [39].

Perhaps of the most concern for individuals with impaired renal function is the threat of hyperkalemia, an abnormally high potassium level in the blood, which results from intracellular potassium shifts and/or from impaired potassium excretion from the kidneys [93]. Patients with renal dysfunction and those taking medications that affect potassium levels are at an elevated risk of its development [94, 95]. Clinical manifestations of hyperkalemia vary with degree of serum potassium elevation [96]. Mild hyperkalemia (serum potassium 5.5–6.5 mEq/L) can alter resting cardiac membrane potential demonstrated early by peaked T-waves on electrocardiogram, while moderate and severe hyperkalemia (serum potassium >6.5 mEq/L) can induce conduction delays, atrioventricular blocks, sinus arrest, bundle branch blocks, and in severe cases, ventricular fibrillation or asystole [97, 98]. Patients with significant coronary artery disease and potassium levels >5.0 mEq/L are at an increased risk of sudden cardiac death compared to patients with lower potassium levels [99]. Further, patients with end stage renal disease experience an increased risk of ventricular arrhythmia and all-cause mortality in the presence of hyperkalemia [100].

24.3.4 Contextual Issues

Renal dysfunction is a common comorbidity that alters the pharmacokinetics (absorption, distribution, metabolism, and elimination) of drugs. Although these parameters change relatively slowly in CKD, they are dynamic in AKI, which can cause difficulty in dosing medications. In this setting, variations in drug response are usually attributed to pharmacokinetic rather than pharmacodynamic changes. In general, drug clearance decreases and the volume of distribution may remain the same or increase. However, sometimes surprising dosing adjustments are needed when pharmacodynamic concepts are considered. Pharmacodynamics mainly refers to a drug's action at its receptor site in regards to the drug onset, intensity, and duration. Pathologic processes such as CKD can affect pharmacodynamics by altering receptor sensitivity, receptor binding, or signal transduction. Further, besides these considerations, it is important to note that lack of data can often lead manufacturers to declare a drug contraindicated in patients with CKD, which deprives patients of important therapies. For example, between 2002 and 2007, it is estimated that only 57% of new drug applications to the FDA examined pharmacokinetics in kidney impairment, and only 44% of those with data in kidney impairment evaluated patients on hemodialysis. Per FDA policy, manufacturers are not required to determine the effect of CKD on drug dosing [101, 102].

24.4 Conclusion

In conclusion, although the prevalence of CRS (with chronic HF and chronic CKD) is growing, there are medical therapies, particularly involving blood pressure management, that can improve prognosis. Even though these drugs are widely administered and generally well-tolerated, there is some reluctance to optimally manage HF in the presence of severe CKD due to various limitations as discussed above. Nevertheless, it is advantageous for patients to remain on medical therapy, adjusting the dose based on severity of renal dysfunction as necessary [103].

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25 Anticoagulation for Atrial Fibrillation in Advanced Chronic Kidney Disease

Simonetta Genovesi and Federico Ronco

25.1 Vitamin K Antagonists in Patients with Advanced Chronic Kidney Disease and End Stage Renal Disease

Non valvular atrial fibrillation (NVAF) is the most common arrhythmia in general population and its incidence and prevalence increase with age [1]. Chronic Kidney Disease (CKD) and NVAF often coexist, and each condition predisposes to the other [2, 3].

Different studies noted a particularly high prevalence of NVAF among patients with end stage renal disease (ESRD): Zimmerman et al. reported a prevalence of 12% of NVAF in this particular population [4] while Genovesi et al. found that one out of four patients with ESRD has a history of NVAF [5]. Such data suggest that the prevalence of the association of the two pathologies is probably underestimated.

As in the general population, NVAF is associated with an increased risk of mortality in patients with CKD [4, 6] and survival in these patients is inversely correlated to the degree of CKD [7].

The prevalence and incidence of stroke are high in patients with CKD [8] and increase with progression of renal failure [9]. The presence of NVAF further increases the risk of stroke, especially in patients with advanced CKD [4]. This, together with the advanced age and the presence of numerous comorbidities, means that thromboembolic risk is particularly high in patients with severe CKD and NVAF and that, according to the cardiological guidelines, there is usually a strong indication for oral anticoagulant therapy (OAT) either with vitamin K antagonists (VKAs) or direct oral anticoagulants (DOACs).

There are, however, a number of issues that make it very difficult to implement what should be a proper therapeutic attitude in this population. The main problem is that there are no data from randomized controlled trials (RCTs) about these patients. The presence of advanced CKD (estimated glomerular filtration rate, eGRF, <30 ml/min) and ESRD was considered exclusion criteria in all RCTs that led to the development of cardiac guidelines indicating VKAs and then DOACs as first-line drugs in thromboembolic stroke prevention in patients with NVAF.

This means that all available evidence is derived from retrospective registers or, more rarely, from non-randomized prospective observational studies.

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Moreover, thromboembolic risk scores (CHADS2, CHA2DS2VASc) which, according to the current guidelines [10] identify AF patients in which OAT is indicated, were validated in a population that excluded patients with severe CKD [11]. In spite of this, it has been shown that classical thromboembolic scores discreetly identify subjects at risk of stroke in this population [12]. However, adding CKD to CHADS2 further improves the performance of the score [13]. The HASBLED score seems to be equally reliable in the determination of haemorrhagic risk in ESRD patients [12].

Moreover, some clinical parameters assessed in the thromboembolic risk scores (arterial hypertension, advanced age and previous stroke), are also predictors of risk of hemorrhagic events. In patients with severe CKD, hemodialysis (HD) patients in particular, thromboembolic and hemorrhagic risk scores are frequently both high, therefore, a balance between risks and benefits must be assessed before starting patients on anticoagulation.

Uremic syndrome predisposes CKD patients to thromboembolic events, but at the same time it is also associated with a number of changes in the coagulation system that favour haemorrhagic events [14], especially in patients with ESRD. Elliot et al., reported that anticoagulation therapy in HD patients is associated with bleeding events rates that are approximately twice as high as those of HD patients not receiving anticoagulation therapy [15].

A recent meta-analysis showed that VKAs prescription in patients with AF and CKD not undergoing renal replacement therapy, is not associated with a significant increase in bleeding events, while the bleeding risk in ESRD patients under OAT with warfarin is increased by 30% [16].

The few data available in ESRD patients in peritoneal dialysis (PD) suggest that VKAs therapy is associated with a lower risk of thromboembolic events compared with aspirin, without a higher risk of hemorrhagic events [17].

High haemorrhagic risk is an obstacle to the completion of clinical trials designed to evaluate the efficacy of VKAs in preventing thromboembolic events in patients with advanced CKD and NVAF. In fact only a minority of subjects who have the indication to anticoagulation are treated with OAT and many of them quit the therapy in the short term [18, 19]. Bleeding risk in patients with reduced eGFR, seems to be particularly high in the first 30 days of treatment with VKAs [20].

As in patients with preserved renal function, the longer the International Normalized Ratio (INR) is maintained in the therapeutic range (TTR), the lower is the risk of hemorrhagic events [19].

Unfortunately, the maintenance of adequate INR range is particularly difficult in patients with CKD and the worse the renal function, the lower the TTR [21–23].

An additional element that discourages nephrologists from prescribing a VKAs in patients with severe CKD or ESRD is the fear of favouring vascular calcifications. Patients with renal insufficiency develop extra-skeletal calcifications that lead to increased vascular stiffness, risk of cardiovascular disease and therefore mortality [24]. Different factors are involved in this phenomenon: uremia, age, gender, inflammation, abnormal mineral metabolism, concomitant diseases such as diabetes and hypertension. Smooth muscle cells of the vascular tunica media (VSMCs) synthesize proteins that are involved in the mechanisms of vascular calcification prevention [25]. In particular, Matrix GLA protein (MGP), synthesized by VSMCs, is one of the key factors in the prevention of vascular calcification. Since MGP is part of the family of vitamin K-dependent proteins, VKAs interfere with its activation [26]. It has been shown that in patients with preserved renal function, VKAs is associated with an increase in coronary calcium score, regardless of age [27]. However, there is no clear evidence that VKAs increase the risk of vascular calcifications in ESRD patients with AF, as such risk is already very high in this particular population [28].

In addition to concerns about the safety of VKAs in patients with AF and CKD, there is also a lack of evidence regarding their effectiveness in the prevention of thromboembolic events.

Even with regard to the efficacy of VKAs in these patients, there are differences between the subjects with non-terminal CKD and those undergoing renal replacement therapy. A meta-analysis showed a reduction of approximately 30% of thrombo-embolic events in AF and CKD patients taking VKAs, while no benefit was found in ESRD patients [16]. This is due to the extreme heterogeneity of the studies included in the meta-analysis. While some studies [29, 30] show an increased incidence of stroke associated with VKAs assumption, particularly in the elderly, the Danish registry shows a clear reduction in thromboembolic events in ESRD patients taking warfarin [31].

As already noted, evaluation of the effects of VKAs in patients with advanced CKD is difficult because of the absence of RCTs, the underutilization of OAT in this population and the frequent suspension of the drug due to the side effects, most represented by bleeding.

Also data regarding the mortality of patients with ESRD treated with VKAs are controversial. Previous studies showed a lower survival rate in HD patients who took VKAs for any reason [32], but more recent findings refuted this data [33, 34].

In particular, recent studies using a statistical approach to mitigate selection bias linked to prescription or non-prescription of VKAs ("propensity score" and "marginal structural models"), strongly suggested that ESRD patients with AF taking VKAs are at a lower mortality risk compared to those who are not under OAT, especially in the presence of a high TTR [12, 18, 35–37]. However, there is no evidence that this trend is associated with a reduction in thromboembolic events.

25.2 DOACs in Patients with Advanced CKD and ESRD

In the last few years, new oral anticoagulants for thromboembolic risk reduction in AF patients have been available. These drugs act on the final common pathway of the coagulation cascade, directly inhibiting thrombin or factor X-activated and are therefore called direct oral anticoagulants (DOACs).

DOACs don't need continuous monitoring such as VKAs, since at certain dosages, their concentration in plasma is constant.

Currently, four molecules have been approved by both the European Medicine Agency (EMA) and the Food and Drug Administration (FDA): dabigatran, rivaroxaban, apixaban and edoxaban.

All four drugs were tested in RCTs versus warfarin in patients with AF.

With regard to the efficacy in the prevention of thromboembolic events, RCTs showed non-inferiority (dabigatran 110 mg twice daily, rivaroxaban 20 mg once daily ed edoxaban 60 mg once daily), or superiority (dabigatran 150 mg twice daily and apixaban 5 mg twice daily) of DOACs compared to VKAs. Considering the safety, major bleeding incidence was the same (dabigatran 150 mg twice daily and rivaroxaban 20 mg once daily), or lower (apixaban 5 mg twice daily and edoxaban 60 mg once daily) in patients taking DOACs compared to those taking warfarin [38–41].

In addition, compared to warfarin, DOACs had a reduced overall mortality for all causes by 10% [42].

All these new molecules are eliminated at least partially by the kidney, albeit in a different percentage: 80% of dabigatran, 50% of edoxaban, 35% of rivaroxaban, and 27% of apixaban.

The degree of their binding with plasma proteins varies (from the lowest of dabigatran, 35%, to the highest of rivaroxaban >90%), causing the different DOACs to be dialyzable differently.

In the RCTs on DOACs different cut-off values were adopted to define renal insufficiency as an exclusion criteria: eGFR ≤30 ml/min for dabigatran, eGFR <30 ml/min for edoxaban and rivaroxaban, and serum creatinine >2.5 mg/dl or eGFR <25 mL/min for apixaban. All trials excluded patients with severe CKD.

Although currently the most validated equations for glomerular filtration estimates (eGFR) are the Modification of Diet in Renal Disease Study (MDRD), and Chronic Kidney Disease

Epidemiology Collaboration (CKD-EPI) [43, 44], patients recruited in RCTs who compared DOACs and warfarin were included or excluded from enrollment based on eGFR values calculated by the Cockcroft–Gault formula (C-G) [45].

It has been shown that in a population of elderly patients, all three equations (C-G, MDRD and CKD-EPI) provided an eGFR value different from that calculated with 24-h creatinine clearance. However, the most accurate formula was C-G, because both MDRD and CKD-EPI were characterised by a systematic overestimation of the eGFR. Given the older age of the patients with CKD and AF currently treated in everyday clinical practice, it is advisable to use the C-G equation in prescribing DOACs, so as not to overdose [46]. For each of the four DOACs vs warfarin comparison RCTs, post-hoc analyses were performed to evaluate the effect of DOACs in the subgroup of patients with reduced renal function (eGFR between 50 and 30 ml/min) [47–50]. These post-hoc studies have shown that the performance of DOACs, both in terms of safety and efficacy, is maintained in this population [51]. Indeed, in patients with moderate CKD, thromboembolic events are reduced by 21% and bleeding events by 20% in patients taking DOACs compared with those taking VKAs.

It has also been shown that the superiority of apixaban versus warfarin in reducing the relative risk of stroke and major bleeding remains over time, regardless of the worsening of renal function present in both groups of randomized patients [49]. In addition, a sub-analysis of the RE-LY trial showed that eGFR reduction at follow up was lower in patients randomized to dabigatran than those taking warfarin [52].

The combination of DOAC and antiplatelet therapy is associated with an increase in haemorrhagic events, as demonstrated by a post-hoc RE-LY study. Such study compared the safety of dabigatran or warfarin as a monotherapy to their assumption in combination with one or more antiplatelet agents [53]. However, a recent RCT showed that a low dose of rivaroxaban is safer than warfarin when associated with antiplatelet drugs in patients with ischemic heart disease. It is important to note that about 30% of patients enrolled in this study had an eGFR between 60 and 30 ml/min, and 1% of them had an eGFR <30 ml/min [54].

Efficacy and safety data on DOACs in patients with AF and severe CKD or ESRD are poor and mainly limited to pharmacokinetic studies. Chan et al., published the only clinical study which reports data on the prescription of dabigatran and rivaroxaban in hemodialysis patients in the United States. Both DOACs were associated with a higher risk of hospitalization and death for haemorrhagic events, compared with warfarin [55].

The guidelines suggest a dosage reduction of rivaroxaban in patients with eGFR between 30 and 50 ml/min and of edoxaban in patients with eGFR <50 ml/min. The dose of apixaban should be decreased in patients with creatinine >1.5 mg/dL with <60 kg body weight and/or age >80 years.

Considering the exclusion of patients with severe CKD or ESRD from RCTs who compared warfarin with different DOACs, the cardiological guidelines do not recommend the use of all DOACs in the presence of eGFR <30 ml/min (<25 ml/min for apixaban) and consider VKAs the first-choice drugs in patients with AF and severe CKD [10].

However, the European Medicines Agency (EMA) and the Food and Drug Administration (FDA), with some differences, allow the prescription of the various DOACs, with a dose adjustment, even in patients with eGFR <30 ml/min. In particular, FDA allows the use of rivaroxaban (15 mg once daily) and apixaban (5 mg or 2.5 mg twice daily) in HD patients. These indications arise from pharmacokinetic studies in which at the indicated doses, the plasma concentration of the two drugs is the same in HD patients and in subjects with preserved renal function [56–58].

However, there are no long-term data on safety and efficacy of the two DOACs in this population. A study performed on a small number of ESRD patients showed that HD had a scarce effect on drug clearance (<7%). The small number of patients, however, does not allow to draw conclusions about the risks and benefits of edoxaban in ESRD patients [59].

A prospective observational study is currently evaluating the efficacy and safety of rivaroxaban at a dose of 15 mg once daily in patients with eGFR between 15 and 49 ml/min (XARENO, NCT02663076). In addition, there are two ongoing RCTs that aim to study the effect of apixaban in terms of safety (primary outcome) and efficacy (secondary outcome) in HD patients with AF (AXADIA NCT02933697 and RENAL-AF NCT02942407). The results of these studies will be important to define the best therapeutic options for patients with advanced CKD or ESRD and AF.

25.3 Percutaneous Left Atrial Appendage Occlusion

Left Atrial Appendage (LAA) occlusion emerged in the last few years as an alternative to OAT, especially for those patients with AF at high risk for thromboembolic events, but with absolute or relative contraindications to OAT [10]. The indication of LAA occlusion as an alternative to OAT when medical therapy is not contraindicated remains a point of discussion. The rationale behind LAA occlusion is based on studies that identify the LAA as the primary site of thrombus formation in patients with NVAF [60]. Surgical approach was never widely adopted, due to a lack of consistent clinical evidence from large CRTs, and is considered mainly when cardiac surgery has to be performed for other reasons. A variety of devices have been developed to percutaneously occlude the LAA. The procedure requires a trans-septal approach from the right atrium to the left atrium and usually is guided by intraprocedural echographic imaging to rule out efficacy and possible complications such as pericardial effusion and device embolization. The Watchman device and the Amulet device are the most diffuse prosthesis. Interestingly, most of data on safety and efficacy were obtained in patients without contraindications to anticoagulants.

The PROTECT-AF [61–63], a multicenter prospective randomized clinical trial comparing Watchman device to long-term warfarin therapy, demonstrated the non-inferiority of the Watchman device to traditional medical therapy using stroke, cardiovascular or unexplained death and systemic embolism as the primary end point at 1 year follow up. The PROTEC-AF trial achieved statistical superiority for the composite primary efficacy endpoint at 4 years of follow up. In the PREVAIL study, implant success rate increased to 95% (from 90% of PROTECT) and procedural adverse events at 7 days decreased to 4.4% [64]. Holmes et al. in a meta-analysis [65], concluded that in patients with nonvalvular AF at increased risk for stroke or bleeding who are candidates for chronic anticoagulation, LAA occlusion with Watchman device resulted in decreased rates of hemorrhagic stroke, cardiovascular/unexplained death, and nonprocedural bleeding compared to warfarin.

Most of the clinical evidence for Amulet device is from pooled multicenter registry data. A pooled analysis of 1047 consecutive patients from 22 centers, reports a procedural success of 97.3% with 5% of periprocedural major adverse events [66]. Santoro et al. reported an ischemic stroke rate of 0.8/100 person-years, embolic event rate of 2.5/100 person-years and all-cause mortality of 2.5% over the follow up period in a population of 134 patients implanted with ACP device [67].

Patients with advanced renal failure represent a particular population in which the best strategy for stroke prevention in the case of AF remains uncertain. DOACs are in fact still not recommended in presence of severe renal impairment by most guidelines. A recent registry study assessed the safety and efficacy of LAA occlusion in 1014 patients with available renal function data: 375 with and 639 without CKD. Procedural and occlusion success were similarly high in all stages of CKD patients. No difference between patients with and without CKD were observed in peri-procedural major adverse events. The annual rate of thromboembolic cerebral events and the observed bleeding rate were similar among patients with and without CKD. LAA occlusion seems to have a similar safety profile in patients with CKD compared to patients with normal renal function and offers an important reduction of stroke and bleeding rates

in all stages of CKD, as compared to expected annual risk [68]. The indication for LAA occlusion for stroke prevention in patients with AF and renal disease should be discussed with a multidisciplinary team as well as with the patient, determining on a case by case basis the risks and benefits of OAT versus LAA occlusion .

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26 Cardiac Consultative Approach to Hemodialysis Patients and Cardiovascular Evaluation and Management of Potential Kidney Transplant Recipients

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Abbreviations

ACC	American College of Cardiology
ACE-I	Angiotensin converting enzyme inhibitor
ACS	Acute coronary syndrome
AHA	American Heart Association
BMS	Bare metal stents
CABG	Coronary artery bypass grafting
CACS	Coronary artery calcium
CAD	Coronary artery disease
CHF	Congestive heart failure
CKD	Chronic kidney disease
CT	Computed tomography
CVD	Cardiovascular disease
CVVHD	Continuous veno-venous hemodialysis
DES	Drug-eluting stents
DSE	Dobutamine stress echo
eGFR	Estimated glomerular filtration rate
EKG	Electrocardiogram
ESRD	End-stage renal disease
HFrEF	Heart failure reduced ejection fraction
MACE	Major adverse cardiovascular events
MPI	Myocardial perfusion imaging
OMT	Optimal medical therapy
PCI	Percutaneous coronary intervention
SCD	Sudden cardiac death
SIHD	Stable ischemic heart disease
SPECT	Single-photon emission computed tomography
STEMI	ST elevation myocardial infarction
USRDS	United States Renal Data System

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26.1 Evaluation and Management of Dialysis-Dependent Chronic Kidney Disease Prior to Renal Transplant and Non-cardiac Surgery

Renal transplant is the only proven, and the most cost effective, therapy to improve survival, quality of life, and morbidity, including major adverse cardiovascular events (MACE), for patients with advanced kidney disease, including those considered high risk [1–5]. However, deceased donor kidneys remain a scarce resource, and availability lags behind the increasing prevalence of end-

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stage renal disease (ESRD) due to improved survival, resulting in waiting times ranging from 3 to 8 years [6, 7]. Policies and professional guidelines suggest selecting potential recipients based on the estimated risk-to-benefit ratio, and the burden of equitable and responsible use of societal resources regarding organ donation and cost [8]. Chronic kidney disease (CKD) affects approximately 13% of the US population. As of 2016, there were over 700,000 prevalent cases of ESRD, and just under 100,000 candidates waitlisted for transplant, with only 12,500–13,500 annual transplants and approximately 30,000 new patients added or removed due to death or deteriorating medical condition [6, 7, 9, 10].

26.2 Challenges in the Evaluation of Patients with Advanced Chronic Kidney Disease and End-Stage Renal Disease for Renal Transplant

When consulting for pre-renal-transplant cardiovascular evaluation, the following information, challenges, and guiding principles should be considered:

1. Although adjusted mortality rates for dialysis patients have decreased by 28% over the past decade and half, annual all-cause mortality remains extraordinarily high (15–20%) compared with Medicare patients with cancer, heart failure, or myocardial infarction [7]. Adjusted mortality rates in 2015 for the general population and for dialysis-dependent CKD patients were 73.3 deaths per 1000 patient-years and 166 deaths per 1000 patient-years, respectively, and markedly lower, 29 per 1000 patient-years, for transplant recipients [7, 11].
2. CKD has a complex bi-directional interaction with cardiovascular disease (CVD). CVD worsens both short- and long-term survival in ESRD patients, and CKD worsens outcomes of common CVDs including myocardial infarction and sudden cardiac death (SCD) [7, 8, 12]. Prevalence of any CVD, including coronary artery disease (CAD), myocardial infarction, congestive heart failure (CHF), valvular heart disease, stroke/transient ischemic attack and peripheral arterial disease, increases with age, but doubles with presence of CKD [7]. For example, among patients aged 66 years or older, prevalence of any CVD is 32%, compared with 66% with concurrent CKD, and atherosclerotic heart disease and CHF account for most of these CVDs [7]. Prevalence of CAD, defined as presence of coronary artery stenosis of 50% or more in at least one epicardial coronary artery territory, in patients receiving dialysis is about 50%, but depends on age and associated comorbidity and may range from 30% to 70% [13–16]. Patients with CKD or ESRD have poor survival and worse prognosis after acute myocardial infarction, with gradient of mortality risk related to decreased renal function, and patients with CKD are more likely to die of CVD than to progress to ESRD and initiate dialysis [17–21]. The adjusted 2-year mortality rates for CHF, CAD, and acute myocardial infarction in patients with advanced CKD increase twofold, 2.5-fold, and fivefold, respectively, compared with no CKD [7]. In addition, mortality and complication rates are higher for CKD patients after revascularization by either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) [7, 9].
3. In dialysis patients, CVD mortality is 10–20 times higher than in the general population, and CVD is the leading cause of death, responsible for 40–50% of all-cause mortality [7, 18, 22, 23].
4. Registry databases and analysis of mortality patterns from clinical trials have shown SCD from arrhythmia or cardiac arrest to cause the most cause-specific mortality in hemodialysis patients, and the yearly rate is the highest among other patient populations [12, 24, 25] (Fig. 26.1). SCD accounts for almost a third of all-cause mortality and a slightly higher proportion for patients initiating hemodialysis, occurring at approximately

5–7% per year and accounting for nearly three-fourths of all cardiac deaths [7, 17, 19, 25–30]. In the post hoc analysis of the EVOLVE trial, which randomized 3883 hemodialysis patients with moderate to severe secondary hyperparathyroidism to cinacalcet or matched placebo over 5.3 years with adjudicated events, 45%, 46%, and 9% of deaths were due to cardiovascular, non-cardiovascular, and unknown causes (presumed cardiovascular), respectively, and sudden death accounted for 24.5% of overall mortality [23] (Fig. 26.2). However, despite remarkable reduction in all-cause mortality rates among dialysis patients in the past decade, SCD rates have remained unchanged, signifying proportionally more deaths due to SCD [7, 31]. This heightened susceptibility, though hypothetical, is most likely due to multifactorial mechanisms instigated by common causes of ESRD and perpetuated by CKD, including diminished tolerance for myocardial ischemia from endothelial dysfunction and inadequate perfusion reserve due to relative mismatch of capillary volume and cardiac myocyte mass, accelerated myocardial fibrosis and left ventricular hypertrophy in the setting of significant CAD burden, rapid electrolyte shifts in

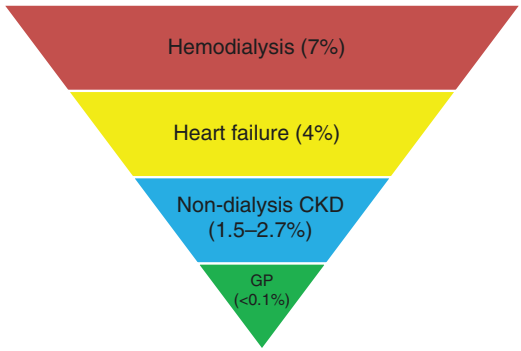


Fig. 26.1 Annual rates of sudden cardiac death in various populations. *CKD* chronic kidney disease, *GP* general population. (From: Chronic kidney disease and arrhythmias: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference [25]. Used with permission)

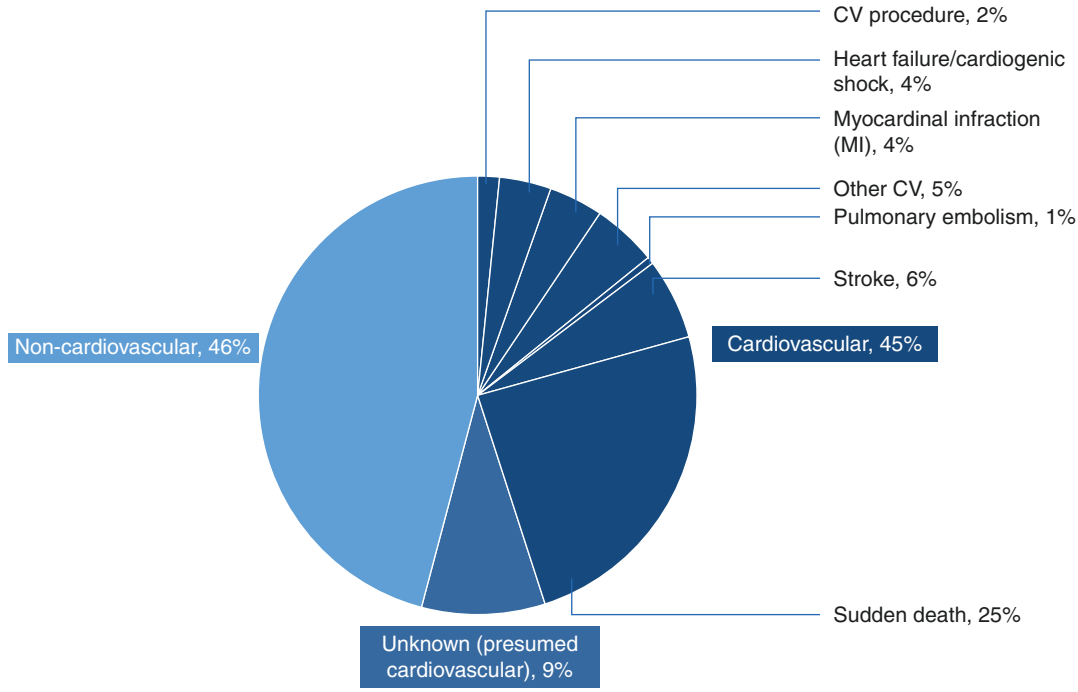


Fig. 26.2 Adjudicated causes of death among 3883 hemodialysis patients randomized to the EVOLVE trial, Evaluation of Cinacalcet HCl therapy to lower cardiovascular events. ([23], Open access)

hemodialysis patients, and autonomic dysfunction [17, 19, 27, 28]. Studies evaluating incidence and temporal distribution of SCD in dialysis patients have shown severe bradycardia and asystole to be the most frequent terminal events, suggesting that modifications of the hemodialysis prescription could reduce SCD [19, 25, 27, 32, 33]. While traditional risk factors, including CAD and revascularization, have not been influential on SCD rates in dialysis patients, the extent and burden of structural and functional CVD correlates with survival and incidence of SCD [9, 34].

5. The risks of cardiovascular mortality and morbidity increase exponentially with reduced renal function independent of other traditional and nontraditional risk factors, including diabetes, and CKD is recognized as CAD-equivalent based on the risk it imposes [18, 21, 22, 35–37]. Assessment of cardiovascular risk in patients with advanced CKD without traditional risk factors must factor in this information.
6. A considerable proportion of patients with advanced CKD and documented CAD are asymptomatic, limiting the usefulness of symptoms in screening for CAD [8, 38, 39]. This is likely because of high prevalence of diabetes with autonomic neuropathy, uremic neuropathy, and impaired exercise tolerance [38].
7. Heart failure is an independent predictor of early mortality in dialysis-dependent CKD patients, with 5-year survival of less than 20% [40]. The diagnosis of heart failure and classification of its severity using the New York Heart Association functional classification and the American College of Cardiology/American Heart Association (ACC/AHA) staging system is challenging in dialysis-dependent CKD because of temporal associations of common heart failure symptoms to ultrafiltration and the ubiquitous presence of structural heart disease [41]. The 11th Acute Dialysis Quality Initiative working group has proposed a diagnostic and classification scheme that considers (1) reported dyspnea in the absence of noncardiac etiologies, (2) response to ultrafiltration, and (3) presence of cardiac structural and functional abnormality on echocardiography, excluding patients with volume overload without concomitant structural heart disease [41].

Structural heart disease attributable to progressive CKD is highly prevalent even before hemodialysis initiation [42, 43]. Furthermore, a unique form of hemodialysis-associated cardiomyopathy develops from perpetual myocardial insult due to long-term hemodialysis [44]. This results from (a) chronic circulatory congestion; (b) chronic inflammatory state and diffuse myocardial fibrosis; (c) myocardial stunning from repetitive ischemic insult during dialysis (which may be another instance of "stress cardiomyopathy" secondary to autonomic activation), reduced coronary flow reserve, and frequent low blood pressures during dialysis; (d) increased afterload from arterial stiffness; and (e) high output state from arterio-venous shunting via dialysis access sites [44].

Several elements in heart failure management improve cardiovascular outcomes, including optimization of dialysis prescription to control volume overload, management of underlying CAD and rhythm abnormality, and use of guideline-directed medical therapy. While presence of heart failure, particularly with reduced ejection fraction (HFrEF), complicates evaluation of potential renal transplant candidates, the following points require careful consideration:

(a) Ejection fraction can be "dynamic," reflecting the underlying pathophysiologic state, and can improve with stricter management of volume status, guideline-directed medical therapy, and management of underlying contributory factors such as ischemic heart disease and rhythm abnormality. Hence, it is important to reconsider potential renal transplant candidates after addressing treatable and modifiable factors.

(b) Kidney transplant improves overall survival including in candidates considered high risk [1]. Furthermore, limited data suggest that kidney transplant may improve left ventricular remodeling, systolic function, and long-term survival in those with HFrEF [45–47].

8. Despite renal transplant improving overall long-term survival and reducing cardiac events compared with no transplant in ESRD patients, CVD remains the leading cause of death with a functioning graft [2, 48, 49]. In addition, renal transplant surgery is associated with increased short-term risk, including more than twofold risk of mortality compared with waitlisted patients [2] due to MACE within 30 days, and with long-term complications, including progression of CVD, infection, and malignancy [49, 50]. All of the above factors, in conjunction with limited availability of deceased donor kidneys, warrant routine evaluation of all ESRD patients, particularly those being considered for renal transplant, for CVD [8, 51]. As of 2016, only about 15% of potentially eligible patients were listed for renal transplant, and this proportion may worsen with rising ESRD prevalence unless the kidney donor pool expands substantially [6, 7].
9. The dilemma physicians face in caring for ESRD patients centers on the most appropriate way to risk-stratify, and the quandary of who is and is not a candidate for renal transplant is reflected in multiple professional guidelines with often differing recommendations [8, 51]. Whereas the tasks of transplant candidate selection committees are broad and incorporate assessment of overall risk based on multi-organ system evaluation vs. benefits of transplant, nutritional status, social support, and psychological status [8, 52], the foundation for cardiovascular evaluation rests on two broad categories: (1) patients with high risk of overall mortality and morbidity from cardiovascular causes in whom transplant is unlikely to provide benefit, and (2) patients expected to experience perioperative cardiovascular events, such as those with unstable angina, acute heart failure, and advanced valvular heart disease; intervene as appropriate to reduce these risks, and identify those with unmodifiable risk [53]. Historically, substantial emphasis has been placed on identifying CAD through noninvasive and invasive methods; however, MACE goes beyond atherosclerotic disease, and most patients die of SCD and CHF unrelated to obstructive CAD [51, 54–56]. In addition [57, 58], few data suggest that screening for CAD in asymptomatic transplant candidates reduces cardiovascular events or mortality [8, 51, 59]. Also important is the higher proportion of fatal to non-fatal cardiovascular events compared with the general population, and the potential effects of "competing death" in dialysis-dependent CKD patients, in whom mortality rates are often higher than cardiac event rates, posing challenges in assessing the effect of intervention on non-fatal cardiac events [56, 60]. Hence, cardiovascular risk assessment entails more than merely excluding CAD and includes assessment of overall cardiovascular and comorbid disease burden and functional capacity that correlates with overall mortality, and estimation of perioperative cardiovascular risk.
10. Finally, although kidney transplant allocation priorities are based on waiting time as the dominant criterion according to the Organ Procurement and Transplantation Network, pre-renal-transplant evaluation balances the rapid expansion of a high-risk recipient pool in the face of organ shortages on one hand, and the intense pressure on transplant programs to meet performance matrices on the other, influencing an individual's candidacy based on the case mix of the recipient pool. This effect is difficult to gauge; however, it would be disingenuous to ignore it. On the contrary, perceived high-risk patients have the liberty to seek additional opinions and the option of listing at multiple programs.

Factors associated with perioperative MACE could be categorized as preoperative, intraoperative, and postoperative [50].

26.3 Preoperative Factors

26.3.1 Chronic Conditions

Multiple prospective studies have confirmed medical conditions such as CKD, diabetes, history of cerebrovascular disease, CAD, and CHF as powerful predictors of MACE during non-cardiac surgery, with rates over 5% for several of these risk factors, which are often present in renal transplant candidates [50, 61–63]. Incidence of MACE with non-cardiac surgery is inversely related to estimated glomerular filtration rate (eGFR), and is particularly marked with advancing CKD [64].

26.3.2 Acute and Recent Events

Evidence-based practice guidelines for preoperative cardiovascular evaluation have been published for the general population [65]. Although many of the principles can be applied to prospective renal transplant candidates, some salient features need particular attention. Based on the practice guideline's definition of surgical necessity, living donor kidney transplant would qualify as "elective" because adequate time is available for patient evaluation and the procedure could technically be delayed for 1 year [65]. Conversely, deceased donor kidney transplant is not elective as it cannot be delayed, although not for urgent or emergent reasons, as there is no active limb- or life-threating medical condition. Time is available for limited clinical evaluation and medical optimization, including dialysis prior to surgery, and deceased donor transplant can be considered "time sensitive or urgent." Recent medical conditions, including myocardial infarction or Canadian Cardiovascular Society class III or IV angina within 6 months, stroke within 3 months, or coronary artery stenting within 6 months before surgery, are independently associated with perioperative MACE [50, 66]; performing preoperative assessment for recent events and acute conditions is therefore mandatory, since the last pre-renal-transplant evaluation occurs when a patient is called for deceased donor transplant. In addition, assessment for significant hypervolemia, progression of known valvular heart disease, or acute decompensated heart failure possibly requiring urgent dialysis or echocardiogram is crucial to minimize perioperative complications, death, or graft loss.

26.3.3 Intraoperative and Postoperative Events

Surgery and anesthesia increase hazards of major cardiac complications through several mechanism [50]. Activation of inflammatory and coagulation cascades, neuroendocrine response to stress, tachycardia, hemodynamic instabilities, bleeding, and hypoxemia may lead to type 2 myocardial infarction via alteration of the myocardial ischemic threshold and increased myocardial oxygen consumption [50, 67, 68]. The same pathophysiologic processes may also lead to vulnerable plaque-related type 1 myocardial infarction, acute heart failure, pulmonary edema, stroke, or pulmonary embolism [50, 67]. Irrespective of the mechanism, postoperative troponin elevations, including from non-ischemic myocardial injury, predict cardiac and non-cardiac morbidity and mortality [67]. Heightened intraoperative monitoring and improved anesthesia techniques have led to reduced incidence of cardiac complications, emphasizing the need to recognize and act promptly on hemodynamic and electrocardiogram (EKG) changes that often precede postoperative events [50, 69].

26.4 Assessment and Management of Potential Renal Transplant Recipients

Even among the healthiest waitlisted subgroup of ESRD patients, in whom the standardized mortality rate is half the rate for unselected hemodi-

alysis patients, mortality remains substantially higher than in non-ESRD patients [2, 70]. Hence, the objective of pretransplant cardiovascular evaluation (Table 26.1) is not to exclude candidates with CVD, given its ubiquitous prevalence, but to identify potential recipients with lower likelihood of or modifiable estimated events (Fig. 26.3). For example, among renal transplant recipients who enjoy long-term survival, CVD remains the major cause of mortality with a functioning graft, and nearly half of deaths within 30 days of transplant are due to cardiac events [49]. While it is important to factor in and closely monitor comorbid conditions that may progress during the expected waiting time for deceased donor transplant, for example moderate aortic stenosis, conditions such as uremic cardiomyopathy and severe systolic dysfunction could potentially improve with appropriate guideline-directed medical and renal replacement therapy.

Although cardiac evaluation and risk modification are continuous processes, to develop a management protocol, they will be categorized as three separate evaluation plans during the anticipated renal transplant timeline: (a) pre-renal-transplant evaluation prior to listing; (b) cardiac surveillance protocol while on the waiting list, and (c) cardiovascular evaluation in the immediate preoperative period.

Table 26.1 Objectives of pre-renal-transplant cardiovascular evaluations

• Identify prevailing cardiovascular disease and implement strategies to reduce morbidity and mortality.
• Emphasize "risk of morbidity and mortality" and not presence of cardiovascular disease, and avoid unfair exclusion of potential recipients.
• Identify patients at high risk for major adverse cardiovascular events in the perioperative period.
• Identify patients with expected short near-term survival due to cardiac morbidity whom transplant would not adequately benefit.
• Recognize the dynamic nature of systolic function in hemodialysis patients based on adequacy of dialysis, volume management, and guideline-directed medical therapy, and the need for continued surveillance.
• Recognize more rapid progression of valvular heart disease in dialysis patients.
• Establish a venue for discussion of complex patients, such as the cardiorenal panel (a multidisciplinary nephrocardiology "heart/kidney team"), to address candidacy and management.

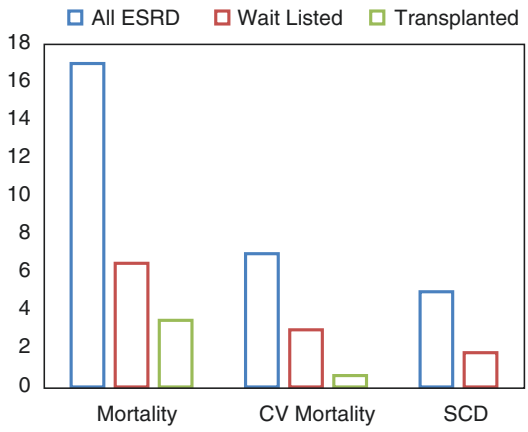


Fig. 26.3 Estimates of annual rates of mortality, cardiovasculr (CV) mortality, and sudden cardiac death (SCD) for end-stage renal disease (ESRD) and waitlisted patients and transplant recipients, demonstrating effects of patient selection, risk factor modification, and kidney transplant [1, 2, 6, 7, 48, 70, 71]

26.5 Risk Stratification and Detection of Cardiovascular Disease in Patients Undergoing Pre-renal-Transplant Evaluation

The ideal initial step in assessing prospective candidates for kidney transplant would be to quantify and predict risks of cardiac complications on the waiting list and perioperatively as accurately as possible [13, 71, 72]. This would provide the basis for risk vs. benefit assessment, inform decisions about transplant candidacy, and guide immediate postoperative care [50]. Several methods are used to estimate perioperative risk: clinical data, clinical risk indices, noninvasive stress testing, cardiac computed tomography (CT), coronary angiogram, and cardiac biomarkers. The 2014 ACC/AHA guideline on perioperative cardiovascular management of patients undergoing non-cardiac surgery classified procedures as low risk if predicted MACE is less than 1% and elevated risk if higher than 1%, and abandoned intermediate- and high-risk categories as

recommendations were similar for both [65]. Further reclassification of renal transplant candidates who would otherwise fall into one category of elevated risk is needed to guide selection and management [8, 59].

26.5.1 Very High Risk

Very high risk is defined as estimated high perioperative morbidity and mortality, or short expected near-term survival due to cardiac morbidity, whereby the risks of transplant outweigh potential benefits. Although accurate quantification of risk is impractical, transplant programs and practice guidelines agree that the following cardiac conditions portend very high risk:

1. Multi-vessel CAD with ejection fraction 30% or below without options for revascularization.
2. Unrevascularizable CAD with evidence of relatively large inducible symptomatic or asymptomatic ischemia on dobutamine stress echocardiogram at a relatively low work load, i.e., heart rate of 120 bpm or below while on optimal medical therapy (OMT).
3. Severe pulmonary hypertension not due to left sided heart failure.
4. Severe aortic or mitral stenosis prior to surgical management.
5. Severe mitral or aortic regurgitation with symptom or systolic dysfunction prior to surgical management.
6. End-stage systolic heart failure (stage D and New York Heart Association functional classification IV) while on optimal medical and device therapy.
7. Untreated recurrent ventricular tachycardia.

26.5.2 High Risk

This group constitutes patients with acute or recent cardiac events and high short-term risk for perioperative events with potential for reduced risk with intervention or time lapse, and presence of underlying cardiac disease or equivalent that is associated with increased risk for perioperative cardiac or non-cardiac complications.

1. Coronary stenting within 6 months increases the risk of acute stent thrombosis postoperatively [50]. This risk is highest within the first 3 months for both for bare metal stents (BMS) and drug-eluting stents (DES).
2. Myocardial infarction within 6 months [39, 73].
3. Symptomatic Canadian Cardiovascular Society class III or IV ischemic heart disease within 6 months [50, 65].
4. Acute decompensated systolic heart failure.
5. Circulatory congestion with significant hypervolemia and elevated left- and right-sided filling pressures.
6. Presence of mechanical prosthetic cardiac valves that increase the risks for heart failure, bleeding, stroke, and valve thrombosis postoperatively.
7. Unprotected left main or multivessel CAD prior to revascularization.
8. Presence of moderate valvular heart disease in conjunction with other comorbidity that may raise risks of perioperative event rates.
9. Diabetes mellitus distinct from other nontraditional risk factors that imposes cardiovascular morbidity and mortality similar to established CAD in patients with CKD should be approached as such [21, 74, 75].

26.5.3 Moderate Risk

Moderate-risk patients are asymptomatic with no prior cardiovascular events but with multiple traditional and other risk factors that may portend moderate perioperative risk. Analysis of pooled individuals without pre-existing coronary disease from large epidemiologic studies showed poor accuracy and substantial underestimation of the Framingham risk model for prediction of cardiac events in patients with CKD [76]. Although diabetes and prior CVD are categorized as high risk based on the risk imposed in CKD, the ACC/AHA scientific statement on cardiac disease evaluation and management

among kidney and liver transplant candidates defines cardiovascular risk factors for patient with CKD as age older than 60 years, diabetes mellitus, smoking, dyslipidemia, hypertension, left ventricular hypertrophy, prior CVD, and more than 1 year on dialysis.

Regarding non-traditional risk factors, people living with HIV have a twofold increase in the risk of CAD and are on average 10 years younger than uninfected people at the time of their first myocardial infarction [77, 78]. Among HIV-positive individuals with CKD stage 4 or higher, over 20% are estimated to develop CVD after 5 years [79]. Moreover, people with HIV at high risk of CVD had a corresponding 5.6-fold increase in risk of CKD [80].

Other risk factors requiring special attention include total time on maintenance dialysis, prior renal transplant, chronic myocardial injury with chronically elevated troponin, proteinuria, severe secondary hyperparathyroidism, and systemic inflammatory diseases such as systemic lupus erythematous, rheumatoid arthritis, and vasculitis.

26.5.4 Low Risk

Younger (age <45 years), non-diabetic patients with normal ejection fraction, fair functional capacity, and less than three traditional risk factors are considered low risk.

26.6 Risk Assessment Methods

26.6.1 Risk Estimation Indices

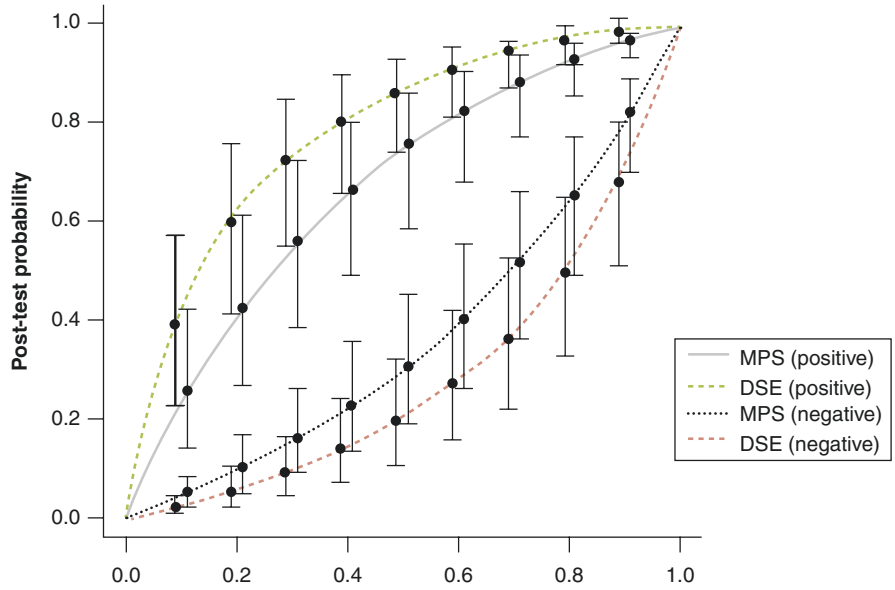
The commonly used perioperative risk prediction models, including the revised cardiac risk index (RCRI) and the Gupta myocardial infarction or cardiac arrest (MICA) calculator derived from the American College of Surgeons National Surgical Quality Improvement Plan (NSQIP), included such a small fraction of advanced CKD patients that the validity of these models in the pre-renal-transplant cohort is unknown and is less likely to be accurate.

26.6.2 Noninvasive Imaging Studies

When interpreting noninvasive stress tests performed primarily for pre-renal-transplant evaluation in patients with ESRD, the objectives, the modality, and the effects of structural and functional alteration of the cardiovascular system on accuracy should be underscored.

1. Pre-renal-transplant cardiac evaluation helps identify patients who most benefit from kidney transplant by instituting therapy that may modify risk and by excluding those in whom CVD has advanced, imparts poor prognosis, and is unmodifiable [51]. The objectives of stress testing, therefore, are to provide an important and powerful element in the evaluation of overall prognosis primarily and as a risk-stratification tool for perioperative cardiovascular events. For example, an asymptomatic nondiabetic person with moderate ischemia but higher than average functional capacity is expected to have a better prognosis than a poorly functional diabetic person with similar degree of ischemia.
2. Based on the Bayesian theorem, in a population in which disease prevalence is as high as CAD is in ESRD patients, the sensitivity and specificity of a test considered for screening should be above 80% to avoid high rates of false negative tests. For example, with average sensitivity and specificity of 80% for the commonly used stress test and 50% prevalence of CAD, 20% of results will be false negatives. On the contrary, stress tests provide important prognostic value independent of the diagnosis of CAD, as discussed below.
3. ESRD is associated with structural and functional alteration in the cardiovascular system, such as endothelial dysfunction and coronary calcification that may affect coronary flow reserve, marked left ventricular hypertrophy, myocardial fibrosis and amyloid deposits that may affect contractile reserve, accelerated valvular disease, and volume overload that may influence test performance and accuracy [9, 81–83].

A large body of data over several decades has shown the value of myocardial perfusion imaging (MPI) and dobutamine stress echo (DSE) in predicting prognosis in the general and in special populations including patients with diabetes or CKD [8, 84–90]. However, there is concern that because of the functional and structural alterations of the cardiovascular system and the relatively high prevalence of multivessel CAD in patients with CKD, MPI and DSE may underestimate the extent of disease [84–86, 88, 91, 92]. It is therefore not surprising that systematic reviews of noninvasive stress tests in asymptomatic CKD patients showed limited accuracy in predicting obstructive CAD, although the pooled analysis suggested that DSE may be better than MPI [86, 93] (Fig. 26.4). More importantly, however, despite controversies regarding which modality is superior, disease burden evaluated by coronary angiography and noninvasive stress testing predicts MACE and all-cause mortality in patients with advanced CKD [15, 51, 89, 94]. A systematic review by Wang et al. that included over 7000 participants who underwent coronary angiogram, MPI, or DSE for pre-renal-transplant evaluation showed that approximately 20–30 patients per 100 and 20 patients per 100 with abnormal test results experienced all-cause mortality and MACE, respectively [87]. Compared with patients with negative test results, those with abnormal results had 1.5–2-fold and three to five-fold increased risk of mortality and MACE, respectively. Nevertheless, the negative and positive predictive values of these tests were low, and



Pre-test probability			
Test	**Pre-test probability of coronary artery disease**	**Post-test probability (%) after positive result**	**Post-test probability (%) after negative result***
Douutamine stress echocardiography (DSE)	Low risk (10–29%)	42-72%	3–10%
	Intermediate risk (30-59%)	73-90%	10-27%
	High risk (60-90%)	91-98%	28-70%
Myocardlal perfusion sclntlgraphy (MPS)	Low risk (10-29%)	24-54%	5-15%
	Intermediate risk (30-59%)	55-81%	16-38%
	High risk (60-90%)	81-96%	39-79%

Fig. 26.4 Accuracy of dobutamine stress echocardiography and myocardial perfusion imaging for the diagnosis of obstructive coronary artery disease in renal transplant candidates. ([93], Used with permission)

a considerable number of patients with negative test results experienced adverse outcomes, while most transplant candidates with abnormal test results did not [87]. This underscores the importance of integrating stress test information with other clinical and demographic data in making decisions regarding candidacy for renal transplant.

Systematic reviews of contemporary studies with large datasets strongly suggest that both DSE and MPI, the most commonly used screening tests, are equivalent to coronary angiography in predicting MACE among patients with advanced CKD, and that one is not superior to the other [87]. While choice of stress test modality depends on the institution's expertise and resource availability, test characteristics described in Table 26.2 are noteworthy for particular patients.

Radiographically quantifiable coronary artery calcium (CACS) is a marker of CAD and predicts cardiac events over established traditional risk factors [95, 96]. Although coronary calcification involves both the media and intima in advanced CKD, as opposed to the intima alone in patients without CKD, and CACS poorly predicts the presence of obstructive CAD or inducible ischemia, it correlates well with atherosclerotic plaque burden and predicts MACE [38, 96–98]. Epidemiologic studies have shown an inverse relation between declining kidney function and CACS [99]. The burden and progression of coronary calcification in patients with advanced CKD are higher and faster than in non-CKD patients [38, 100, 101]. While the combination of less than three traditional risk factors and Agatston coronary calcium score of less than 400 identified advanced CKD patients with the lowest risk of MACE, the added value of traditional risk factors in predicting MACE diminishes with score above 400 and evidence remains inconsistent regarding sensitivity compared with single-photon emission CT (SPECT) [89, 101].

Multiple comparative and outcome studies have shown the diagnostic and prognostic value of cardiac CT in non-CKD patients with high negative predictive values [102, 103]. Despite high coronary calcium scores associated with ESRD, small studies have shown the feasibility of cardiac CT to diagnose obstructive CAD and predict outcomes, but studies for a considerable proportion may be uninterpretable because of heavy calcification [38, 104]. Expanding the role of structural imaging in risk stratification of potential renal transplant candidates and emphasizing the concept of plaque/disease burden over obstructive luminal stenosis, a recent prospective study of 154 patients demonstrated coronary CT angiography to predict MACE and mortality better than invasive coronary angiography and SPECT [101].

Table 26.2 Comparison dobutamine stress echocardiogram versus myocardial perfusion imaging for specific clinical indications

Stress echo (dobutamine or exercise)	Myocardial perfusion imaging
Provides essential hemodynamic data in the presence of valvular heart disease and prosthetic heart valves	In the setting of left bundle branch block and paced rhythm
Provides information on contractile reserve and filling pressure in the presence of systolic dysfunction	For patients with chronotropic incompetence
Identifies ischemic threshold that could be used to guide therapy in the perioperative period	For patients with poorly controlled blood pressure and previous hypertensive blood pressure response to exercise or dobutamine
Better tolerated than vasodilatory MPI in the setting of low blood pressure	
Probably better sensitivity in patients suspected of having multivessel CAD	
Better tolerated in the presence of obstructive airway disease and suspected arteriovenous block	
Probably better sensitivity in patients whose coronary flow reserve has been "used," such as in the presence of larger arteriovenous fistula with high resting cardiac output, large doses of nitrates, and left ventricular hypertrophy with concomitant anemia.	

26.6.3 Cardiopulmonary Stress Testing

Functional capacity as estimated by activities of daily living such as blocks walked or stairs climbed is inversely proportional to the likelihood of perioperative complications, with four blocks and two flights of stairs considered markers of poor functional capacity [105]. A single-center experience with a small number of patients using cardiopulmonary exercise testing without noninvasive stress imaging for those with VO2 >17 ml/kg/min and no prior coronary revascularization appeared to be a promising and cost-effective strategy [106].

26.6.4 Biomarkers

Although the accuracy of stable and chronically elevated troponin (chronic myocardial injury) in predicting obstructive CAD is poor, and it and other novel biomarkers have not been incorporated into the long-term risk-prediction tools/models, patients with CKD and elevated troponin have three to fivefold increased all-cause mortality risk even after adjusting for multiple factors [107, 108]. Hence, presence of chronic myocardial injury should be factored in when assessing global long-term risk.

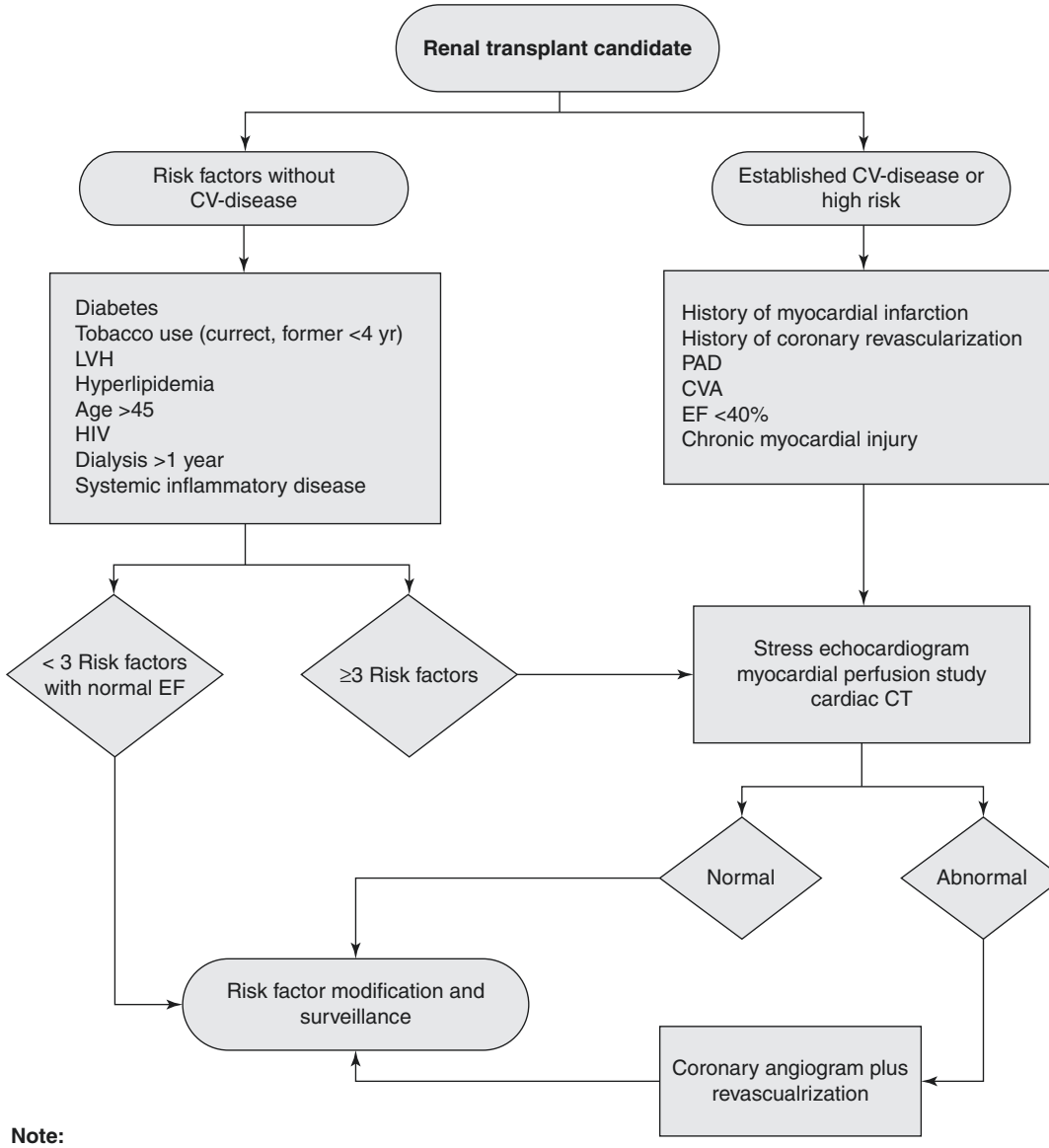
26.6.5 Invasive Coronary Angiogram

Invasive angiographic studies in renal transplant candidate with dialysis-dependent CKD have shown prevalence of CAD, generously defined as coronary artery stenosis above 50%, to be about 50%, with higher prevalence in patients with diabetes and extra-cardiac vascular disease [15, 51, 74]. However, several studies have shown that the correlation between angiographically defined CAD and future cardiac events and all-cause mortality is poor and inconsistent [51]. However, the absence of stenosis 50% or higher is associated with a lower rate of coronary events [88]. Focal plaques prone to unstable course, rupture, and thrombosis in patients undergoing major non-cardiac surgery are less likely to be obstructive [109]. On the contrary, the likelihood of harboring unstable plaque and hence risk of future cardiac events correlates with overall disease burden [13, 15, 101, 109]. Although coronary angiography uncovers high-risk anatomic features, such as left main disease and multivessel CAD involving proximal epicardial coronary arteries that have been shown to predict outcomes, prevalence of such lesions is not high enough to merit routine screening coronary angiography in all renal transplant candidates [8]. However, coronary angiography should be considered in those with high-risk features (diabetes, prior myocardial infarction, and extra-cardiac vascular disease) who had non-diagnostic noninvasive stress tests or cardiac CT.

26.6.6 Approach to Screening Potential Renal Transplant Candidates

Assessing overall CVD burden is essential, including valvular heart disease, heart failure, left ventricular hypertrophy/left ventricular mass, CAD, and vascular disease burden in conjunction with assessment of functional capacity. Although there is no universally accepted screening algorithm and other recommendations exist, we propose the following approach [8, 38, 51]:

1. Twelve-lead EKG in all potential candidates to assess for prior silent infarct, left ventricular hypertrophy, rhythm abnormality, and as a baseline [110].
2. Transthoracic echocardiogram in all dialysis patients obtained when approaching estimated dry weight to assess for systolic and diastolic function, valvular heart disease, volume status, and pulmonary arterial pressure [110].
3. When evaluating for CAD in asymptomatic candidates, categorize candidates as with and without established CAD or CAD equivalent/high risk, including peripheral arterial disease, cerebrovascular accident, ejection fraction less than 40% or chronic myocardial injury (Fig. 26.5). Because of abundant data over several decades showing the value of



Note:
Renal transplant candidates: excluding very high risk patients
CVA: cerebrovascular accident
CV-disease: cardiovascular disease
EF: ejection fraction
LVH: left ventricular hypertrophy
PAD: peripheral arterial disease
Systemic inflammatory disease: lupus, rheumatoid arthritis

Fig. 26.5 Evaluation algorithm for asymptomatic renal transplant candidates

MPI and DSE in predicting prognosis, these two imaging modalities (Table 26.2) remain central to the evaluation, with cardiac CT used in select patient populations (younger patients with no prior cardiac events, and in centers with special expertise). Coronary calcium score (alone or hybrid with other imaging modality) may refine risk further; however, how to incorporate this information on evaluation algorithms is not yet clear.

4. Estimation of functional capacity based on history, results of exercise stress testing when available, and observations during clinical evaluations. In the absence of robust data to support its routine use, cardiopulmonary stress testing should be reserved only for patients for whom the added information leads to significant changes in their candidacy for kidney transplant.

26.7 Surveillance and Perioperative Management

Clinical surveillance with frequency tailored to baseline risk for all transplant candidates for interval cardiac events, symptoms, status of risk factors, progression of pre-existing valvular heart disease, and functional capacity is appropriate.

Whether a strategy of routine screening for CAD is effective in reducing cardiac events is at best uncertain. However, most kidney transplant programs employ a rigorous surveillance protocol to identify CAD with annual stress testing for candidates with diabetes or prior cardiac events, and every 2 years for those with three or more risk factors, with the aim of decreasing perioperative myocardial infarction [110]. However, revascularization is associated with delay in renal transplant and a three to fivefold higher risk of mortality and complications than in patients without advanced CKD [7]. In addition, the negative and positive predictive values of these tests for MACE and mortality is suboptimal in advanced CKD, as noted [87]. Moreover, an observational study among 604 waitlisted kidney transplant candidates that compared symptom-guided testing with routine testing showed no difference in cardiovascular events between the two groups [71]. A large-scale trial, the Canadian Australasian Randomized Trial of Screening Kidney Transplant Candidates for Coronary Artery Disease (CARSK) (Clinicaltrials.gov NCT03674307) is enrolling kidney transplant candidates to test whether eliminating regular use of non-invasive screening tests for surveillance after initial listing is not inferior to regular screening on the waiting list to prevent MACE [111]. The 2011 scientific statement from the AHA and the ACC Foundation on cardiac disease evaluation and management among kidney and liver transplant candidates defines as uncertain the usefulness of periodically screening asymptomatic waitlisted kidney transplant candidates for myocardial ischemia to reduce risk of cardiac events [8].

In our own center, we have continued to follow the 2005 Kidney Disease Outcomes Quality Initiative [110, 112] regarding routine surveillance of waitlisted patients (annually for patients with diabetic ESRD or known CAD with incomplete revascularization, every 2 years for other non-diabetic high-risk patients, and every 3 years for lower-risk patients). We acknowledge the paucity of data to support this practice, and eagerly await the results of the CARSK trial (which could end this practice).

In patients with moderate aortic stenosis, surveillance imaging and clinical evaluation is performed earlier than is recommended for non-CKD patients because of faster disease progression at 12-month intervals.

When a candidate on the active kidney transplant waiting list is called for transplant surgery, preoperative evaluation including for intercurrent and recent cardiovascular events, new ischemic symptoms, and volume status should be performed. Preoperative 12-lead EKG should be obtained in patients with high-risk features and history of cardiac disease at baseline and compared with prior EKGs. Echocardiogram should be considered in select patients when worsening systolic function and progression of valvular heart disease is suspected and clinical assessment of volume status is challenging.

The most consequential perioperative cardiac events during renal transplant surgery include acute myocardial infarction, rhythm abnormalities (principally atrial fibrillation), and pulmonary edema [48, 50, 113]. Management strategies to reduce these events include:

1. Preoperative optimization of volume status with dialysis used as appropriate based on clinical exam and bedside ultrasound.

2. Avoiding extremes of blood pressure and heart rate with appropriate use of antihypertensive medication and pain control. Evidence suggests that use of beta blockers in CKD patients undergoing non-cardiac surgery improves cardiovascular outcomes, with benefits inversely related to renal function [114]. The 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery recommends continuing beta blockers in patients who have been on beta blockers long term as Class I, and initiating beta blockers before surgery as Class IIb in patients with intermediate- or high-risk myocardial ischemia identified during preoperative risk stratification tests, and in those with multiple risk factors including diabetes mellitus, heart failure, CAD, renal insufficiency, and cerebrovascular accident [65].
3. For candidates with stable ischemic heart disease (SIHD) already taking beta blockers preoperatively with known ischemic threshold (based on DSE), judicious use of intravenous short-acting beta blockers to keep heart rate below this threshold is reasonable [8, 65].
4. In candidates who have been on aspirin and statins, these agents should be continued preoperatively.
5. High index of suspicion for acute coronary syndrome (ACS), as symptoms are often atypical. Although routine testing for troponin is not recommended, cardiac biomarkers, EKG, and echocardiography should be strongly considered in the appropriate clinical setting. In the unfortunate occurrence of ACS, management should follow standard guidelines, including judicious use of contrast agents in the immediate posttransplant period [115].

26.8 Revascularization in Dialysis-Dependent ESRD Patients

Approaches to coronary revascularization in patients with dialysis-dependent ESRD are complex for several reasons, including markedly high mortality and complications with revascularization procedures compared with non-dialysis patients, lack of randomized clinical trials that guide evidence-based therapy, and high prevalence of atypical or absent ischemic symptoms.

26.9 Revascularization in Acute Coronary Syndrome

Among patients with ACS, those on dialysis and with advanced CKD are well known to experience worse outcomes, including higher mortality and complications, including bleeding. Despite encouraging recent trends in in-hospital mortality rates that suggest hopeful signs of decline in mortality among patients with ST elevation myocardial infarction (STEMI) [116], 2-year mortality in those who present with acute myocardial infarction is extraordinarily high at 73% [73, 116].

A substantial proportion of dialysis patients (up to 60%) do not present with chest pain, and prevalence of chest pain parallels eGFR, decreasing with worsening renal function [39]. Hence, there is need for a high index of suspicion for ACS or ischemic heart disease in general, with new onset unexplained dyspnea, heart failure that persists despite adjusting dry weight, new intradialytic hypotension/syncope that precludes achieving dry weight, new recurrent hypotension during inter-dialytic days, and new acute fatigue/weakness.

Despite the high prevalence of chronically elevated troponin (chronic myocardial injury) and frequent occurrence of abnormal baseline EKGs from left ventricular hypertrophy and electrolyte abnormalities, the diagnosis of type I myocardial infarction hinges on the demonstration of rise and/or fall of cardiac troponin with at least one value above the 99th percentile and at least one of the following: (1) symptoms consistent with acute myocardial ischemia, often atypical in ESRD patients; (2) new ischemic EKG changes; (3) development of pathological Q waves; (4) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology; and (5) identification of a coronary

thrombus by angiography, including intracoronary imaging [68]. Often, distinguishing true type I myocardial infarction secondary to plaque rupture from type 2 myocardial infarction secondary to demand-supply mismatch in the context of high pretest probability for CAD and baseline elevated troponin (chronic myocardial injury) is difficult, particularly in the setting of heart failure and hypervolemia, respiratory failure of various causes, hypotension, or sepsis syndrome with minimal fever. This conundrum may continue in some patients even after coronary angiography from lack of pathognomonic angiographic signs of plaque rupture and thrombus in the background of multi-vessel CAD with heavy calcification necessitating intracoronary imaging. Although the high incidence of atypical presentation leads to under-diagnosis and treatment of ACS, careful clinical evaluation and judicious judgment are crucial in making decisions about revascularization.

Renal function worse than stage 3B CKD is an independent predictor of presenting with acute myocardial infarction versus stable angina as the initial manifestation of CAD and among dialysis-dependent ESRD patients; 54% of revascularization procedures, both PCI and CABG, are accomplished in the setting of ACS [93, 117]. With worsening renal failure, the proportion of non-STEMI rises and comprises the major form of ACS among ESRD patients [39]. Moreover, prevalence of multi-vessel CAD in those who present with ACS is much higher than in patients without CKD [118]. It is therefore not surprising that observational data suggest improved long-term survival with CABG versus PCI in the setting of ACS. Nevertheless, revascularization modes should be dictated by type of myocardial infarction and coronary anatomy. About 20% of dialysis-dependent ESRD patients with ACS present with STEMI, and primary PCI of the infarct-related artery should be performed promptly [119]. Evidence is not yet strong to recommend non-infarct-related artery PCI unless multiple complex lesions are identified and EKG localization is uncertain or there is evidence for cardiogenic shock from pump failure, and PCI of concomitant severe stenosis is believed to improve hemodynamic stability [119]. Although DES reduces risk of restenosis and re-intervention compared with BMS, and does not reduce risk of mortality or myocardial infarction in the general population, observational data suggest that use of DES in dialysis-dependent ESRD patients may improve long-term survival, although well-founded recommendations cannot be made because of potential selection bias in using BMS for sicker high-risk patients [93]. CABG has a limited role in the acute phase of myocardial infarction, indicated only in the setting of failed PCI, severe multi-vessel CAD, or mechanical complications.

Because of risk of increasing rates of intracranial bleeding with progressive decline in renal function, and lack of efficacy and safety data on fibrinolytic agents in patients with ESRD, primary PCI is preferable over fibrinolytic agents. However, in the absence of contraindication and when PCI is not available, fibrinolytic agents should be considered in patients with STEMI with symptom onset less than 12 h and if primary PCI cannot be performed within 120 min [119]. Among pharmacologic agents used in the setting of ACS, eptifibatide, enoxaparin and fondaparinux are contraindicated while adjusted-dose bivalirudin, unfractionated heparin, and abciximab are preferred in dialysis-dependent ESRD patients.

Although the ideal time for dialysis during ACS or soon after revascularization is uncertain, it makes clinical sense to avoid hypotension and acute electrolyte shifts associated with dialysis to reduce risk of recurrent ischemia, bleeding, and arrhythmia [120]. Hence, in the absence of urgent indication, it is reasonable to delay dialysis by 24 h.

26.10 Revascularization in Stable Coronary Artery Disease

The principles of treating SIHD hinge on (1) improving symptoms and quality of life, (2) modifying the natural course such that incidence of acute coronary events is minimized, and (3) improving survival. CAD in the setting of ESRD has unique characteristics, including earlier

onset, rapid progression, intimal and media calcification, and multi-vessel involvement, presenting challenges for revascularization by PCI or CABG. Patients with advanced CKD and SIHD often have asymptomatic ischemia and are undertreated, with less frequent use of guideline-directed medical therapy and rates of revascularization ranging from 10% to 45% [121, 122]. The most effective treatment strategy between initial OMT alone versus initial revascularization is unknown, as these patients have been excluded from landmark trials comparing these treatment strategies [123]. Prevailing clinical practices are therefore derived from limited observational studies and extrapolated from cohorts without advanced CKD.

A secondary analysis of a subgroup of CKD patients enrolled in the COURAGE trial (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation), which randomized SIHD patients with coronary stenosis above 70% in at least one proximal epicardial coronary artery and evidence of ischemia to receive PCI + OMT versus OMT alone, showed high baseline risk compared with non-CKD patients, but no difference in the primary endpoints of death and myocardial infarction [124]. On the contrary, observational studies in advanced CKD patients suggest possible long-term survival benefit of revascularization with either PCI or CABG over medical therapy alone [122, 125]. However, whether the long-term survival benefits outweigh the high short-term mortality risk is unclear, and the limitations of observational studies, including selection and ascertainment bias, blur study conclusions. In addition, in these observational studies, medical therapy was not optimized, comorbidity and high risk were likely the reasons for excluding patients from revascularization, and DES was seldom used. To determine the best management strategy for patients with SIHD with at least moderate ischemia, irrespective of symptoms and advanced CKD (eGFR <30 or on dialysis), the ISCHEMIA-Chronic Kidney Disease Trial (ISCHEMIA-CKD), a multicenter, prospective randomized controlled trial comparing two treatment strategies (OMT alone versus OMT plus coronary angiography, and, where appropriate, coronary revascularization with PCI or CABG for the primary composite endpoint of all-cause mortality and non-fatal MI), has randomized 777 participants [57, 58]. The results of this trial will have significant implications for clinical practice, professional guidelines, and health policy.

Cardiologists are often consulted regarding revascularization in this cohort, where SIHD is frequently uncovered in the setting of (a) renal transplant work-up in asymptomatic patients, (b) evaluation of symptoms that are often atypical, and (c) recurrent intra- and inter-dialytic hypotension with the aim of improving symptoms, quality of life, tolerance of dialysis, or overall prognosis and candidacy for renal transplant. When making these decisions, the following salient points should be considered:

1. In patients whose symptoms are attributable to SIHD and who are on OMT, revascularization with the aim of improving symptoms and quality of life is indicated.
2. The evidence for and clinical decision making regarding revascularization in asymptomatic or minimally symptomatic patients without high-risk anatomic features that confer survival benefit, such as unprotected left main disease or multi-vessel coronary stenosis involving the proximal vessels with or without left ventricular systolic dysfunction, are less clear, as described above. However, shared decision making involving the patient, nephrologist, cardiothoracic surgeon, and interventional cardiologist in a "heart-team" approach should be central to this process.

   The long-awaited publication of the ISCHEMIA-CKD trial [126] on March 30, 2020, should cause us to reconsider our clinical approach to management of renal transplant candidates with asymptomatic myocardial ischemia (and without acute coronary syndrome). At a median follow-up of 2.2 years for the primary outcome (composite of all-cause mortality and nonfatal MI), the 3-year event rate was 36.4% for the invasive strategy versus 36.7% for the conservative

strategy (adjusted hazard ratio 1.01 [95% CI 0.79–1.21]). ISCHEMIA-CKD enrolled subjects with an eGFR <30 mL/min/1.73 m^2 (including those receiving dialysis), no recent acute coronary syndrome, and moderate or severe myocardial ischemia by cardiac stress testing, a population not dissimilar (apart from the eGFR threshold, which would be <20 for US renal transplant candidates) from patients undergoing cardiac screening before renal transplant. One key aspect of the medical treatment employed in this trial was the implementation of guideline-directed therapy (recommended for treatment of patients with ischemic heart disease in the "general" population), including intensive treatment of dyslipidemia. As in all clinical trials, the generalizability of the ISCHEMIA-CKD findings must be carefully interpreted and applied to the management of individual patients.

3. The optimal mode of revascularization in dialysis-dependent CKD patients is unknown. In patients without advanced CKD with multivessel coronary stenosis, CABG is superior to PCI only in select anatomic and clinical conditions, including unprotected left main, complex three-vessel CAD with SYNTAX score above 22, systolic dysfunction, or diabetes [127, 128]. Conversely, observational studies and systematic reviews of dialysis-dependent ESRD patients derived from the United States Renal Data System (USRDS), large state databases, and hospital systems suggest potential long-term survival benefit of CABG over PCI after adjusting for CAD severity, systolic function, and comorbidity, albeit at high short-term risk [93, 122, 129, 130]. Analysis of over 21,000 dialysis-dependent ESRD patients form the USRDS who underwent initial coronary revascularization with CABG or PCI between 1997 and 2009 showed a 10–15% lower risk of death and the composite of death or myocardial infarction with CABG [131]. In a contemporary clinical-practice registry involving 5920 propensity-score-matched patients with CKD (8.3% dialysis dependent) and multi-vessel CAD that compared CABG with PCI using everolimus-eluting stents, CABG was associated with higher short-term risk of death, stroke, and repeat revascularization, and PCI with higher long-term risk of repeat revascularization and myocardial infarction, with no mortality difference between the two strategies except in a subgroup of dialysis patients where results favored CABG over PCI [132]. Of note, however, because the survival benefit of CABG over PCI is delayed by 1 year, patients with expected short term survival at baseline are less likely to benefit from CABG [131].
4. One key aspect of surgical coronary revascularization is the apparent survival benefit associated with use of the internal mammary graft. In a large retrospective, observational USRDS study [133], the survival benefit of CABG (vs. PCI) in dialysis patients was solely attributable to use of internal mammary grafts (the implication being that the benefit of CABG is attributable to both the conduit [internal mammary graft] and the target vessel [i.e., LAD] receiving the internal mammary graft). In our opinion, this observation should guide decisions regarding potential coronary revascularization in dialysis patients. Figure 26.6 shows estimated survival of dialysis patients following CABG (related to use of internal mammary graft, drug-eluting stents, and bare metal stents).
5. Overall long-term mortality in dialysis-dependent CKD patients requiring revascularization is substantial, with 1-year and 5-year survival rates of 70% and 25% respectively, irrespective of revascularization strategies [93, 129, 131]. However, estimated 30-day mortality after CABG is twice that after PCI, at 11% and 5%, respectively, compared with 2–10 times higher for CABG and 1.7–5 times higher for PCI for non-CKD patients, underscoring the high baseline risk [131, 134].

Rates of repeat revascularization and myocardial infarction are higher with PCI, particularly in patients with incomplete revascularization [132]. In addition, the risks of myocardial infarction related to stent thrombosis with non-cardiac sur-

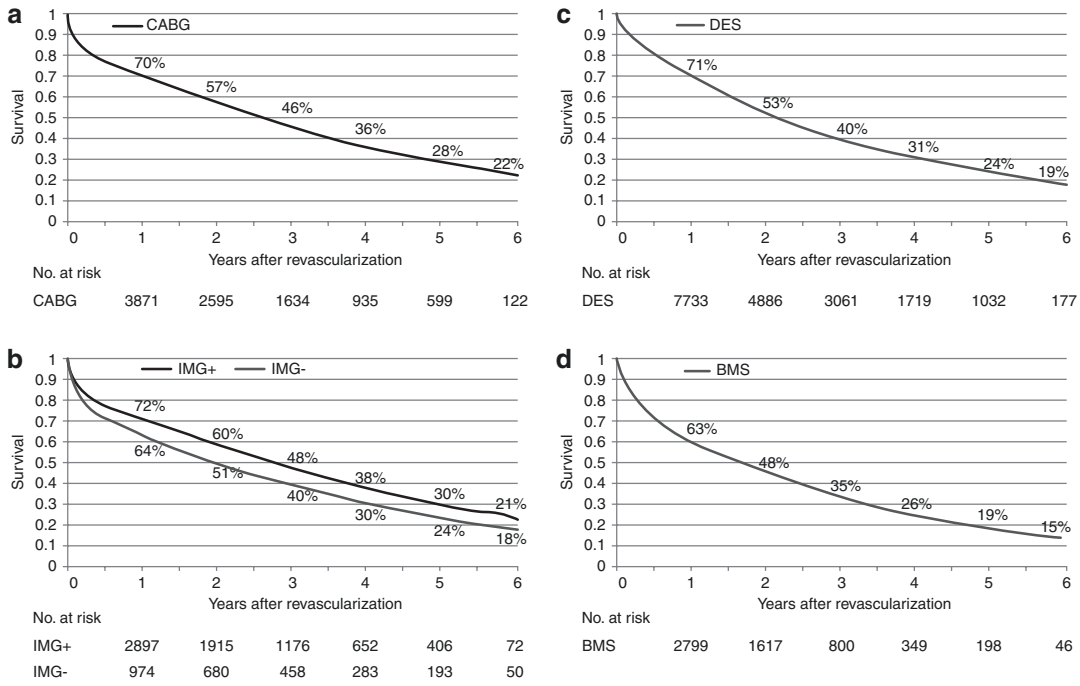


Fig. 26.6 Kaplan-Meier survival curves depicting all-cause survival after (**a**) coronary bypass surgery (**b** with or without internal mammary graft) and percutaneous coronary intervention (using **c** drug-eluting stents and **d** bare-metal stents) in dialysis patients, 2004–2009. *BMS* bare-metal stent *CABG* coronary artery bypass graft surgery, *DES* drug-eluting stent. ([133] Open access)

geries, including renal transplant, are highest in the first 12 weeks, with steady reduction thereafter. In general, such procedures should be postponed by at least 3–6 months after PCI based on the type, size, and location of stents.

26.11 Cardiac Surgery in Dialysis-Dependent CKD

Increasing numbers of dialysis-dependent CKD patients are undergoing cardiac surgery, not only because of improved survival but also because of the aging population and higher prevalence of cardiac comorbidity [135–137]. Published reports from single and multicenter studies found adjusted in-hospital mortality rates considerably higher than in non-CKD patients, ranging from 5.4% to 24% [134, 135, 137, 138]. With advances in surgical techniques and expertise, and increasing surgical volume in dialysis-dependent CKD patients, there is an encouraging trend in short-term mortality [93, 135]. Analysis of a large national US database (Nationwide Inpatient Sample database) of cardiac surgeries from 1988 to 2003 showed a sixfold decline in annual in-hospital mortality rates among dialysis-dependent CKD patients, from over 31–5.4%, despite increasing prevalence of comorbidity [135]. Nevertheless, compared with non-ESRD patients, whose mortality declined from 4.7% to 1.8% in the same time period, mortality in ESRD patients remained threefold higher.

Factors associated with higher in-hospital mortality rates include urgent or emergent surgery, combined valve or valve and CABG surgery, prior cardiac surgery, history of cerebrovascular accident, and active infective endocarditis, with 30-day mortality as high as 42% [134–139].

Perioperative management of dialysis-dependent CKD patients includes the following:

1. In view of the high prevalence of CAD, coronary angiogram should be strongly considered for all non-CABG surgeries.
2. Preoperative volume status should be optimized with the help of transthoracic echocardiogram to determine left and right sided filling pressures with dialysis as necessary [140]. This will avoid postoperative respiratory failure, ensure normal platelet function, and optimize electrolyte status, which in turn will avoid rhythm abnormality, prolonged endotracheal intubation, and bleeding.
3. Left and right heart catheterization should be performed for patients with pulmonary hypertension that appears out of proportion to volume status. Severe pulmonary hypertension is associated with worse postoperative outcomes, with risks that may be prohibitive to surgery, and requires proper evaluation and management prior to cardiac surgery.
4. Available and usable venous access sites should be sought prior to cardiac surgery and clearly documented for potential urgent or emergent continuous veno-venous hemodialysis (CVVHD), particularly for hyperkalemia and hypervolemia in the immediate postoperative period, as standard hemodialysis is less likely to be hemodynamically tolerated.
5. Careful consideration of indications for cardiac surgery is in order after evaluation of other organ systems, particularly of the liver for early cirrhosis that may compound in-hospital mortality.
6. Incidence of vasoplegia, defined as hypotension with mean arterial pressure below 60 mmHg refractory to vasopressor drugs (norepinephrine ≥0.2 μg/kg per minute or equivalent) with decreased systemic vascular resistance index below 1600 dyn s/cm^5/m^2 and high cardiac index above 2.5 L/min/m^2, is higher than in non-CKD patients after cardiac surgery [141, 142]. The mechanism is complex and linked to inflammatory and nitric oxide cascades. Risk factors may include duration of surgery on pump cardiopulmonary bypass, preoperative use of angiotensin converting enzyme inhibitors (ACE-I), and heart failure. Aggressive correction of postoperative acidosis and electrolytes with CVVHD and cautious use of methylene blue in selected cases, and avoidance of ACE-I for 48 h before surgery is recommended [141].
7. Dialysis-dependent CKD patients develop non-occlusive mesenteric ischemia more frequently than non-CKD patients [143, 144]. A high index of suspicion is needed, particularly after cardiac surgery associated with frequent hypotension. Other risk factors include aortic valve insufficiency, excessive or rapid ultrafiltration, myocardial infarction, and heart failure.

A multidisciplinary team approach from preoperative evaluation to postoperative care involving the nephrologist, cardiothoracic surgeon, cardiologist, and intensivist is crucial for optimal patient outcomes.

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27 Nephrology Inpatient Consultative Approach in Patients with Cardiovascular Disease

Janani Rangaswami

27.1 Introduction

The dual burden of kidney and heart disease (especially heart failure) is a growing epidemic resulting in escalating need for hospitalizations, advanced therapies, higher health care costs and worse clinical outcomes [1]. The clinical spectrum of hospitalized patients with heart and kidney disease extends from decompensated cardio-renal syndrome (CRS), atherosclerotic cardiovascular disease (ASCVD) related clinical syndromes in patients with chronic kidney disease (CKD), need for advanced therapies for heart failure (HF) such as inotropes, mechanical circulatory support and ventricular assist device therapies, urgent arrythmias and electrolyte imbalances in CKD and when appropriate, de-escalation of care in patients with advanced cardio-renal disease. In this context, the inpatient nephrologist plays a pivotal role in the co-management of several of these conditions including risk stratification for complex cardiac interventions, optimizing hemodynamics in decompensated HF and cardiogenic shock and providing renal replacement therapy when appropriate. This chapter discuses key areas in the care of the hospitalized patient with cardio-renal disease where a nephrologist plays a critical role with regards to medical and peri-procedural management. It also emphasizes the need for cross-specialty collaborative efforts to deliver optimal care at lower costs to reduce care fragmentation in this vulnerable population. Finally, it outlines the need for cross-training and educational/research efforts between cardiology and nephrology to reduce hospitalizations, health care costs and deliver effective clinical care in this under-served population.

27.2 Consultative Approach to the Patient with Acute Heart Failure and Diuretic Resistance

27.2.1 Pathophysiological Considerations in Acute Heart Failure

The Acute Dialysis Quality Initiative (ADQI) proposed and described a systematic classification of the clinical phenotypes of cardio-renal syndrome based on the 'primum movens' of the disease i.e. 'cardio-renal' vs 'reno-cardiac' disease. Table 27.1 describes the cardio-renal syndromes based on this outline with clinical examples of each phenotype. Amongst the phenotypes of CRS, type 1 CRS (renal impairment

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Table 27.1 Classification of the cardio-renal syndromes based on the proceedings of the consensus conference of the Acute Dialysis Quality Initiative

Phenotype	Nomenclature	Description	Clinical examples
Type 1 CRS	Acute cardio-renal syndrome	Acute heart failure resulting in AKI	ACS with cardiogenic shock and AKI
Type 2 CRS	Chronic cardio-renal syndrome	Decompensated heart failure resulting in CKD	HFrEF with recurrent hospitalizations for heart failure
Type 3 CRS	Acute reno-cardiac syndrome	Acute kidney injury resulting in acute heart failure	Acute glomerulonephritis with volume overload and increased markers of inflammation
Type 4 CRS	Chronic reno-cardiac syndrome	Chronic kidney disease resulting in chronic heart failure	CKD associated cardiomyopathy
Type 5 CRS	Secondary cardio-renal syndrome	Systemic process resulting in heart and kidney failure	Cirrhosis, amyloidosis, Fabry's disease
* "Functional" AKI	Unclear (not part of original ADQI classification)	WRF in setting of high dose loop diuretics in HF from impaired plasma refill and mesangial cell contraction	Rising serum creatinine with high dose loop diuretics in type 1 CRS with negative urine AKI biomarkers, with good CO and diuretic sensitivity.

CRS cardio-renal syndrome, *AKI* acute kidney injury, *ACS* acute coronary syndrome, *CKD* chronic kidney disease, *HFrEF* heart failure with reduced ejection fraction, *CO* cardiac output

in the setting of acute cardiac decompensation, most commonly acute heart failure), represents a major cause for hospitalizations, and may account for anywhere between 25% and 33% of patients admitted with acute heart failure (AHF) [2]. Venous congestion, sympathetic nervous system dysfunction, anemia, activation of the renin-angiotensin aldosterone system (RAAS), disruption of the hypothalamic-pituitary axis, and a marked alteration of immune and somatic cell signaling have all been implicated in the pathogenesis of type 1 CRS [2]. Symptomatic pulmonary congestion usually drives hospitalization needs as shown in the Acute Decompensated Heart Failure National Registry (ADHERE) registry wherein 50% of patients who were admitted to the hospital had a systolic blood pressure of 140 mmHg or higher, and only 2% had a systolic blood pressure of <90 mmHg, likely reflecting the sodium avid state and increased sympathetic tone associated with type 1 CRS [3]. In addition to increased afterload with a failing left ventricle (LV), chronic cardiac remodeling leads to functional mitral regurgitation, further increase in left atrial pressure and pulmonary hypertension ultimately culminating in worsening dyspnea, signs and symptoms of fluid overload and the need for acute decongestive therapies [4].

While the inability of the failing heart to generate "forward" flow with resultant pre-renal hypoperfusion has been the focal point of emphasis in the cardiac-centric primum movens model for type 1 and type 2 CRS, the critical role of renal venous congestion as a determinant of reduced GFR has been shown in older literature and confirmed in more contemporary settings [5, 6]. The ADHERE registry noted that the incidence of rising serum creatinine was similar among patients with AHF with reduced versus preserved systolic function, suggesting that a low flow state *per se* was not the only determinant of CRS [7]. Mullens et al. demonstrated that central venous congestion was the most important determinant of worsening renal function in a cohort of 145 patients admitted with AHF [8], and a *post hoc* analysis of the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial confirmed that right atrial pressure was one of the key hemodynamic metrics associated with baseline renal dysfunction [9]. These patho-physiological mechanisms are also represented in the phenomenon of diuretic resistance which is one of the key clinical challenges encountered in achieving effective decongestion in subjects with type 1 CRS from AHF. Key concepts involved in the pathogenesis of diuretic

resistance and appropriate strategies to restore diuretic efficiency are discussed in detail in subsequent sections.

27.2.2 Determinants of Renal Perfusion in Acute Heart Failure

Different hemodynamic profiles have been proposed in AHF based on the clinical phenotypes of patients as determined by adequacy of perfusion [decreased cardiac output (CO), decreased effective circulation fluid volume (ECFV), and extent of pulmonary congestion (increase in CVP or wedge pressure)]. As such, these can be combined into four distinct profiles deemed "wet or dry" and "warm or cold" [10]. While it is plausible that the cause of kidney injury in the setting of type 1 CRS may be determined by the combination of forward filling and venous congestion by these hemodynamic models, there are scarce data on the relative contributions of reduced CO and central venous pressures towards determining intra-renal blood flow distribution in AHF. In hemodynamic profiles with the "cold" phenotype, the predominant alteration in systemic hemodynamics is a reduction in CO and ECFV, and this may be accompanied by marked increase in CVP in the "wet" profile. In addition to renin-angiotensin system and systemic nervous system activation result in afferent (and relatively lower efferent) vasoconstriction leading to a decrease in renal perfusion pressure, low CO and ECFV may also be associated with low systemic blood pressure in patients with "cold" profiles [10–12]. The low resistance nature of the renal vasculature and parenchyma and very low oxygen tension in the outer medulla contribute to the unique sensitivity of the kidneys for hypotension-induced injury. In this context, it is important to note that global renal perfusion pressure (the difference between mean arterial pressure and central venous pressure) becomes the difference between mean arterial pressure (MAP) and intra-abdominal pressure (IAP) when IAP is increasingly elevated in CRS. Thus, elevated IAP, along with the vasomotor tone of the renal arterioles and precapillary sphincters (which determine renal critical closing pressure [Pcc]), ultimately influence renal end organ perfusion over and above the gradient between MAP and CVP in CRS. This is reflected in the concept of the "vascular waterfall" effect by Pinsky et al. [13]. Understanding the key balance between these factors is critical in determining strategies to optimize perfusion in patients with decompensated CRS.

27.2.3 Diuretic Resistance: Mechanisms and Clinical Approach in Worsening Renal Function with Acute Heart failure

One of the main clinical challenges encountered in achieving effective decongestion in subjects with type 1 CRS from AHF is the phenomenon of diuretic resistance (DR). DR is defined as the attenuation of the maximal diuretic effect that ultimately limits sodium and chloride excretion and is a prognostic marker for increased HF related re-admissions as well as mortality [14, 15]. Contributing factors towards generating DR include oral loop diuretic bio-availability, pharmacokinetics, baseline glomerular filtration rate, structural remodeling induced in the nephron from exposure to chronic loop diuretic therapy and impaired plasma refill. Free, unbound loop diuretics must reach the urinary lumen of the thick ascending limb and bind to the site of chloride entry to inhibit NKCC2, thus limiting the efficacy of oral diuretics in congestive states. Bumetanide and torsemide have higher bioavailability than furosemide, which demonstrates a wide range in bio-availability [16]. However, gut congestion in acute and chronic HF and food intake are under-recognized factors in DR that can prolong the time to reaching peak therapeutic drug concentrations [17]. The recent availability of alternative routes of outpatient administration of furosemide subcutaneously may offer ways to bypass this mechanism of DR [18, 19]. Hypoalbuminemia increases the vol-

ume of distribution and reduces the availability of loop diuretics (which are 95% protein bound) for facilitated diffusion. A reduction in GFR in patients with CRS does not limit the peak effect of drug delivered to the lumen *per se*; however diuretic-induced sodium excretion is reduced in these conditions due to reduced and diminished filtered load of sodium [17]. Thus, administration of higher doses of loop diuretics multiple times per day can circumvent the above limitations [20]. Finally, elevated intra-abdominal pressures (IAP) may indirectly increase CVP as well as directly 'compress' the kidneys, both leading to reduction in renal perfusion [21, 22]. Recently, Kashani et al. elegantly demonstrated the correlation between renal ultrasound based elastography and kidney intra-capsular pressure (KIP) and IAP measured directly in a swine model [23]. This approach, if validated in humans, may guide decongestive strategies in CRS based on non-invasive renal imaging to quantify KIP. Elevated IAPs have been shown to be associated with worsening renal function and DR in patients hospitalized with AHF (type 1 CRS) [24]. Reduction of IAP by therapeutic paracenteses has also been shown to improve renal function in patients with type 1 CRS, thus underscoring the importance of IAP as a treatable hemodynamic target in optimizing patients with AHF [25, 26].

The phenomenon of "diuretic braking " in patients with type 1 and type 2 CRS is another key factor contributing to DR. The braking phenomenon refers to diminished diuretic efficacy with each successive dose of loop diuretic. Sodium loss plays a role with up-regulation of proximal and distal sodium transporters, and sodium repletion can attenuate this compensation, and in turn, the braking phenomenon [27]. Indices of proximal vs. sodium reabsorption in subjects with HF treated with furosemide indicates that enhanced distal sodium transport, more than proximal transport, attenuates the maximal efficacy of furosemide [28]. This forms the basis for the use of thiazide-type diuretics to augment furosemide-induced sodium excretion [29]. Additionally, hypochloremia is an underrecognized cause of DR in patients with HF and CRS, with chloride depletion suggested as a candidate mechanism [30]. The key factors involved in the patho-physiology of DR in patients being treated for AHF are depicted in Fig. 27.1. While not formally described in the ADQI classification of the

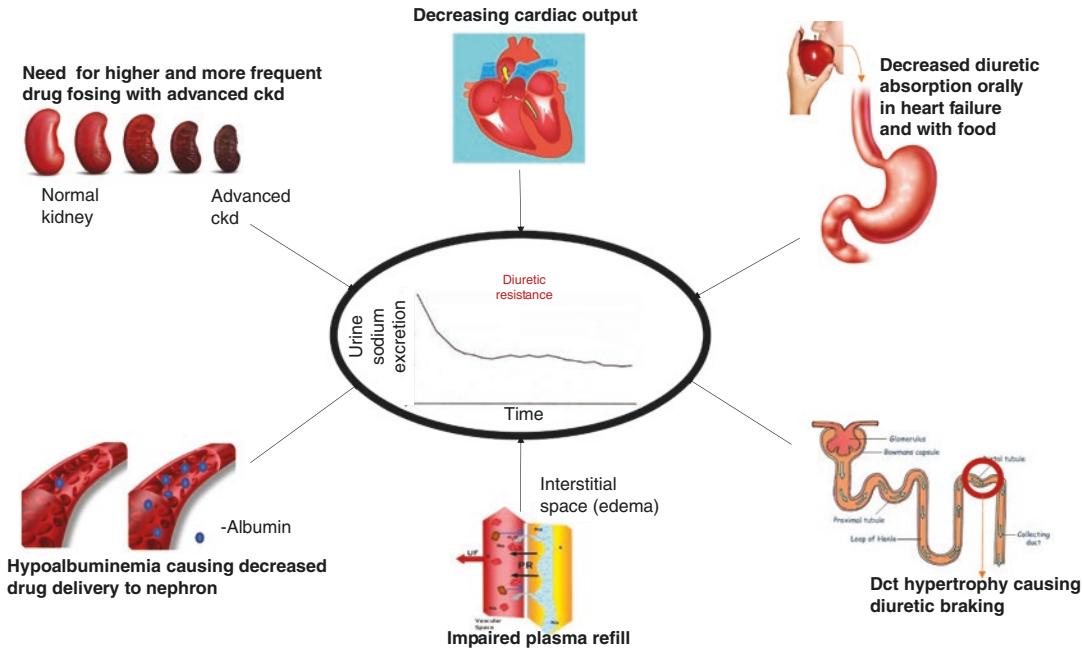

Fig. 27.1 Key clinical factors involved in the pathophysiology of diuretic resistance

cardio-renal syndromes, worsening renal function in the setting of delivering decongestive therapies and goal directed medical therapies (GDMT) in AHF represent a distinct clinical entity, wherein distinguishing between " true" vs "functional" AKI is rate limiting step in delivering optimal decongestion and optimizing myocardial mechanics and renal perfusion using GDMT. To this end, the use of biomarkers of cardiac and renal tubular injury may help distinguish "functional" AKI from impaired plasma refill and the *intended* effects on filtration fraction such as the use of RAASi from true intrinsic AKI, and help deliver GDMT in a precise fashion, thus reducing the vicious cycle of recurrent HF related admissions with its resultant long term morbidity [31].

27.2.4 Ultrafiltration for Decongestion in Acute Heart Failure: Is There a Role in Contemporary Cardio-Renal Medicine?

Ultrafiltration (UF), achieved by passing blood through hollow fibers made of semipermeable material while applying a negative pressure to the space surrounding the fibers, causes isotonic fluid to be removed from the intravascular space. The composition of ultrafiltrate contrasts with the much lower sodium content in the urine produced by loop diuretics [32], and allows decongestion without the use of loop diuretics with potential benefits including less potassium wasting, less renin and aldosterone release and increased sodium loss. The UNLOAD trial (Ultrafiltration Versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure) randomized 200 patients within 24 h of hospitalization for AHF to either loop diuretics or UF [33]. The primary end of weight loss at 48 h was significantly higher in the UF group (5.0 ± 0.68 kg vs. 3.1 ± 0.75 kg, P = 0.001), while dyspnea scores between the groups were not significantly different. There was a significant reduction in 90-day rehospitalization rates in the UF arm, a secondary endpoint. These data are in contrast with those reported by the CARESS-HF trial (Ultrafiltration in Decompensated Heart Failure with Cardiorenal Syndrome), which enrolled 188 patients admitted with AHF and worsening renal function [34], and of all randomized trials for UF in AHF, represents the only study that included patients with type 1 CRS. In this study, no significant differences in weight loss were noted between the two groups (5.5 ± 5.1 kg for diuretic group vs. 5.7 ± 3.9 kg in the ultrafiltration group, P = 0.58). The UF group had an increase in serum creatinine of 0.23 mg/dL vs a decrease of 0.04 ± 0.53 mg/dL in the diuretic group (P = 0.003). In addition, the patients in the UF group experienced a higher rate of adverse events (72% vs 53%, P = 0.03). Differences in patient selection, diuretic algorithms and inclusion criteria may explain the contrasting data reported in these trials. At this time, an " ultrafiltration first" approach to decongestion in HF or CRS cannot be recommended as first line therapy, and further studies that address the utility of UF in patients with functional diuretic resistance and frequent re-admission for AHF are necessary to see if clinically and economically meaningful outcomes can be achieved in these high-risk populations. Figure 27.2 summarizes the step-wise clinical approach to the patient with AHF and worsening renal function using a combination of clinical findings, non-invasive imaging, cardiac and kidney biomarkers, and when appropriate, invasive hemodynamic parameters.

27.2.5 Optimization Prior to Cardiac Catheterization and Cardiac Surgery: Role of the Nephrologist

With the escalating burden of atherosclerotic cardiovascular disease, there is an emergence of increasingly complex cardio-vascular interventions including percutaneous coronary and peripheral vascular interventions, trans-catheter interventions for structural heart disease (such as trans-catheter aortic and mitral valve interventions) and a spectrum of surgical options for vascular and structural heart disease. Baseline chronic kidney disease (CKD) is a common

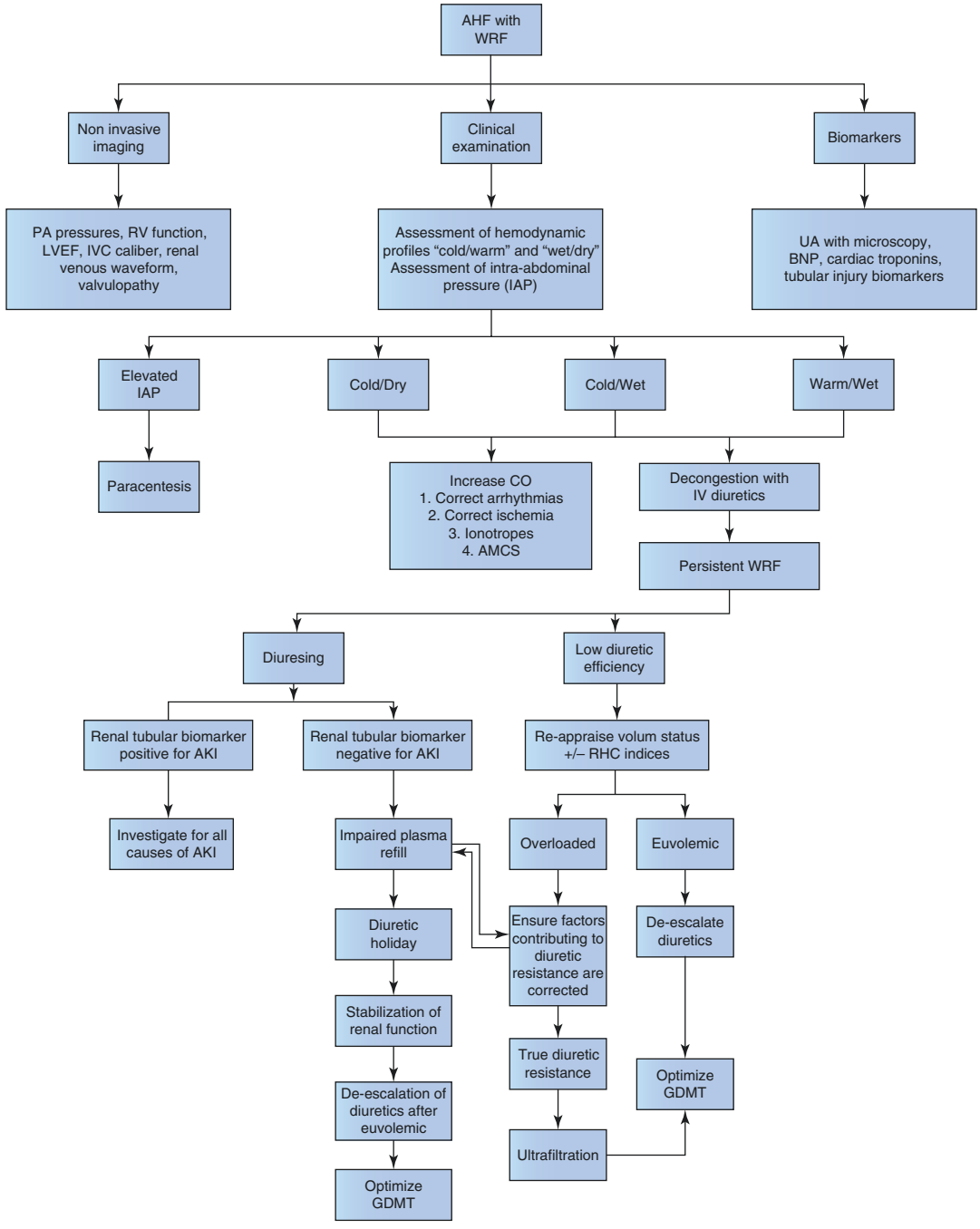

Fig. 27.2 Clinical algorithm describing the approach for the diagnosis and management of acute heart failure with worsening renal function. *AHF* acute heart failure, *WRF* worsening renal function, *PA* pulmonary artery, *RV* right ventricle, *IVC* inferior vena cava, *UA* urine analysis, *BNP* B type natriuretic peptide, *IAP* intra-abdominal pressure, *CO* cardiac output, *IV* intravenous, *AKI* acute kidney injury, *RHC* right heart catheterization, *AMCS* acute mechanical circulatory support, *GDMT* goal directed medical therapy

comorbidity in patients and several of these procedures carry a significant risk of acute kidney injury (AKI), especially in the background of CKD. The nephrologist plays an important role in the peri-procedural optimization of renal function, management of hemodynamics and volume status in these subjects and in post-procedural AKI risk reduction. Some of the salient aspects of the renal consultation in these settings are described below.

27.2.6 Reduction of Contrast Induced Acute Kidney Injury

Reduction of contrast induced acute kidney injury (CI-AKI) with percutaneous interventions in the catheterization laboratory is a major area where co-management with a nephrologist is critical. Key strategies for CI-AKI reduction include achieving euvolemia prior to the procedure, reduction of contrast media volume to the extent feasible, use of low or iso-osmolar contrast media, elimination of concomitant agents that would impact renal blood flow/filtration fraction (relative hypotension, non-steroidal anti-inflammatory drugs, renin angiotensin aldosterone system inhibitors) and involvement of experienced operators with expertise in contrast reduction techniques with these procedures [35]. In the recent literature, the Prevention of Contrast Renal Injury with Different Hydration Strategies (POSEIDON) trial [36] and the Prevention of Serious Adverse Events Following Angiography (PRESERVE) trial [37] validated an LVEDP based approach to fluid management after PCI (POSEIDON), and the choice of normal saline for intravenous fluid repletion after cardiac catheterization (as opposed to bicarbonate containing fluids), and the lack of benefit with N-acetyl cysteine for CI-AKI reduction (PRESERVE). In contrast, the A MAstricht Contrast-Induced Nephropathy Guideline (AMACING) trial which randomized 660 individuals deemed high risk for CI-AKI to receive standard hydration therapy prior to and after iodinated contrast exposure or no hydration, found no difference in the rate of CI-AKI between the two groups [38]. There is considerable concern regarding the generalizability of these findings. These include the spectrum of procedures that were included (diagnostic and therapeutic interventions), intra-arterial and intravenous contrast use and the non-inferiority design of the trial [39]. In a recent randomized controlled trial using bio-impedance plethysmography pre and post angiography and protocol based modifications of intravenous fluids based on data from bio-impedance measurements, a significant decrease in the incidence of CI-AKI was demonstrated by Maioli et al. [40]. Techniques using forced diuresis and maintenance of high urine flow rates have been shown to reduce risk of CI-AKI after angiography within conducive hemodynamic parameters [41, 42]. Statins have also been demonstrated to have a protective effect against CI-AKI [43, 44]. Ensuring that patients with non-dialytic CKD are maintained on pre-existing statin therapy prior to a scheduled cardiac catheterization should part of best clinical practices considerations [35]. Finally, there are no data showing benefit with providing hemodialysis (HD) after contrast administration, and in some instance this may lead to prolonged renal injury [45, 46]. Similarly, there are no high quality data addressing the question of preemptive dialysis initiation prior to contrast media exposure in subjects with advanced pre-dialytic CKD; how-ever a recent Markov model analysis examining the relative merits of PCI, medical management or HD initiation prior to PCI demonstrated no benefit to initiation of HD prior to PCI [47].

27.2.7 Reduction of Acute Kidney Injury After Cardiovascular Interventions: Procedural Aspects

The advent of techniques such as the recently described “zero contrast” PCI method in patients

with advanced pre-dialytic CKD utilizing minimal dosages of contrast media, have been major advances in the ability to achieve optimal revascularization in patients with advanced CKD with minimal impact on kidney function [48]. In patients undergoing trans-catheter aortic valve replacement (TAVR), several pre-existing factors impact post TAVR AKI rates including baseline CKD, high Society of Thoracic Surgeons (STS) scores, intra-procedural hypotension and transfusion requirements [49]. However, despite several risk factors for AKI after TAVR, a recent propensity score matched analysis showed that TAVRs were associated with significantly lower rates of AKI (including dialysis dependent AKI) when compared to surgical AVR [48]. The recently conducted Acute Kidney Injury after Radial or Femoral Access for Invasive Acute Coronary Syndrome Management (AKI-MATRIX) trial demonstrated the impact of radial access choice in cardiac catheterizations on reduced rates of post procedural AKI, likely driven by less risk of bleeding and athero-embolic disease [50]. In patients with stable multivessel coronary artery disease (MVCAD), staged PCIs have been favored with the rationale that this may reduce the impact on post PCI AKI by delivering less contrast volume per procedure, and the temporal separation of procedures to achieve complete revascularization. However, this approach is not backed by high quality data despite the perception of "reno-protection" based on survey data from the interventional cardiology community [51]. A single center study by Shah et al. showed that staged PCI in fact had a deleterious effect on kidney function, particularly in subjects with underlying CKD in a propensity score matched cohort study comparing ad hoc vs staged PCI for stable MVCAD [52]. Given the complexity of coronary and other vascular lesions in patients with CKD and end stage kidney disease and higher rates of post procedural complications from these interventions, a close collaboration between the general cardiologist, interventionalist and nephrologist is essential in optimizing these patients prior to these interventions and minimizing post procedural AKI.

27.2.8 Reduction of Acute Kidney Injury After Cardiovascular Interventions: Targeting Renal Blood Flow and Filtration Fraction

Renal perfusion pressure is pivotal in maintaining glomerular filtration rate as well as renal tubular perfusion. Given the possibility of variation in systemic pressures, the kidneys have the ability to autoregulate perfusion pressure at the level of the glomerulus and this is typically maintained over a wide range of systemic pressures (80–180 mmHg). These parameters are often altered and " shifted to the right" with CKD and hypertension. In a hypertensive patient, a drop in blood pressure into "normal" ranges could lead to critical drops in glomerular perfusion pressure resulting in "normotensive acute kidney injury" [53]. There is limited evidence on what the optimal peri-procedural target blood pressure range should be during cardiac catheterizations or cardiac surgery, that may reduce the risk of AKI. How-ever the Intraoperative Norepinephrine to Control Arterial Pressure (INPRESS) study which randomized 298 subjects at increased risk of postoperative complications with moderate to high risk of postoperative kidney injury undergoing major surgery, showed that targeted BP management to keep SBP within 10% of baseline SBP post-operatively reduced several clinically important adverse outcomes, including AKI and all-cause mortality [54]. Whether these data can be extrapolated into percutaneous cardiovascular interventions and cardiac surgeries remains a question for future studies. However, on this continuum, Brown and colleagues identified pre-procedural hypertension as protective against the development of AKI after coronary angiography after adjusting for several pre-procedural characteristics (OR: 0.94, 95% confidence interval 0.91–0.98) [55]. Finally, despite the need to avoid relative renal hypo-perfusion in the setting of complex cardiovascular interventions, long term optimal blood pressure control is important in reducing risk of progression of CKD and its associated complications and should be contin-

ued prior to and after cardiac catheterization in the outpatient setting [56].

Renin angiotensin aldosterone system (RAAS) inhibitors such as angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) are of particular concern in their potential to reduce filtration fraction given their mechanism of action—decrease in efferent arteriolar vasoconstriction, which limits autoregulation of intraglomerular hydrostatic pressure in the setting of reduced systemic arterial pressure. However, it must be noted that the effect of RAASi on filtration fraction occurs with minimal to no impact on renal blood flow. Bainey et al. randomized 208 individuals with moderate renal insufficiency to either withhold ACEI/ARB >24 h prior to cardiac catheterization or continuation of ACEI/ARB therapy. Withholding ACEI/ARB therapy resulted in a non-significant reduction in primary outcome (rise in serum creatinine ≥0.5 mg/dl post cardiac catheterization) and the secondary outcome (mean rise in serum creatinine post cardiac catheterization) as compared to continuing ACEI/ARB therapy the day of cardiac catheterization. However, while withholding RAASi prior to cardiac catheterization or CABG translates the stability of serum creatinine as a biomarker post procedure into an actual reduction in true intrinsic AKI or preservation of long term renal function is less clear. Coca et al. examined changes in biomarkers that represented renal tubular injury (interleukin 18, neutrophil gelatinase associated lipocalin, liver-fatty acid binding protein, and kidney injury molecule 1) following coronary artery bypass grafting (CABG) surgery in relation to maintenance, cessation or never starting an ACEI/ARB prior to CABG [57]. They found that despite a higher relative risk of a >50% or 0.3 mg/dL rise in serum creatinine from baseline following CABG in whom ACEI/ARB was continued prior to CABG (compared to non-initiation or maintenance of RAASi), there was no significant difference among the groups in markers of tubular injury following CABG. This would suggest that the clinically evident changes in renal function in the setting of RAASi are hemodynamically mediated and may not represent true renal injury. Strategies to maintain optimal renal perfusion during procedures that are high risk for bleeding, inducing hypotension and administration of contrast media may be supplemented by the use of tubular biomarkers of kidney injury in future clinical algorithms to help distinguish "functional" AKI from hemodynamic fluctuations from "true" or intrinsic AKI, thereby providing valuable information towards implementing peri-procedural nephroprotective strategies.

27.2.9 Pre-procedural Medical Optimization of Patients with Advanced Chronic Kidney Disease

Given the high pre-existing cardiovascular risk burden in patients with CKD and end stage kidney disease (ESKD), several aspects of CKD related care need careful attention during and after complex cardiovascular interventions. Pun and colleagues examined the effect of serum potassium levels and sudden cardiac arrest among patients with CKD undergoing cardiac catheterization [58]. They identified that hyperkalemia (K > 5 mEq/L) was present in about 6.5% of patients whereas hypokalemia was present in about 3.5%. After adjustment for various baseline demographic and clinical features including baseline eGFR, hyperkalemia/hypokalemia were not associated with an increase in sudden cardiac arrest within 30 days following cardiac catheterization. However, severe degrees of hyperkalemia (K > 6.5 mEq/L) would necessitate urgent corrective measures and stabilization prior to planned procedures, as this is independently associated with an increased risk of short term events [59]. In this setting, cessation of contributing drugs such as RAASi and mineralocorticoid receptor antagonists (MRA), administration of loop diuretics in patients with CKD and dialysis in the patients with ESKD would be some of the corrective measures instituted to optimize potassium balance. The availability of two oral anti hyperkalemic agents (patiromer calcium sorbitex and sodium zirconium sulfate) offers additional ability to control potassium in a narrow range in high risk patients [60, 61].

While no high quality study has addressed the question of optimal timing of planned cardiovascular interventions in subjects on dialysis, the inter-dialytic period represents the optimal time frame clinically for elective interventions with least risk of extremes of electrolytes and fluid related shifts. Similarly, obtaining invasive hemodynamic measurements in patients with ESKD on hemodialysis are best accomplished on inter-dialytic days to establish true "baseline" values to guide advanced heart failure therapies. While the reduction in post PCI AKI rates with radial site access in patients has been established from the AKI-MATRIX trial [50], a discussion with the interventional cardiologist in subjects with pre-dialytic CKD on anticipated needs for future arteriovenous fistula placement for dialysis access must be planned prior to the percutaneous intervention, to ensure availability of optimal access choice for dialysis. The importance of avoiding compression of a viable arteriovenous fistula with blood pressure cuffs and tourniquets during procedures must be emphasized in patients with ESKD on hemodialysis, as part of physician and nursing communication hand-offs prior to these procedures.

Anemia is associated with an increased risk for contrast related AKI [55] and post procedural AKI after TAVR [49]. However, given the significant thrombotic risk with erythropoietin stimulating agents (ESAs), patients with CKD and ESKD undergoing cardiovascular interventions should be maintained at pre-specified CKD related guideline based hemoglobin targets, pending any rigorous data on optimal hemoglobin targets prior to these interventions. There is a paucity of data on the timing, dosage and hemoglobin targets in subjects that are ESA dependent undergoing cardiovascular interventions in the setting of an acute coronary syndrome or shock/critical illness, wherein the risk/benefit profile of these drugs may be less than optimal due to the expected hypo-responsiveness to ESA in these inflammatory states and the endothelial toxic and pro-thrombotic nature of ESAs themselves [62].

Patients on PD should have their abdomen drained completely prior to a planned cardiac catheterization, to decrease the likelihood of inaccurate hemodynamic measurements. The importance of minimization of contrast media load to preserve renal residual function in patients on PD must be emphasized to the cardiac interventionalist team, to ensure preservation of PD adequacy after the procedure [63]. Hypokalemia is more common among patients on peritoneal dialysis [64], and maintaining normokalemia prior to cardiac catheterization in patients on PD with hypokalemia would be advisable to minimize the risk of arrythmias. Finally, patients with CKD and ESKD are at high risk for complications from severe medications given impaired excretion of renally cleared medications, underlying biological factors contributing to subtherapeutic/toxic effects (such as bleeding/clotting), drug-drug interactions and narrow therapeutic windows for several medications in CKD [65, 66]. Thus, a careful assessment of periprocedural medications especially relating to anticoagulation and antiplatelet therapy after cardiovascular interventions is critical in achieving optimal outcomes with these complex procedures. Table 27.2 outlines a summary checklist of key pre-procedural factors

Table 27.2 Multi-disciplinary evaluation checklist in patients with chronic kidney disease or at high risk for acute kidney injury prior to cardiac catheterization of cardiac surgery

Multi-disciplinary evaluation checklist in patients with CKD or high risk for AKI prior to cardiac catheterization or cardiac surgery
Has volume status been optimized to clinical euvolemia prior to the procedure ?
Has a protocol for CI-AKI reduction been instituted prior to procedure including measuring LVEDP to guide fluid therapy?
Has access route for catheterization been considered as part of nephroprotective strategies ?
Have concurrent nephrotoxic medications or interventions been reviewed and minimized prior to the procedure?
In patients with advanced pre-dialytic CKD has the use of "zero dye" PCI been considered if appropriate and available?
In patients with advanced CKD and ESKD, have electrolyte and anemia targets been reviewed and optimized prior to the procedure?
If mechanical support is used in patients with reduced EF for high risk PCIs, have the independent AKI risks with these devices been thoroughly evaluated and individual risk/benefit profiles established?

that are targets for optimization prior to cardiac catheterization or cardiac surgery to reduce the risk of post procedural AKI.

27.3 Continuous Renal Replacement Therapy for Severe Acute Kidney Injury

AKI is a major complication in critically ill patients and is encountered frequently in the cardio-renal space. Notable examples include cardiogenic shock from ACS or advanced decompensated heart failure, complications from interventional procedures or cardiac surgery, refractory arrythmias and related hemodynamic instability and multi-system involvement with sepsis. In addition to the high morbidity and mortality burden from AKI in the critical care setting, severe AKI also serves as a spring board for future CKD and ESKD with its attendant cardio-vascular risks [67]. Notably, in the setting of the need for continuous renal replacement therapy (CRRT) in severe type 1 CRS, very high mortality rates have been reported, especially in the elderly [68]. In these settings, the need for CRRT is frequently encountered and is managed with the input of the collaborating nephrologist. A detailed description of the mechanics of CRRT and its prescription are beyond the scope of this chapter, and have been described in other contexts [69, 70]. The cardiologist and nephrologist must be cognizant that several aspects pertaining to the CRRT prescription represent moving targets in the literature and in clinical practice, with conflicting supporting evidence on some counts. These include the timing of initiation of CRRT (early vs standard), optimal modality of RRT, timing of discontinuation of CRRT, best strategies to ensure optimal dosing (effluent based/clearance based prescriptions) and optimal anticoagulation methods. A concise summary of the evidence pertaining to several of these questions as well as future directions in the evolution of the field of CRRT including eventual transitioning into extra corporeal multi organ support systems (MOST), have been described by Ronco et al. [71–73]. The decision to initiate, continue and stop CRRT in the critical care setting should be based on a careful assessment of the severity and temporal course of AKI, concurrent metabolic "demand/need" balance, degree of electrolyte/volume dysregulation and underlying cardio-renal reserve in the backdrop of available evidence on the risk/benefit profiles for CRRT, rather than a "one size fits all" approach, to achieve optimal outcomes in patients with acute severe CRS.

27.4 Conclusions and Future Directions

An optimal model of health care delivery for patients in the cardio-renal interface rests on a joint cardio-nephrology interdisciplinary team approach, with leadership from both specialties providing collaborative input to integrate best practices in both specialties into patient care [74]. This is particularly true in the setting of complex cardiovascular percutaneous and surgical interventions wherein the risk of AKI, electrolyte imbalances, bleeding, clotting and arrythmias are high in the vulnerable population of patients with CKD. Integration of nephrologists as a part of the "Heart Team" will help with the pre-operative assessment and optimization, hemodynamics management and post-operative management of these complex patients. There is an urgent need for educational and research collaborations in a "cardio-nephrology" practice model to facilitate the care of patients with CKD and cardiovascular disease [75]. Incorporation of novel clinical end points such as major adverse kidney events (MAKE) and major adverse cardiovascular and renal events (MARCE) in ongoing and future clinical trials will help define best practices and interventions in this population [76]. Finally, implementing health care policy changes that emphasize the need for collaborative specialty models in cardio-renal medicine and increasing public awareness of the needs of this group of patients, will help deliver optimal and targeted care at lower costs in the future.

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