Cardio-Renal Clinical Challenges

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Foreword

Historically, cardiology and renal medicine have been regarded as separate entities and managed by independent specialist teams as a result. This new book is timely as it has become clear that an increasing number of patients are found to suffer from diseases that affect both systems. This does not occur simply by chance. Cardiovascular and renal diseases share many common risk factors and co-morbidities such as hypertension, diabetes and inflammation. These become more prevalent and cause disease progression with increasing age. Cardiovascular risk factors, together with the metabolic consequences of renal impairment, have a complex and very powerful adverse impact on the arterial wall. These effects include early arterial stiffening with medial calcification and internal changes of atherosclerosis. As a result, many patients with chronic kidney disease (CKD) now die of cardiovascular complications. Similarly, the outlook for patients who develop cardiac events, such as myocardial infarction, is much worse if they also have renal impairment. These patients represent major clinical challenges for their medical teams, for both prevention and treatment. Furthermore, there is currently little "evidence-based" medicine to guide practitioners. *Cardio-Renal Challenges*, edited by Prof. Goldsmith, brings together in a single text the views of experts on the management of a range of these problems which are frequently encountered in clinical practice. Several chapters in the first part focus on the metabolic consequences of CKD, including FGF23, calcium and phosphate, and vitamin D metabolism. Contributors also address the management of cardiovascular complication in CKD patients such as arrhythmia, sudden death, heart failure and anticoagulation issues. The second part moves on to focus on patients who present with heart disease, but who also have CKD whose management is equally challenging. Chapters in this part cover topics such as systemic and pulmonary hypertension, and renin angiotensin system (RAS) blockade. The third and final part of the book is thought provoking and challenges the reader to consider new approaches that will be required in the future for prevention, risk stratification and treatment of complex long-term diseases. The editor and the various authors should be congratulated for delivering an integrated body of work which is highly relevant to a broad medical audience, and which aims to improve patient care. It should also stimulate thinking that is not "silo based" and encourage new research from collaboration between experts from both the cardiac and renal communities.

London, UK

John Deanfield

Preface

Population ageing together with the prolonged survival of cohorts of chronically, co-morbidly challenged patients as a result of better medical and surgical treatments has meant that the two previously silo'd disciplines of cardiology and kidney medicine now find more and more of their time being spent in fruitful collaboration managing complex patients who previously would have perished hastily from their cardiac and renal problems.

Cardiorenal insufficiency is more than just an association of cardiac and renal disease, as both share many of the factors causing either and hastening disease progression of the other, such as vascular dysfunction, atherosclerotic vascular damage, inflammation, hypertension and heart failure, often worsened by physical inactivity, obesity and diabetes mellitus. Unfortunately, these challenging patients are typically not the ones we enter into the big complex randomised controlled trials of interventions, and so the evidence-base for the decisions we need to make is much too slender for comfort. In this setting, we have to rely on opinion and consensus as much as we do on high-grade evidence.

The idea of this book was to help synthesise recent knowledge and information with direct clinical relevance, comparing, contrasting and collating information which previously would have been restricted to only one of the two disciplines. There are two nice examples – the first is the vexed issue of whether or not a patient with advanced CKD and who has atrial fibrillation should be treated with warfarin. There are no trials featuring this cohort of patients. Another example is the conditions we know as "fluid" or "volume" excess. Quite what this represents, and how best to assess this in terms of the "heart" and the "kidney" components, is still remarkably tricky to achieve a consensus on. Our chapter authors in this book make some important and highly pertinent observations on both of these tricky clinical areas.

We have divided the book into three sections: one dealing with cardiac manifestations and challenges in kidney patients, another on kidney manifestations in cardiac patients, and the third with new healthcare approaches and ideas for the second decade of the twenty-first century.

In the end we tried to choose issues and concerns of direct relevance to practicing cardiologists, nephrologists, pharmacologists and internists – these are the people above all who are faced with a very unwell cohort of patients, and also with an incomplete if not contradictory evidence-framework upon which to base therapeutic clinical decisions.

We hope you will find the book both stimulating and useful!

London, UK — David Goldsmith

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Part I

Cardiovascular Disease (CVD) in Chronic Kidney Disease (CKD): Same or Different?

Epicardial Coronary Heart Disease in CKD: Diagnosis and Management

1

Rachel L. Littrell, Martin A. Alpert, and Kul Aggarwal

Clinical Case Scenario

Ms. M is a 57 year old female with a history of hypertension and chronic kidney disease, stage 3, with a glomerular filtration rate (GFR) of 40 mL/min/1.73 m^2. She has been referred to a cardiologist for evaluation of chest discomfort, which has been present for the past year. She describes brief episodes of substernal pressure and shortness of breath that occur three to four times per month, usually after moderate to strenuous exertion. Her electrocardiogram showed normal sinus rhythm with voltage evidence of left ventricular hypertrophy. Her current medications include daily aspirin, a beta-blocker, an angiotensin converting enzyme (ACE) inhibitor and a statin. What are the appropriate steps to evaluate and treat her symptoms?

Chronic Kidney Disease (CKD) and Coronary Heart Disease: General Considerations

Chronic kidney disease (CKD) is an increasingly common problem, affecting approximately 10 % of the world's population [1]. Patients with CKD are at increased risk of cardiovascular disease, and in fact, cardiac causes account for more than 50 % of deaths in CKD patients [2]. And yet, coronary artery disease remains underdiagnosed and undertreated in this population. Recognition of underlying coronary artery disease can be complicated in CKD patients because many are asymptomatic [3]. Several small studies have demonstrated obstructive coronary lesions (defined as stenosis greater than 50 % of the lumen diameter) in up to 50 % of asymptomatic patients with CKD (stages 4 and 5) [4, 5]. The paucity of symptoms may be due to a variety of factors, including neuropathy [6] and decreased exercise tolerance. In addition, subtle symptoms such as dyspnea on exertion or fatigue may be attributed to other causes, such as anemia.

The presence of CKD also predicts higher risks and worse outcomes for patients with coronary artery disease [7]. Patients with CKD who suffer myocardial infarction have increased risk of death and other adverse outcomes such as heart failure and stroke [8]. One observational study found that patients with CKD who are hospitalized for acute myocardial infarction have an adjusted odds ratio for in-hospital mortality of 1.44 when compared to patients with acute myocardial infarction without CKD [9]. Reductions in GFR are associated with increasing risk of sudden cardiac death in patients with underlying coronary artery disease [10]. The association between end-stage renal disease and coronary artery disease has been well-recognized for decades. But, it is only in recent years that we are beginning to appreciate the association between lesser degrees of CKD and coronary heart disease risk. Increased serum creatinine concentration and microalbuminuria are associated with increased cardiovascular risk [11]. Gansevoort and colleagues demonstrated this risk to be two to four times higher, even when adjusted for traditional cardiovascular risk factors [12]. These recent studies suggest that more aggressive identification and treatment of coronary heart disease should be pursued in CKD patients. This may include formally establishing CKD as a cardiovascular risk equivalent [13] and aggressively pursuing risk factor modification and secondary prevention measures in this population. There are many reasons for the increased incidence of coronary heart disease in the CKD population, some of which are not well understood. The increased cardiovascular risk may relate to co-existing risk

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factors, such as diabetes mellitus, dyslipidemia and hypertension. Other factors may include accelerated atherosclerosis, abnormal mineral metabolism, hyperhomocystenemia and increased pro-inflammatory cytokines [14]. Increased attention is also turned toward emerging risk factors related to uremia [15].

Clinical Evaluation of Coronary Heart Disease in CKD

Evaluating for myocardial ischemia in patients with CKD can be roughly divided into non-invasive versus invasive strategies. Each carries benefit and risk. It should be noted that most data regarding non-invasive cardiac testing in CKD patients come from studies of patients undergoing evaluation for renal transplantation. Table 1.1 summarizes non-invasive diagnostic cardiac testing modalities used to evaluate coronary heart disease in CKD patients. Exercise electrocardiography has limited in value in most CKD patients for a variety of reasons, including presence of left ventricular hypertrophy and electrolyte abnormalities that complicate electrocardiogram interpretation. Patients with CKD may also have decreased exercise tolerance and difficulty reaching target heart rate due to chronotropic incompetence. Exercise stress echocardiography and exercise myocardial perfusion scintigraphy (MPS) have similar exercise-related limitations. Dobutamine stress echocardiography can help provide prognostic information [16]; however, this modality may have poor sensitivity in advanced-stage CKD patients [17]. Some patients with CKD develop a hypertensive response to dobutamine. Patients with CKD are also less likely to reach target heart rate due to chronotropic incompetence [18]. Myocardial perfusion scintigraphy (MPS) using stressors such as dipyridamole, adenosine or dobutamine is commonly used, but may also have a poor sensitivity in CKD patients. In a meta-analysis, the sensitivity and specificity of MPS in patients who were candidates for renal transplantation (74 and 70 %, respectively) was lower than found with dobutamine stress echocardiography (sensitivity 79 %, specificity 89 %) [19]. Computed tomographic angiography of the coronary arteries (CTA) is of limited value in patients with CKD, due to potential nephrotoxicity of the contrast media. Also, as renal function worsens, coronary calcium scores increase [20]. This can make interpretation of CTA images more challenging, as it can be difficult to identify the vessel lumen in the setting of extensive calcification. However, in one small series of asymptomatic diabetic patients starting hemodialysis, coronary arteries were unable to be visualized only 14 % of the time [21]. In that series, multidetector row CT detected coronary stenoses ≥50 % with a sensitivity of 86 % and specificity 81 % when compared with coronary angiography. Further studies of this modality in patients with CKD are needed. Cardiac

Table 1.1 Non-invasive diagnostic cardiac testing for coronary heart disease

Imaging modality	Description	Advantages	Disadvantages	Special consideration with CKD
CT angiography of the coronary arteries	Contrast CT angiography	Non-invasive, high negative predictive value	Radiation and contrast exposure	Contrast nephropathy; often have high coronary calcium scores making this test less diagnostic
Treadmill exercise testing	ECG baseline and with exercise	Inexpensive compared to other stress tests	Baseline ECG and hypertension can lead to false positive tests	Inability to exercise adequately; left ventricular hypertrophy with ST-T abnormalities at baseline may make interpretation difficult
Treadmill exercise testing combined with echocardiography or myocardial perfusion imaging	Treadmill ECG combined with imaging	Increases sensitivity and specificity for detection of ischemia	Exercise still required	ECG part may be false positive; patient may not be able to exercise to target heart rates
Dobutamine stress echocardiography	Eliminates need for exercise with chemical stressor	LVH often makes imaging easier	Lower sensitivity	Increased incidence of intracavitary obstruction due to left ventricular hypertrophy during dobutamine infusion
Regadenoson or adenosine myocardial perfusion imaging	Eliminates need for exercise with use of pharmacologic stressor	Perfusion and scar analysis	Radiation exposure; high cost	None
Adenosine stress MRI	Eliminates need for exercise with use of pharmacologic stressor	Excellent delineation of myocardial scar as well as assessment of ischemia	High cost	Relative contraindication for administration of gadolinium in patients with CKD due to risk of nephrogenic systemic fibrosis

Abbreviations: *CT* computed tomographic, *ECG* electrocardiogram, *LVH* left ventricular hypertrophy, *MRI* magnetic resonance imaging

magnetic resonance imaging (MRI) and stress cardiac MRI perfusion are newer noninvasive options. Cardiac MRI has been shown to detect previously unrecognized myocardial infarction in patients with end-stage renal disease [22]. Stress cardiac MRI perfusion can be used to detect inducible ischemia. However, it has some limitations. In patients with arrhythmia (such as atrial fibrillation or frequent ventricular ectopy), gating problems may make the images uninterpretable. MRI also uses a gadolinium-based contrast agent. This agent is known to cause nephrogenic systemic fibrosis and is contraindicated in patients with acute kidney injury and in patients with GFR less than 30 mL/min/1.73 m^2 [23]. Cardiac enzymes or biomarkers, especially troponins, are widely used in the diagnosis of myocardial necrosis in patients suspected of acute coronary syndromes. Cardiac troponins are extremely sensitive and a rise and fall on serial testing typically accompanies myocardial infarction. Patients with advanced kidney disease on dialysis often show mild increases in troponin levels without having an acute coronary syndrome [24]. Symptoms, ECG abnormalities and rise and fall in enzymes should all be considered in arriving at the diagnosis.

Coronary Angiography

Coronary angiography offers the diagnostic standard for coronary artery disease, and offers the opportunity for intervention when appropriate. It carries risks of an invasive procedure, and some of these risks must be carefully considered in patients with CKD. Patients with CKD are less aggressively referred for cardiac catheterization due to concerns about further worsening of kidney function. In general, cardiac catheterization is indicated for patients with CKD under similar indications as for the general population. Some special considerations are addressed below.

Contrast-Induced Acute Kidney Injury (CI-AKI)

CI-AKI occurs in approximately 10–20 % of patients with CKD undergoing cardiac catheterization [25]. It is directly associated with the volume of contrast media used in the procedure [26]. CI-AKI is associated with longer hospital stays, higher costs, and worse cardiovascular outcomes [27]. Some pre-procedure properties, such as anemia and proteinuria [28], may help identify patients most at-risk for developing CI-AKI. Other known risk factors for CI-AKI include congestive heart failure, hypotension, age greater than 75 years, peripheral vascular disease and diabetes. Heart failure alone seems more predictive than GFR [29]. Periprocedural bleeding has also been shown to be associated with CI-AKI, with more severe bleeding resulting in increased incidence of CI-AKI [30]. Prevention is currently focused primarily on ensuring adequate hydration pre- and post-procedure [25]. Other strategies include limiting the quantity of contrast medium used in the procedure (for example, by using biplane angiography or adjunctive intravascular ultrasound). Complex procedures may be staged to minimize exposure to large volumes of contrast.

Risk of Bleeding

Patients with CKD have baseline platelet dysfunction that may increase the likelihood of perioperative bleeding during coronary angiography and percutaneous intervention. Patients with CKD who present with ST-segment elevation myocardial infarction have significantly higher rates of major bleeding than patients without CKD (19.3 vs 6.7 % in one large trial [31]).

Anemia

Screening for anemia is often part of the routine preprocedural evaluation for patients undergoing coronary angiography. Due to erythropoietin deficiency, patients with advanced CKD are often anemic prior to the procedure. Correction of significant anemia may be required prior to cardiac catheterization.

Technique

The femoral approach was for many years the standard approach for arterial access in the cardiac catheterization laboratory. More recently, the popularity of radial arterial access has grown as its advantages have been proven. However, the radial approach also carries the risk of radial artery thrombosis or occlusion. In patients with advanced CKD in whom dialysis may be required in the future, maintaining the integrity of upper extremity vasculature is important for future creation of an arteriovenous fistula. At this time, data are limited regarding the impact of radial arterial access on arteriovenous fistula formation in patients with CKD [32]. CKD and potential future dialysis requirements remain one factor for consideration by the interventionalist when selecting an access site in the cardiac catheterization laboratory.

Type of Stent

In patients undergoing coronary angiography who require percutaneous intervention, multiple studies have shown that placement of a drug-eluting stent, when no contraindication exists, is preferable to bare metal stent placement. Drug-eluting stent placement results in lower rates of major adverse cardiac events at 1 year [33]. The randomized, multicenter RENAL-DES study demonstrated reduced rates of clinical restenosis for drug-eluting stents compared to bare metal stents in patients with CKD [34].

Other Peri-procedural Complications

Patients with CKD have higher rates of vascular complication at the access site, particularly for femoral access sites. These complications are more likely to require blood transfusion [35]. Peri-procedural myocardial injury, as reflected by troponin levels, is also more likely to occur in patients with CKD who are undergoing elective percutaneous intervention [36]. Despite these potential complications, cardiac catheterization should be pursued when indicated. Additional risks for patients with CKD should be taken into consideration on an individual basis, but appropriate therapy should generally not be withheld in this population. The 23,262 subject SWEDEHEART trial concluded that: Early invasive therapy is associated with greater 1-year survival in patients with non-ST-elevation myocardial infarction and mild-to-moderate renal insufficiency, but the benefit declines with lower renal function, and is less certain in those with end-stage renal failure or on dialysis [37].

Surgical Intervention

Several recent studies have assessed the risks and benefits of surgical revascularization versus percutaneous coronary intervention in patients suitable for either approach. Coronary artery bypass grafting appears to have higher initial risks in patients with CKD, but the long-term outcomes appear equivalent and in some studies, better [38]. When compared to percutaneous coronary intervention, coronary artery bypass grafting has been shown, in a variety of studies, to have further benefits such as reduced revascularization, higher angina-free survival and increased vessel patency [39, 40].

Medical Treatment

Guideline-recommended medical treatment of coronary artery disease is often withheld in patients with CKD. Even many of the cornerstones of medical management of coronary artery disease are under-utilized in patients with CKD [41]. This includes anti-platelet therapy, anticoagulations, beta blockers, statins [42] and renin-angiotensin-aldosterone system blockers. The reasons are variable, but include safety concerns and the lack of high quality clinical trial data in the CKD population [43].

Aspirin

The benefit of aspirin in medical treatment of coronary artery disease is clear, and extends to patients with CKD. Its use at low dose in patients with CKD does not lead to increased major bleeding, or contribute to worsening CKD [44]. Current guidelines recommend that aspirin be prescribed for secondary prevention of coronary artery disease in patients with CKD. It may also be used for primary prevention, even in patients who require dialysis. Monitoring for gastrointestinal bleeding is reasonable.

Clopidogrel

Clopidogrel is a thienopyridine that inhibits the adenoside diphosphate receptor, and therefore helps to block platelet aggregation. Use and safety of clopidogrel in patients with CKD has been studied. Clopidogrel is recommended for up to 1 year after an acute coronary syndrome, and for a variety of other indications. Several studies have shown that clopidogrel can be used safely in CKD patients with acute coronary syndrome, with reduced mortality and without increased risk of bleeding [45]. However, a sub-analysis of the Clopidogrel for the Reduction of Events during Observation (CREDO) trial suggested that patients with mild or moderate CKD may receive less benefit from clopidogrel [46]. In addition, patients with CKD may have lower response to clopidogrel as measured by adenosine diphosphate-induced platelet aggregation, which may lead to poorer outcomes [47].

Prasugrel

Prasugrel is a third-generation thienopyridine P2Y12 receptor antagonist. It has potent P2Y12 inhibition and offers a faster time to peak effect than clopidogrel. The TRITON-TIMI 38

trial demonstrates its superiority over clopidogrel in patients with CKD and in patients without CKD but this benefit was observed at the cost of a smaller but significant increase in bleeding complications [48]. Pharmacokinetics and pharmacodynamics of prasugrel do not appear to differ between healthy subjects and patients with moderate CKD [49]. Dose adjustment in renal impairment is not necessary. There is limited published data regarding its use in patients with severe CKD.

Ticagrelor

Ticagrelor is a reversible P2Y12 receptor antagonist. Ticagrelor, like prasugrel, offers more effective platelet inhibition than clopidogrel. In the PLATO trial, ticagrelor significantly reduced the primary endpoint (a composite of cardiovascular death, myocardial infarction and stroke) at 12 months when compared with clopidogrel in patients with acute coronary syndrome [50]. Patients receiving ticagrelor in this study did not have significantly increased major bleeding but did have numerically more non-procedure related bleeding. Side effects of ticagrelor include ventricular pauses and shortness of breath. Ticagrelor is cleared hepatically and does not require dose adjustment in patients with chronic kidney disease, although there is limited published data regarding use in patients with severe CKD and end-stage renal disease.

Unfractionated Heparin and Low Molecular Weight Heparin

Heparin is frequently used in the cardiac catheterization laboratory, and is a standard of care treatment in patients with acute coronary syndrome. Unfractionated heparin is only available parenterally and requires monitoring and dose adjustment in patients with CKD [51]. Low molecular weight heparin (LMWH) has similar efficacy and more convenient dosing. However, LMWH is renally cleared and its use in patients with CKD may result in supratherapeutic levels and increased risk of bleeding. It is frequently avoided in patients with advanced CKD, and if used, does require dose adjustment based on renal function and measurement of Anti-Xa levels.

Glycoprotein IIb/IIIa Inhibitors

Glycoprotein (GP) IIb/IIIa inhibitors may improve outcomes in some subsets of patients with acute coronary syndrome. Currently available agents include abciximab, tirofiban and eptifibatide. Abciximab does not require dose adjustment for renal dysfunction; tirofiban and eptifibatide do require dose adjustment. Each of these agents has been studied in patients with CKD, but further study is needed. National Kidney Foundation clinical practice guidelines recommend abciximab or tirofiban for CKD patients who require dialysis [52].

Bivalirudin

Bilvalrudin is a direct thrombin inhibitor. In a substudy of the ACUITY trial, Bivalirudin therapy was compared with heparin plus a glycoprotein IIb/IIIa inhibitor in patients with CKD undergoing percutaneous intervention for acute coronary syndrome. There were no significant differences in ischemic outcome, but patients with CKD who received bivalirudin monotherapy had fewer bleeding events at 30 days [53]. Adjustments for renal dysfunction must be made, and patients with GFR less than 30 mL/min/1.73 m^2 were excluded from the study.

Beta-Blockers

Beta-blockers are a cornerstone of management and secondary prevention in patients with coronary heart disease. Their benefit in reducing the risk of future cardiovascular events extends to patients with chronic kidney disease [54], although their use in this population is more limited than in the general population. In one large trial, even after myocardial infarction the utilization of beta-blocker therapy declined as renal function worsened [55]. In patients with CKD and systolic heart failure, beta-blockers result in a 28 % relative reduction in all-cause mortality, and a 34 % relative reduction in cardiovascular mortality [56]. Side effects of beta-blockers include bradycardia and hypotension. Most beta-blockers do not require dose adjustment for renal impairment.

Statins

Statin therapy is recommended for both primary and secondary prevention of coronary artery disease in a wide variety of clinical scenarios. Studies of statin therapy specifically in patients with CKD are less common. A meta-analysis of statin use in patients with varying stages

of CKD demonstrated a significant reduction in fatal and non-fatal cardiovascular events in patients using statin therapy, but no overall mortality benefit [57]. One recent study of CKD patients following percutaneous coronary intervention demonstrated reduced all-cause mortality in patients prescribed statin therapy [58]. Most statins have some degree of renal excretion [59], but in general do not require dose adjustment. It should be noted that the American College of Cardiology and American Heart Association 2013 Guidelines for lipid management provide no recommendations for lipid lowering in dialysis patients due to insufficient information [60].

Renin-Angiotensin-Aldosterone System Blockers

Use of ACE inhibitors or angiotensin-2 receptor blockers is recommended for most patients with CKD, as it has been shown to slow the progression of kidney disease and may reduce cardiovascular risk [61]. Doses should be titrated carefully, and patients should be monitored for the development of hyperkalemia or hypotension.

Nitrates

Nitrate therapy may be used to treat angina pectoris. Extended release isosorbide dinitrate does not accumulate in patients with CKD and no dose adjustment is needed.

Control of Other Risk Factors

Co-existence of other conditions such as diabetes mellitus and hypertension is very common in patients with CKD. Aggressive management of risk factors is important for all patients with coronary artery disease.

Special Considerations for Evaluating Patients Prior to Renal Transplantation

Patients awaiting renal transplantation often undergo preoperative evaluation of cardiovascular status, even if they are asymptomatic from a cardiovascular standpoint. Current guidelines offer variable recommendations. This is because there is a very concerning and serious dearth of quality evidence in this important field, which relies as a result far too much on personal opinions and bias.

National Kidney Foundation clinical practice guidelines currently recommend evaluation for coronary disease (via pharmacologic or exercise stress echocardiogram or nuclear imaging testing) every 12 months for patients awaiting transplant who: are diabetic, have known coronary disease that has not been revascularized, have history of percutaneous coronary intervention, or have history of incomplete revascularization with coronary bypass surgery. Non-diabetic patients awaiting transplant who are considered "high risk" should have coronary evaluation every 24 months, and non-high risk patients every 36 months [62]. "High risk" is defined as a greater than 20 % 10 year cardiovascular event rate risk per Framingham data, and includes patients with two or more "traditional" risk factors, a known history of coronary disease, left ventricular ejection fraction $\leq$40 %, or peripheral vascular disease.

In 2012, the American Heart Association issued a Scientific Statement [63] recommending noninvasive stress testing for asymptomatic patients awaiting renal transplant who have multiple (generally accepted to be three or more) risk factors for coronary disease, which include: diabetes, prior coronary disease, greater than 1 year on hemodialysis, left ventricular hypertrophy, history of smoking, hypertension and dyslipidemia. Proceeding directly to coronary angiography in patients over the age of 40 years who are awaiting renal transplant is a class IIb recommendation per current American College of Cardiology/American Heart Association guidelines.

According to British Transplantation Society guidelines, there is no compelling evidence that pre-transplant screening for asymptomatic coronary disease prevents future cardiac events or reduces mortality after transplantation. Until better evidence emerges, they suggest that screening tests be used to identify high-risk patients for exclusion from the transplant waiting list [64].

Current European Renal Best Practice guidelines [65] recommend basic clinical data, physical exam, electrocardiogram and chest x-ray for asymptomatic, low-risk patients. Higher risk patients (older, diabetes, history of cardiovascular disease) should undergo a standard exercise tolerance test and transthoracic echocardiogram. Only those with positive or inconclusive results should then go on to non-invasive stress imaging. If stress testing is positive for ischemia, coronary angiography is recommended.

See Table 1.2 for a summary of current recommendations.

Table 1.2 Published recommendations for testing for CAD in asymptomatic kidney transplantation candidates

Reference	Recommendations
2012 AHA scientific statement	Noninvasive stress testing may be considered in kidney transplantation candidates with no active cardiac conditions on the basis of the presence of multiple CAD risk factors regardless of functional status (Class IIb, Level of Evidence C)
	Relevant risk factors among transplantation candidates include diabetes mellitus, prior cardiovascular disease, >1 year on dialysis, LV hypertrophy, age >60 year, smoking, hypertension, and dyslipidemia; the specific number of risk factors that should be used to prompt testing remains to be determined, but the committee considers ≥3 to be reasonable
2007 ACC/AHA perioperative guidelines for noncardiac surgery	No testing recommended if functional status ≥4 METS
	If functional status <4 METS or unknown, then consideration of noninvasive stress testing is recommended based on the following clinical risk factors
	Ischemic heart disease
	Compensated or prior heart failure
	Diabetes mellitus
	Renal insufficiency
	Cerebrovascular disease
	Recommendations for testing are stronger if ≥3 clinical risk factors are present but may be considered in those with 1–2 risk factors
2005 NKF/KDOQI guidelines	Noninvasive stress testing recommended for
	All patients with diabetes; repeat every 12 months
	All patients with prior CAD
	If not revascularized, repeat every 12 months
	If prior PCI, repeat every 12 months
	If prior CABG, repeat after first 3 year and then every 12 months
	Repeat every 24 months in "high-risk" nondiabetic patients defined as
	≥2 traditional risk factors
	Known history of CAD
	LVEF ≤40 %
	Peripheral vascular disease
2013 European best practice guidelines	Low risk patients should have basic clinical data, physical exam, electrocardiogram and chest x-ray. Higher risk patients (older, diabetes, history of cardiovascular disease) should undergo a standard exercise tolerance test and transthoracic echocardiogram.
	Those with positive or inconclusive results should undergo non-invasive stress imaging
	Coronary angiography recommended if stress imaging is positive
	Revascularization advised if lesions are suitable

Adapted from table published in Journal of American College of Cardiology 2012 by Lentine et al. [64] … and used with permission from Elsevier…

ACC American College of Cardiology, *AHA* American Heart Association, *AST* American Society of Transplantation, *CABG* coronary artery bypass grafting, *CAD* coronary artery disease, *KDOQI* Kidney Disease Outcomes Quality Initiative, *LV* left ventricular, *LVEF* left ventricular ejection fraction, *METS* metabolic equivalent tasks, *PCI* percutaneous coronary intervention

Back to the Clinical Case

The patient mentioned at the beginning of this chapter underwent treadmill exercise testing with nuclear imaging due to baseline ST-T abnormalities. The test showed moderate reversible ischemia in the antero-apical region. She was scheduled for cardiac catheterization. Pre-procedure hydration with 1,000 ml of normal saline was administrated prior to the procedure. Coronary angiography showed an 80 % stenotic lesion in the mid-left anterior descending artery and she underwent deployment of a drug-eluting stent, resulting in relief of her symptoms. Her serum creatinine remained stable post-procedure.

Summary and Conclusions

Coronary heart disease is highly prevalent in the CKD population and is the leading cause of death in this population. Clinical presentation may be atypical with symptoms such as fatigue and shortness of breath. The electrocardiogram is often abnormal due to pre-existing left ventricular hypertrophy and electrolyte disturbances. Modality of stress testing has to be considered carefully, taking into account ability to exercise and baseline electrocardiogram. Indications for medical management and coronary angiography mostly parallel those in patients without CKD and should be implemented. Coronary angiography and percutaneous coronary intervention are becoming safer and are effective, especially in patients with acute coronary syndromes. Pre-procedure hydration and use of bivalirudin and drug eluting stents should be considered. Attention to dose adjustment for some drugs, especially anticoagulants, is needed in order to reduce bleeding complications.

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Small Vessel Disease in CKD, Diabetes, Obesity and Hypertension

2

Reza Aghamohammadzadeh, Emma C. Wylie, and Anthony M. Heagerty

Clinical Case Scenario

78 year old moderately obese previously smoking gentleman is referred to the renal clinic for progressive deterioration in renal function. Over the past five year his eGFR has declined from 45 to 30mls/min/1.73 m^2. His past medical is remarkable for type 2 diabetes which is quite well managed with a HbA1C of 62 mmol/mol, while his hypertension is poorly controlled despite 4 antihypertensive drugs. His blood pressure is 174/76 mmHg and he has microalbuminuria (35 mg/mmol).

In the Western world diabetes and hypertension are the most common causes of renal disease and the consequent need for renal replacement therapy. Obesity has emerged as one of the major healthcare challenges afflicting the populations of developed and developing countries alike. In the clinic setting, obesity is seldom seen in isolation; rather it is often encountered together with diabetes mellitus, or impaired glucose homeostasis, and hypertension, a constellation of diseases defined as the metabolic syndrome. The disease entities under the umbrella of the metabolic syndrome each contribute to small vessel changes that ultimately lead to end organ damage including renal failure.

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What Has Occurred in This gentleman's Kidneys over the Antecedent Years, and How Could This Have Been Prevented?

It is estimated that somewhere between 1 and 5 % of patients with hypertension, depending on BP cut-offs and co-morbidity, go on to develop end-stage renal disease (ESRD) [1, 2]. This clearly suggests that there are different responses to hypertension which may be in part due to both genetic and concurrent environmental factors [3]. The presence of diabetes is of paramount importance given that in combination with hypertension, it has a particularly deleterious effect. A unique and important characteristic of the kidney is the ability to maintain a steady glomerular filtration rate over a wide range of perfusing pressures, this auto-regulatory response is essential in preserving normal renal function. The ability of the glomerulus to protect itself from systemic hypertension has been largely attributed to the degree to which the afferent arteriole can auto-regulate in response to a high systemic BP load [4, 5]. The mechanisms underlying this are incompletely understood, however there are at least two, the fast myogenic response and the slower tubuloglomerular feedback [6, 7]. When these systems are overloaded there is progressive glomerulosclerosis with ischaemic loss of functional nephrons [8].

Renal blood flow and the integrity of the glomerular membrane barrier are the main determinants of glomerular filtration rate (GFR) and albuminuria. Under normal circumstances, renal autoregulation allows for a stable renal GFR despite large fluctuations in renal blood flow which occur as a consequence of changes in blood pressure during the normal cardiac cycle. Caution should be applied when using GFR as a surrogate marker for assessment of renal function in diabetes. In early diabetic nephropathy, dysfunctional autoregulation is observed in the form of hyperfiltration which is present in up to 66 % of individuals with type1 diabetes and precedes albuminuria. Hyperfiltration can compensate for reduced number of nephrons or a dysfunctional membrane barrier and result in a normal GFR in a clearly diseased setting [9, 10].

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Small Artery Function and Dysfunction: Remodelling, Myogenic Tone and the Endothelium

In uncomplicated hypertension, the increase in intraluminal pressure leads to eutrophic inward remodelling. There is no change in the number of smooth muscle cells in the arterial wall, nor is there a contribution in the form of hypertrophy. The re-orientation of vessel wall constituents means that the vessel cross-sectional area remains the same; however there is an increased number of smooth cell layers and a decreased internal diameter of the vessel [9].

A key player in the autoregulation of renal blood flow is myogenic tone. This is the ability of small vessels (internal diameter <300 μm) to constrict in response to a range of physiological pressures independently of neurohormonal interference. The renal afferent arteriole vasoconstricts in response to increased luminal pressure with a stepwise increase in myogenic response [11, 12]. The myogenic response occurs in three phases: (1) Calcium influx through the L-type voltage gated calcium channels results in a large increase in intra-cellular calcium and attendant changes to membrane potential; (2) Myogenic reactivity: there is no change in intracellular concentrations of calcium, however the mechanical apparatus within the cell becomes more sensitive to calcium resulting in a further constriction in response to an increase in intraluminal pressure; (3) Forced dilatation: the arterial wall is unable to maintain a constriction against increasing pressures resulting in vessel dilatation. In the presence of an intact myogenic reflex, raised blood pressure results in eutrophic remodelling of the vessels and has a protective effect on the downstream organs including the kidneys by limiting the transmission of the raised pressures. In pathological states, when the myogenic response breaks down, there is a shift away from eutrophic towards hypertrophic remodelling where there is also an increase in wall thickness but there is no reduction in lumen diameter and the elevated central pressure will be transferred directly to the microcirculation resulting in pressure-related damage to organs such as the glomeruli [9, 10].

The mechanisms involved in vascular remodelling are numerous. Of note, integrins play a key role in the myogenic process and wall remodelling. Integrin $\alpha_5\beta_1$ is implicated in the initial influx of calcium necessary for basal vessel tone establishment, and integrin $\alpha\upsilon\beta_3$ mediates force maintenance via calcium sensitisation of contractile apparatus during the myogenic reactivity phase [13] and is necessary for the pressure induced inward remodelling process. Further research has highlighted the potential involvement of the epithelial sodium channel (ENaC) and related proteins such as the acid-sensing ion channel proteins [14].

In patients with type 1 or 2 diabetes mellitus and co-attendant hypertension, growth of the arterial wall occurs in an outward fashion with an increase in wall thickness and preservation of the lumen diameter (hypertrophic remodelling) [15, 16]. It is important to note that no such structural changes are observed in patients with diabetes but normal blood pressure. A 10-year follow-up study of patients with type 1 diabetes has shown that improved metabolic control leads to eutrophic remodelling and an increase in vessel distensibility, thus the patients benefit from a reduction in transmission of the elevated central blood pressures to end organs [9]. Studies have shown that in hypertensive patients with diabetes, a significant regression of vascular remodelling of small resistance arteries is achieved with drugs blocking the renin-angiotensin system (angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers) [17].

Co-attendance of obesity and diabetes confounds vascular remodelling. Similar to patients with diabetes, obese patients demonstrate an increase in media-to-lumen ratio in keeping with hypertrophic remodelling [18]. Interestingly, persistent weight loss following weight reducing surgery is able to regress these vascular changes as well as improve metabolic parameters including insulin sensitivity [19].

Endothelial Dependent Mechanisms

The endothelium is the lining of all blood vessels throughout the body and is highly specialised to each vascular bed. Even within the kidney there are different specialised endothelial beds with unique adaptations; these include the glomerular, peritubular and juxtamedullary capillaries [20].

It has long been recognised that there is widespread endothelial dysfunction found in patients with CKD [21], this applies not only to patients with significant CKD (stages 2–5) [22, 23] but may also be found in individuals with normal excretory renal function and only microalbuminuria, a potent predictor of cardiovascular disease [24] and progression of kidney disease in both the diabetic and non-diabetic population [8, 25]. Endothelial dysfunction evaluated as vasodilator response to acetylcholine has also been reported in the obese population thus confounding the pathophysiology observed in patients with the metabolic syndrome [18]. The exact mechanisms and causality remain to be fully determined; however it is clear that there is a complex interplay between low grade inflammation and endothelial activation. There is either increased production and/or accumulation of a variety of cytokines and endothelial activators, including, but not limited to, vWF, TNFa [26] and ADMA [27].

Glomerular Endothelial Changes in Diabetes

The exact nature and pathophysiology of diabetic small vessel disease is beyond the scope of this chapter; however there is a complex interplay between oxidative stress, endothelial dysfunction [28] and vessel remodelling.

An important feature of this small vessel disease within the kidney in diabetes is aberrant vasodilation of the afferent arteriole and impaired renal auto-regulation allowing greater transmission of systemic pressures to the glomerular capillaries [29]. This contributes to glomerular hyperfiltration, one of the earliest features of pre-diabetic nephropathy [30] as previously introduced.

An emerging player in the evolution of diabetic nephropathy would appear to be the glomerular endothelium with its fenestrations covered by the endothelial glycocalyx [31], a highly specialised extra-cellular matrix which covers all endothelial cells [32]. The endothelial glycocalyx, including that within the glomerulus, is an important molecular sieve, permitting selective filtration of plasma constituents from the blood into the interstitium [33]. Damage to this endothelial glycocalyx causes increased passage of proteins which may be pivotal in the development of disease, and indeed hyperglycaemia has deleterious effects on the glycocalyx causing shedding from the endothelial surface and increased macromolecule permeability [34].

Retinal Microvasculature and Cardiovascular Risk

The retinal microcirculation provides a non-invasive and readily accessible window to the human microvasculature and the recent advances in imaging technology using computer-based analysis of retinal photographs allow retinal vascular calibre to be quantified in a reproducible way. Changes in retinal vascular calibre are associated with demographic factors such as age and ethnicity, and more recently genetic factors have been implicated [35]. However, changes such as narrowing of retinal arteriolar calibre, enhanced arteriolar wall reflex and wider venular calibre are associated with the metabolic syndrome [36, 37] and its components such as larger waist circumference [38, 39], higher triglyceride levels [39], diabetes and hypertension [38, 40], as well as stroke [41, 42], coronary microvascular disease [43] and coronary artery disease [44]. Retinal microvascular changes can even predict subsequent vascular events following ischaemic stroke [45]. These changes are also observed in the paediatric and adolescent population [46–48]. Although fewer data are available from individuals with CKD, retinal microvascular signs such as venular dilatation are associated with CKD both in the presence and absence of diabetes, thus reinforcing the link between renal and retinal microvasculature independently of diabetes [49]. Furthermore, associations have been observed between CKD and a greater decrease in central retinal venular equivalent over time [50]. In a study of adolescents with type1 diabetes but normal albumin excretion rate and no retinopathy at baseline, higher venular length-to-diameter ratio and lower simple tortuosity independently predicted incident renal dysfunction [51]. In a further study, arteriovenous (AV) nicking and opacification were associated with lower eGFR, and a smaller fractal dimension and presence of focal arteriolar narrowing, AV nicking and opacification were associated with higher albumin/creatinine ration. Moreover, narrower retinal arterioles, smaller fractal dimensions and focal arteriolar narrowing as well as AV nicking and opacification were shown to be associated with higher likelihood of having microalbuminuria [52].

In conclusion, this non-invasive tool can be utilised to predict outcomes in diseases with cardiovascular complications and further longitudinal data are required to assess the ability of retinal studies to predict future event rates in patients with CKD.

Inflammation and Perivascular Adipose Tissue

The contribution of low grade inflammation to hypertension has been identified as a potential new pathophysiological process implicated in vascular remodelling in diseases obesity and hypertension. Studies have shown that both innate and adaptive immune systems may be play a role and T cells have been identified as important players. The balance between Th1 effector lymphocytes and Treg lymphocytes may be crucial for blood pressure elevation and consequent organ damage development. Activated Th1 cells may contribute to damage to the vasculature, kidney and perivascular fat. Tregs represent exhibit an anti-inflammatory role offering protection from blood pressure elevation and from the development of organ damage, including micro and macrovascular alterations. Inflammation results in vascular remodelling through cytokine activity, smooth muscle cell proliferation and oxidative stress [53].

For years, fat cells or adipocytes found throughout the body have been dismissed as mere energy stores; however a growing body of evidence suggests that fat cells are engine rooms producing and secreting a number of metabolically active substances with both endocrine and paracrine properties. Surrounding almost every blood vessel in the human body are white adipocytes which together with a number of other, predominantly inflammatory, cells are collectively termed perivascular adipose tissue (PVAT). It is now recognised that PVAT not only provides mechanical support for any blood vessel it surrounds but also secretes vasoactive and metabolically active cytokines known as adipokines which regulate vessel function and affect vessel tone in health and disease. The emergence of obesity as a major challenge to our healthcare systems has contributed to the growing interest in adipocyte dysfunction with a view to discovering new pharmacotherapeutic agents to help rescue damaged PVAT function and enhance its vasorelaxant effect. PVAT function has been investigated in mammals including dog, pig and rat

models as well as some ex-vivo, in-vitro studies of human blood vessels [54, 55]. There are a number of functional and structural characteristics of PVAT which vary between species and anatomical site. Recent studies have reported that healthy human PVAT can exert a local vasorelaxant effect on adjacent blood vessels and elegant pharmacological protocols have suggested that adiponectin [56], angiotensin 1–7 [57, 58] and hydrogen sulphide [59] may all be implicated. The mechanism of action of these molecules in this context remain to be clarified, however our most recent data has highlighted the pivotal role of the large calcium sensitive potassium (BKCa) channel in facilitating the action of adiponectin as we have demonstrated that absence of BKCa leads to a loss of normal PVAT relaxing function. Furthermore, microelectrode studies of de-endothelialised rat mesenteric vessels have shown that in constricted arteries, the hyperpolarisation to exogenous adiponectin is inhibited by selective blockade of BKCa [60]. In support of this theory, there is evidence that stimulation of the $ß_3$ adrenoreceptor, which leads to a degree of lipolysis, releases a factor which indirectly activates myocyte BKCa channels. In obesity adipocytes hypertrophy and angiogenesis does not keep up with the increase in adipocyte growth, thus rendering fat cells hypoxic and inflamed [56]. There is evidence of increased macrophage numbers, higher concentrations of TNFα, heightened oxidative stress levels and loss of normal PVAT vasorelaxant activity in obesity. In support of this proposed theory, in models where there is a reduction or absence of activated macrophages PVAT anticontractile function is preserved despite induced inflammation by hypoxia protocols [61]. Intuitively, one would conclude that the abolishment of PVAT vasorelaxant effect would result in an increase in basal vessel tone, contributing to peripheral vascular resistance in obesity. Weight reducing (bariatric) surgery is associated with a restoration of normal PVAT vasorelaxant function despite patients remaining morbidly obese [62] and there is clear evidence from several laboratories that the loss of anticontractile activity can be rescued using either antioxidants such as superoxide dismutase [62], or inhibitors of the renin angiotensin system or antagonists of the angiotensin II receptor as well as aldosterone blockers. There is the possibility of the prevention of diabetes as a result of introducing agonists that can preserve PVAT vasorelaxant function and adiponectin analogues pose the greatest potential in the cohort of patients with the metabolic syndrome as this molecule can potentially treat obesity-related hypertension by helping to reduced basal vessel tone and offering anti-diabetic effects in this cohort.

"What Importance Does This Have for Our Patient in Clinic? And What Further Advice Can We Offer?"

It is known that patients who are seen in renal clinics have a slower progression of renal dysfunction and improved patient survival [63]. Lifestyle assessment and modification should form part of all outpatient consultations. The Joint British Societies [64] have published extensive guidelines regarding lifestyle advice in primary and secondary cardiovascular prevention. These also apply to patients with all forms of CKD.

Of particular note is that exercise has been demonstrated to reduce mortality and improve health-related quality of life in patients with CKD [65, 66] whether this acts solely through improvement of arterial stiffness [67] or also has beneficial effects on the microvasculature remain to be determined.

In this context it would be easy to focus on the immediate problems of improved glycaemic and blood pressure control; however, to reduce vascular dysfunction and improve survival it is important to reduce all risk factors by implementing measures such as smoking cessation, a healthier diet and increased levels of exercise. Large clinical trials (e.g. HOT and UKPDS) have recommended maintaining blood pressure below 130/80 in individuals with diabetes [30], and more recently, the European Society of Hypertension guidelines (2013) [68] state emphasise a systolic BP target of <140 mmHg in all while <130 mmHg should be considered in the presence of overt proteinuria. Individual targets should be set lower for younger high risk patients but these might not be deemed safe in the elderly population at risk of complications from a low BP.

Lowering cholesterol using statins in the at-risk population is also of paramount importance to reduce cardiovascular risk and overall morbidity and mortality. Beyond their lipid lowering effects, it is postulated that statins might have a role in treating adverse microvascular changes such as endothelial dysfunction encountered in CKD, diabetes and obesity [69]. This is partly explained by their ability to reduce caveolin-1 expression in endothelial cells thus promoting nitric oxide production [70, 71] and also via their anti-inflammatory effects by reducing superoxide generation on endothelial cells [72].

A recent systematic review and meta-analysis of statin use in CKD patients has shown a significant relative risk reduction in cardiovascular events, coronary events and cardiovascular or all-cause deaths [73].

In conclusion, microvascular disease is a major concern in CKD and metabolic syndrome and its components. A multi-faceted and holistic approach must be taken when assessing and treating patients with these disorders in order to reduce their cardiovascular risk.

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Sudden Cardiac Death and Arrhythmia in CKD

3

Sean P. Martin and Patrick S. Parfrey

Clinical Case Scenario

On a Monday evening, paramedics were sent to a residential home after a frantic woman calls 911 explaining that her husband had suddenly collapsed and was unresponsive. Upon arrival, the paramedics discovered a 59 year old who was pulseless. A rhythm strip revealed ventricular tachycardia. The patient was defibrillated, but remained pulseless and died.

The patient had end stage kidney disease for the past 7 years and was treated with hemodialysis for 3.5 h on Mondays, Wednesdays and Fridays. He also had a 10-year history of type-2 diabetes mellitus, hypertension, dyslipidemia, peripheral vascular disease, benign prostatic hypertrophy, but no known cardiac history. Medications included subcutaneous insulin, enteric coated aspirin, atorvastatin, long-acting nifedipine, terazosin, ramipril, calcium carbonate, intravenous calcitriol and intravenous epoetin alfa. There were no known drug allergies. The patient was a lifelong non-smoker and consumed ethanol socially. He was non-compliant in the use of calcium carbonate.

Predialysis serum potassium was generally 5.5–6 mmol/L. Intradialytic weight gain was, on average, 2.3 kg but on this Monday it was 3.5 kg. His dry weight had been stable, pre-dialysis blood pressure was on average 170/95 and post-dialysis levels were 130/80. Dialysate potassium was 1 mmol/L and dialysate calcium was 1.25 meq/L. Kt/V was 1.2.

The most recent bloodwork revealed serum potassium 5.9 mmol/L, sodium 138 mmol/L, bicarbonate 19 mmol/L, albumin 25 g/L, serum inorganic phosphate 3.2 mmol/L, serum calcium 2.4 mmol/L, and plasma parathyroid hormone 732 pg/mL. The C-reactive protein was moderately elevated for the past 2 years. The hemoglobin level was within target at 11 g/dl. HbA1C was 8.3 %.

Post mortem analysis revealed diffuse coronary artery disease with calcification, no critical stenosis, severe left ventricular hypertrophy with mild left ventricular dilatation, and severe cardiac fibrosis.

Introduction

Sudden cardiac death (SCD) is defined as unexpected natural death from cardiac causes within 1 h of sudden loss of consciousness [1]. The United States Renal Data System (USRDS) includes "cardiac arrest/cause unknown" and "arrhythmia" in its definition of SCD and reported that SCD was the leading cause of death in hemodialysis patients, accounting for 26 % of all cause mortality [2]. CKD is a risk factor for SCD. The Cardiovascular Health Study assessed 4,465 community-based participants without a history of CHF or MI and found that the incidence of SCD was >2.5 fold higher in those with decreased eGFR [3]. The MADIT-II study involving patients with a previous myocardial infarction reported increased rates of SCD in those with decreased GFR and advanced heart failure [4]. Furthermore, in 19,440 patients who had undergone cardiac catheterization, rates of SCD increased as eGFR decreased [5] (Fig. 3.1).

Atrial and ventricular arrhythmias are also a very common phenomenon in individuals with CKD. The prevalence of atrial fibrillation in hemodialysis patients is increasing (reported rates are 7–20 %), thus increasing the risk of ischemic stroke and death [6]. Multiple small studies have

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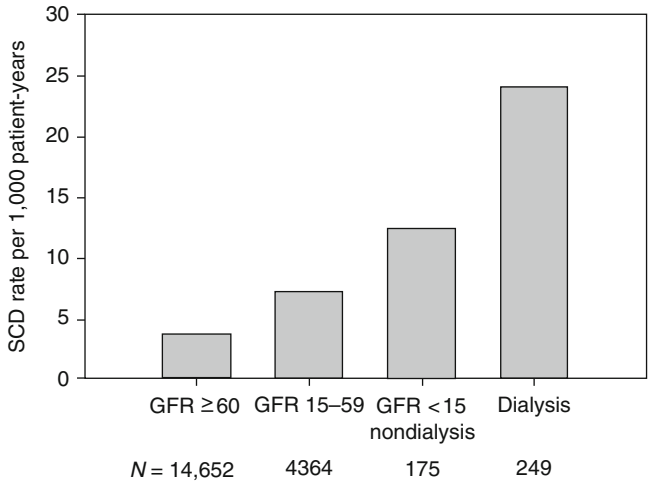

Fig. 3.1 Sudden cardiac death rate according to stage of chronic kidney disease. Rates shown as events per 1,000 patient-years and were as follows: eGFR ≥60 ml/min, 3.8 (95 % CI: 0, 8); eGFR 15–59 ml/min, 7.3 (95 % CI: 2, 13); eGFR <15 not on dialysis, 12.5 (95 % CI: 5, 20); and dialysis, 24.1 (95 % CI: 14, 34) (Reprinted by permission from Macmillan Publishers Ltd: [KIDNEY INTERNATIONAL] (Pun et al. [5]), © (2009))

assessed ventricular arrhythmias in hemodialysis patients with reported rates of 5–75 % during HD treatments [7, 8].

The very high rate of cardiovascular death and the substantial contribution of SCD to these rates in patients with CKD and ESRD is not fully explained by the high prevalence of traditional cardiac risk factors including hypertension, smoking, diabetes and dyslipidemia [9, 10]. This chapter focuses on the cardio-renal interplay that predisposes to SCD and examines the evidence for prevention and intervention.

Risk Factors and Mechanisms

Sudden cardiac death occurs in patients who encounter stressors to a vulnerable myocardium (Fig. 3.2) [11]. The predisposition for arrhythmias and SCD increases as CKD deteriorates. Also, the hemodynamic and metabolic milieu present in patients undergoing dialysis is multifaceted, complex and malignant [12]. These patients develop cardiomyopathy with diastolic and systolic dysfunction, fibrosis and vascular disease. In addition, sympathetic overactivity, inflammation, abnormalities in mineral metabolism, electrolyte shifts, hyper/hypovolemia, and QT prolongation together predispose to arrhythmias and SCD [13, 12].

Coronary Artery Disease

In the general population, coronary artery disease (CAD) is an important cause of SCD. In patients with CAD, for each 10 ml/min decrement in eGFR the risk of SCD increased by 11 % [5]. CAD is present in at least 38 % of the prevalent dialysis population [14]. In these patients, the intra- and post-dialytic period is associated with a high frequency and lengthy persistence of ventricular arrhythmias [15]. However, unique factors other than CAD likely contribute to the increased risk of SCD in ESDR patients [1].

Arteriosclerosis and Arterial Calcification

Arteriosclerosis occurs frequently in patients with CKD and ESRD and is characterized by diffuse dilatation, wall hypertrophy and stiffening of the aorta and large central arteries. Arterial stiffening leads to increased systolic and decreased diastolic blood pressure. This widened pulse pressure has two major results; (1) left ventricular hypertrophy from increased systolic blood pressure and (2) diminished coronary and subendothelial blood flow during diastole [16, 17]. Arteriosclerosis and increased vascular stiffness in adults with CKD is more related to age, systolic blood pressure, diabetes and vascular calcification rather than uremic toxicity [18].

Arterial calcification is associated with cardiovascular death and SCD in patients with ESRD [19]. In CKD and ESRD patients, metastatic vascular calcification occurs as a result of an elevated calcium phosphate product, diabetes, dyslipidemia, oxidative stress, uremia, hyperphosphatemia and elevated promoters of calcification in the vessel wall [20]. Two major types of arterial calcification occur: patchy calcification of the intima associated with atherosclerotic plaques and diffuse calcification of the media, in the absence of cholesterol deposits, associated with arteriosclerosis [20]. Vascular calcification worsens as CKD progresses [18], resulting in a loss of arterial elasticity, increase in pulse wave velocity, left ventricular hypertrophy, decreased coronary artery perfusion and myocardial ischemia [20].

Microvessel Disease

Compared to non-uremic controls, an autopsy study of a small group of deceased dialysis patients reported inadequate capillary growth relative to the degree of cardiac hypertrophy [21]. Therefore, uremic patients are at increased risk of ischemia related arrhythmias due to the capillary: myocyte mismatch [1]. Furthermore, microvessel disease may occur as a result of diabetes, hypertension or calcium phosphate deposition.

Myocardial stunning during hemodialysis may contribute to myocardial damage because reduction in regional wall motions have been observed, presumably the result of

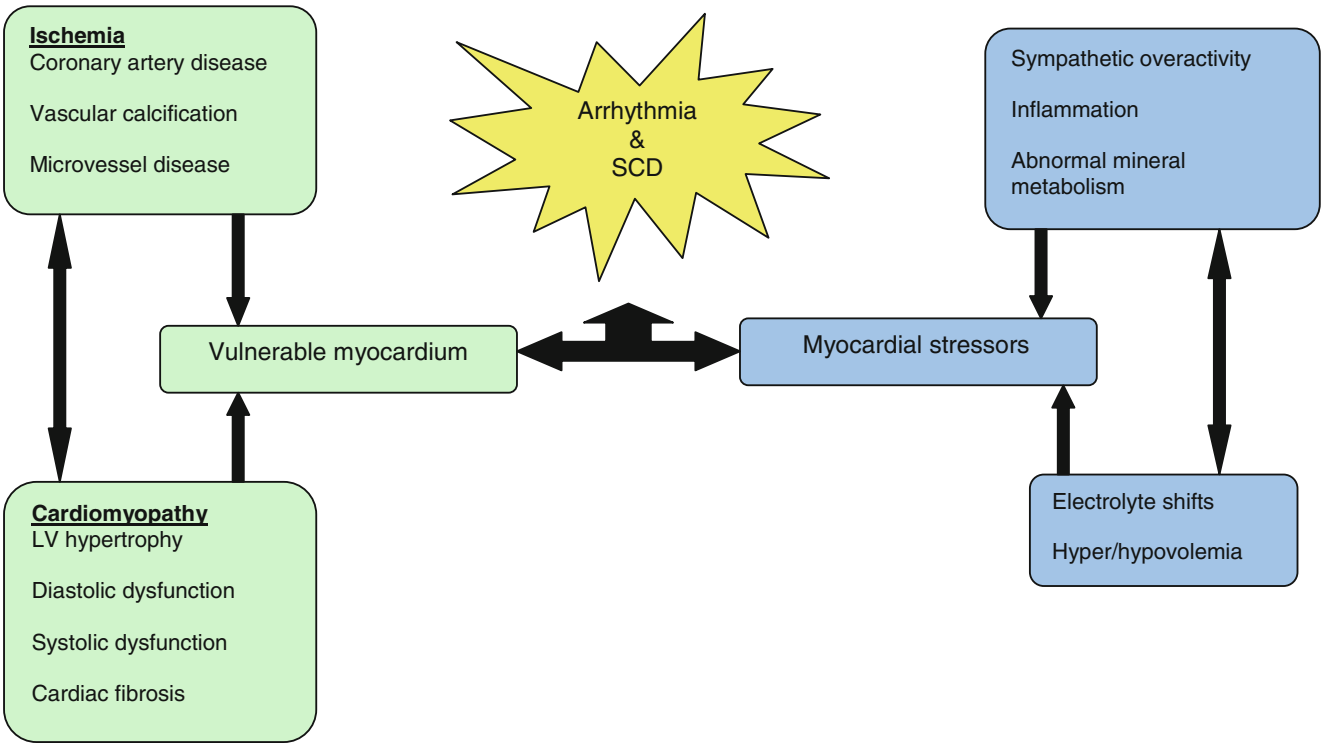

Fig. 3.2 The etiology of sudden cardiac death occurs in uremic kidney disease

transient hypoperfusion causing ischemia, followed by reperfusion necrosis [22].

Cardiomyopathy and Cardiac Fibrosis

Approximately half of patients with congestive heart failure (CHF) have CKD [23]. Furthermore, the Case Mix Adequacy Study of the USRDS found that 59 % of patients with SCD also had CHF [24]. CHF is the major manifestation of left ventricular dysfunction, and both diastolic and systolic dysfunction occurs frequently in ESRD.

Left ventricular hypertrophy (LVH), both concentric and eccentric [25, 26], is very common in patients with CKD, and in up to 75 % of patients starting HD [27, 28]. Hypertension, arteriosclerosis and aortic stenosis predispose to concentric LVH whereas anemia, blood volume expansion, and the arteriovenous fistula predispose to eccentric LVH [13]. Progressive LVH and left ventricular dilatation occurs after dialysis is initiated [28]. As myocytes are lost systolic dysfunction may occur. An Italian study of a small cohort of dialysis patients revealed that LVH is associated with increased risk of SCD [29]. This is consistent with what is seen in the general population: in the Framingham Heart Study, SCD increased for each 50 g/m increase in left ventricular mass (adjusted for height) [30]. Systolic dysfunction on starting dialysis is an adverse predictor of subsequent CHF and death [31].

The uremic heart is associated with increased interstitial myocardial fibrosis on post mortem examinations. Gadolinium enhanced magnetic resonance imaging also revealed images consistent with fibrosis in patients on dialysis [32]. On a molecular level, activation of growth factors, proto-oncogenes, plasma noradrenalin, cytokines, and angiotensin II also play a role in promoting LVH, fibrosis and apoptosis [12]. These changes cause slowing of conduction across diseased tissue and the development of both atrial and ventricular arrhythmias – likely triggers for SCD [1].

Sympathetic Overactivity

Coronary artery disease, arteriosclerosis, arterial calcification, microvessel disease, cardiomyopathy, and cardiac fibrosis all increase the vulnerability of the myocardium to stressors. In kidney failure the sympathetic nervous system is inappropriately activated which begins in the early stages of CKD and increases with worsening eGFR [33]. Multiple mechanisms for this phenomenon have been proposed. Kidney ischemia associated with progressively damaged renal parenchyma triggers sympathetic nerve activity, a theory supported by the fact that sympathetic overactivity was

normalized after the correction of renal artery stenosis in patients [34]. In addition, patients undergoing hemodialysis (N = 18) had higher levels of sympathetic discharge; hemodialysis patients with bilateral nephrectomy had normal rates of sympathetic discharge [35, 36]. Vasoconstriction of the kidney also activates the renin-angiotensin-aldosterone system leading to elevated levels of angiotensin II and as a result more sympathetic activation. Another novel mechanism for sympathetic overactivity involves renalase – a monoamine oxidase. Renalase is released from the kidney and is responsible for catecholamine catabolism. Levels of renalase are reduced in ESRD with a consequent increase in catecholamine levels [37].

Sympathetic overactivity results in enhanced sympathetic and norepinephrine release, predisposing to hypertension, LVH, heart failure and arrhythmias [38].

Inflammation

Patients on dialysis are "at high risk for chronic inflammation due to the non-physiologic nature of the dialysis procedure, infections, vascular access, and multiple co-morbid conditions" [39]. The highest tertiles of the inflammatory markers C-reactive protein (CRP) and interleukin-6 (IL-6) were associated with a doubled risk of SCD compared with the lowest tertiles in a cohort study of 1,041 dialysis patients. The same study reported a decrease in serum albumin (a manifestation of inflammation) was associated with a 1.35 fold increased risk of SCD [39]. In patients with CKD, elevated levels of inflammatory mediators induce the production of reactive oxygen species that may accelerate vascular atherosclerosis [40]. Inflammation could trigger sudden cardiac death by multiple mechanisms including: (1) direct effect on the myocardium and the electrical conduction system (2) cytokine induced plaque instability and (3) aggravation of sympathetic tone [39].

Abnormalities in Mineral Metabolism

Hyperphosphatemia is a common disturbance of mineral metabolism in patients with ESRD affecting up to 40 % of patients undergoing hemodialysis [41]. SCD has been associated with hyperphosphatemia in a large study of 12,833 patients [42]. After adjusting for several known mortality predictors, higher levels of serum phosphate (PO_4 >6.5 mg/dl) had a 41 % greater risk of death resulting from CAD and a 20 % greater risk of death resulting from sudden death compared to patients with serum PO_4 between 2.4 mg/dl and 6.5 mg/dl.

It is unclear how hyperphosphatemia increases the risk of SCD. It is postulated that hyperphosphatemia affects intracellular handling of calcium and therefore triggers electrical instability [43]. In addition it provokes secondary hyperparathyroidism, smooth muscle proliferation, vascular calcification, and coronary atherosclerosis [44]. Hyperparathyroidism is a predictor of death in ESRD [45]. The calcimimetic, cinacalcet, reduces PTH levels and in elderly patients (≥65 years old) significantly lowered the risk of death or a major cardiovascular event, suggesting that in this sub-group of patients hyperparathyroidism is an important risk factor [46].

Electrolyte Shifts and Hypervolemia

During the hemodialysis session, there is a rapid change of the extracellular potassium concentration, leading to secondary shifts between the intracellular and extracellular compartments, and cellular membrane instability [47]. In a study from the United Kingdom, 40 patients had continuous EKG holter monitoring during the hemodialysis session, using a dialysate potassium concentration of 1 mmol/L. Lower post-dialysis potassium concentrations were associated with more premature ventricular complexes (PVCs) and complex ventricular arrhythmias [48]. Another study showed that dialysate potassium concentrations of 0 or 1 mmol/l were a significant risk factor for cardiac arrest [47]. A case control study involving 502 cases of cardiac arrest compared with matched controls reported a dialysate potassium of <2 meq/L was associated with a two-fold increase in sudden cardiac arrest (Fig. 3.3)

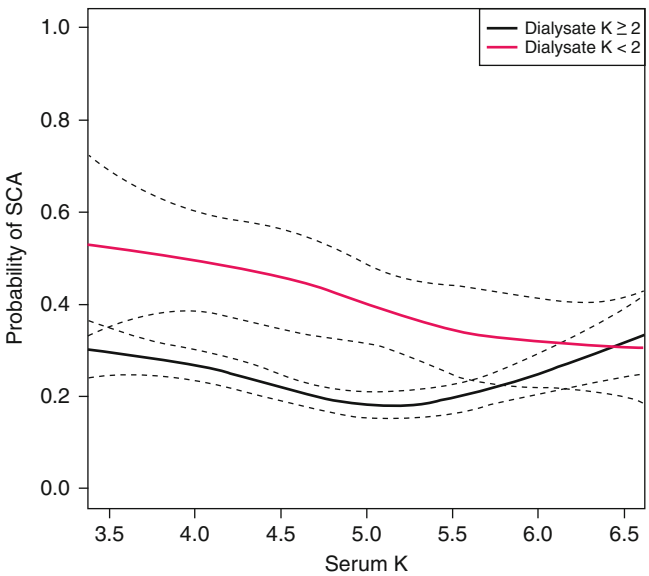

Fig. 3.3 Probability of sudden cardiac arrest (SCA) by dialysate potassium concentration (2 meq/l, *black line*; <2 meq/l, *red line*) and last recorded serum potassium. *Dashed lines* represent 95 % confidence intervals. Difference in risk is greatest for lower levels of serum potassium, and the risk difference decreases as serum potassium increases. No significant advantage of low potassium dialysate is observed at any level of serum potassium (Reprinted by permission from Macmillan Publishers Ltd: [KIDNEY INTERNATIONAL] (Pun et al. [49]), © (2011))

[49]. In the same study, low calcium dialysate (<2.5 meq/l) was associated with cardiac arrest (OR 1.88, CI 1.28–2.76).

Ultrafiltration of consistently large volumes during hemodialysis was a risk factor for peridialytic cardiac arrest [49]. Significantly increased rates of dysrhythmia and cardiac arrest occur following the long interdialytic period, typically on Monday, particularly in those on dialysis three times per week [49, 50]. The increased rates of arrhythmia and cardiac death following 3 days without dialysis may be due to hyperkalemia, increased blood volume or changes in divalent ion levels [43, 13].

QT Prolongation

QT prolongation (a sign of abnormal electrical signal propagation) increases the risk of fatal arrhythmia, notably in the form of torsades de pointes – a polymorphic ventricular tachycardia [51]. Patients with advanced CKD and ESRD have prolonged QTc (corrected QT) presumably resulting from left ventricular hypertrophy and uremic cardiomyopathy [52]. Furthermore, during the hemodialysis session itself, in 68 nondiabetic patients without EKG evidence of LVH, the QTc interval increased [53].

Dialysate containing lower concentration of potassium and calcium was associated with the prolongation of the QT interval [54]. Also, higher pre-dialysis calcium and lower serum calcium levels after dialysis were associated with greater increases in QTc intervals [54]. These data suggest that abnormalities of calcium associated with derangement of the QT interval may predispose to SCD.

Evidence for Best Management

The above case presentation is a familiar one in the nephrology world, but sometimes SCD comes as a shock to care providers. The patient had no symptoms of IHD or CHF. So why did this man die suddenly? Postmortem analysis revealed that he had a myocardium susceptible to ventricular fibrillation including coronary artery disease, uremic cardiomyopathy and fibrosis. Risk factors for SCD included hyperphosphatemia, hyperparathyroidism and systemic inflammation with elevated CRP and hypoalbuminemia. Also, his death came on a Monday following his longest interdialytic period. Moreover, he was being dialyzed with a 1 mmol/L potassium bath, had a relatively high ultrafiltration volume and a short dialysis time.

Could this SCD have been prevented? Unfortunately, the risk factors for sudden cardiac death in dialysis patients are not fully understood and prevention studies are limited.

Beta-Adrenergic Blockers

B-blockers may prevent SCD in dialysis patients by improving blood pressure, decreasing arrhythmias, decreasing ischemia, and diminishing sympathetic overactivity [36], but little randomized trial data using clinical outcomes in large numbers of patients is available. Observational studies are limited by the difficulty in controlling for selection bias.

A Japanese cohort involving 2,075 dialysis patients examined beta-blocker use and mortality [55]. There was a lower rate of all cause mortality in the B-blocker group ($p<0.007$). However, the study was limited due to the small number of patients in the treatment group (247) and the total duration of B-blocker use was difficult to determine. Also, it must be noted that the Japanese dialysis population is very unique as it has the lowest dialysis mortality rate in the world, patients receive more total dialysis and are very compliant with their prescribed medical care [56]. A post hoc analysis of the HEMO study assessed beta-blockers for prevention of SCD in 1,747 hemodialysis patients in which 39 % had ischemic heart disease and 12 % had moderately severe CHF [57]. Beta-blocker use was not associated with a decrease in SCD. However, a benefit with B-blockers was seen in those with pre-existing ischemic heart disease ($p=0.03$). This study was limited by its observational nature but a propensity-matched comparison strengthened the statistical analysis. The only prospective randomized control trial to assess beta-blocker use and mortality in dialysis patients examined carvedilol in 103 dialysis patients with cardiomyopathy [58]. At 2 years, there was a significant difference in mortality with 30 deaths (51.7 %) in the carvedilol group compared with 41 (73.2 %) in the placebo group (HR 0.51, 95 % CI 0.32–0.82, $p<0.01$). There were also fewer all-cardiovascular deaths (29.3 vs. 97.9 %, HR 0.32, 95 % CI 0.18–0.57, $p<0.00001$). Furthermore the treatment group had fewer deaths from fatal MI and stroke.

With regards to mortality benefit after cardiac arrest, a large retrospective study of 43,200 dialysis patients reported B-blockers increased the odds of survival by 40 % [59]. Another study examined he safety profile of B-blockers in dialysis patients and reported no significant increase in the risk of bradycardia or hyperkalemia [60].

In conclusion, as there is limited randomized trial data pertaining to the use of B-blockers in patients with CKD, the indications for these agents derived from patients without renal disease should probably be applied to those with CKD.

Renin-Angiotensin System (RAS) Blockade

Blockade of the renin-angiotensin system could reduce the incidence of SCD in dialysis patients by curbing sympathetic overactivity and by limiting cardiac remodeling. In one

small, randomized control trial of 80 dialysis patients with no evidence of cardiac disease, the use of the angiotensin receptor blocker candesartan was associated with a reduced incidence of cardiac events and mortality versus placebo [61]. Conversely, a prospective controlled trial with the angiotensin converting enzyme inhibitor fosinopril in ESRD patients had no significant impact on mortality. However, after adjustment for risk factors, there was a trend towards decreased cardiovascular events [62]. With regards to mortality benefit after cardiac arrest, the large retrospective study on 43,200 dialysis patients mentioned above reported that the use of ARB and ACE inhibitors was also associated with better survival after cardiac arrest [59]. Again, due to the lack of good evidence on the blockage of the renin-angiotensin system, the indications for these agents derived from patients without renal disease or from trials to slow kidney disease progression should be applied to those with CKD. However, caution must be taken because of the risk hyperkalemia. Also, the overuse of RAS blockers in ESRD patients may detrimentally reduce residual urine output. Certainly, caution is necessary in the use of combined RAS blockade with ACE inhibitor/ARB, in view of the harms reported in the recent VA NEPHRON-D trial [63].

Dialysis Dose and Avoiding low Potassium Dialysate

Although a higher dialysis dose improves the uremic milieu particularly through reducing phosphate levels and deceasing levels of inflammation and middle molecules, there was no major clinical benefit with high dialysis dose or high flux membrane use [64]. However, longer dialysis time may provide hemodynamic benefits, with less fluctuation in blood pressure and better ultrafiltration. More frequent dialysis sessions than the conventional three times per week was associated with significant reduction in death or LVH [65].

As detailed above, rapid shifts of potassium and the use of low potassium dialysate are associated with arrhythmia and SCD. Therefore, the dialysis prescription should be evaluated on a regular basis [1]. Our patient should probably have been prescribed a 2 meq/L potassium bath and longer dialysis to manage the increases in interdialytic weight gain.

Management of Mineral Abnormalities

Poor clinical outcome data from randomized control trials exists to inform clinicians on treatment of hyperphosphatemia with calcium and non-calcium based phosphate binders. Meta-analysis suggests a survival benefit for non-calcium based phosphate binders compared to calcium-based binders but the evidence is weak [66]. Use of vitamin D derivatives is driven by biochemical consideration because little clinical outcome data has been reported. Evidence from the randomized trial of cinacalcet versus placebo in hemodialysis patients with moderate to severe hyperparathyroidism reveals a clinical benefit in the prevention of cardiovascular events in patients ≥65 or in the prevention of severe unremitting hyperparathyroidism in all patients [46, 67].

Implantable Cardiac Defibrillator

There are no randomized trials that assess the use of ICD implantation for primary or secondary prevention in CKD patients. Much of the present data highlights persistently high mortality rates in this patient population despite ICD use. A longitudinal, prospective study followed 146 patients with chronic heart failure, an ICD, mean ejection fraction <29 % and CKD in 75 % of patients. CKD was independently associated with increased mortality [68]. A retrospective cohort of 9,528 dialysis patients with ICDs reported a very high mortality rate after ICD implantation at (45 deaths/100 patient years). This is double the adjusted mortality rate of unselected dialysis patients in 2008. Thirteen deaths/100 patient years were due to arrhythmia. Furthermore, there was a very high complication rate with infections and bacteremia occurring at rates in excess of 1 infection/2 person years of follow-up [69]. A meta analysis of 2,516 patients with 89 receiving dialysis observed an increase in mortality in ICD patients receiving dialysis compared to those who were not (RR 2.67, 95 % CI 1.68–4.25, $p<0.0001$), implying limitation in the effectiveness of ICDs in reducing overall mortality in this population. Mechanisms of death other than SCD are important in the dialysis population as only 4/27 patients with documented death died from arrhythmic deaths. In this study, a proposed mechanism for an arrhythmic death despite ICD implantation was inappropriately high defibrillation thresholds observed in dialysis patients (i.e. ventricular fibrillation that could not be terminated by high ICD energy levels) [70].

Although CKD patients have a significant risk of SCD, there is a high mortality rate from other causes that limits the use of ICDs. Furthermore, an increased complication rate from ICD insertion must be considered [71]. Nevertheless, current ICD guidelines do not distinguish between patients with and without CKD [71], but ICD therapy is contraindicated in patients who do not have "a reasonable expectation of survival with an accepted functional status for at least 1 year" [70].

A decision analysis and Markov modeling assessing the utility of implanting ICDs in patients with CKD to prevent SCD found the benefit is dependant on age and severity of kidney disease: ICD implantation was preferable in patients aged <80 for stage 3 CKD, ages <75 for stage 4 CKD and ages <65 years for stage 5 CKD [72].

Provision of Healthcare

The real window of opportunity in the prevention of SCD is in the earlier pre-dialysis phases of CKD where appropriate use of antihypertensive agents, lipid lowering agents, antiplatelet agents, blood volume optimization, diabetic control and cessation of smoking may slow progression of coronary artery disease and cardiomyopathy. Furthermore, as CKD advances, treatment of anemia and hyperparathyroidism together with individualization of dialysis prescription will be necessary. Efficacious therapies should be provided if patients are expected to live long enough to benefit from them. B-blockers are significantly less likely to be prescribed to patients on hemodialysis [36]. This even occurs in patients with advanced heart failure despite a randomized control trial that showed improved outcomes with carvedilol. This decreased usage is likely due to concerns about adverse side effects. However, the available data suggests the risk of dangerous side effects appear to be "rare and manageable" [38]. Furthermore, dialysis patients are much less likely to undergo angiography or revascularization despite a high mortality rate after MI [73]. However, evidence exists that there is a survival benefit with revascularization after MI [74].

Certain groups of CKD patients are at increased risk of cardiac arrest including those with advanced age, diabetes, dialysis catheter use and recent hospitalization [47]. A recent hospitalization is particularly important due to the effects of acute illness, changes in diet and medications, along with alterations in extracellular fluid volume. Consequently, evaluation of total body sodium and low dialysate potassium concentrations, the achievement of dry weight and a review of dialysis prescription, particularly for ultrafiltration volumes and dialysis time, is necessary. Moreover, patients who are prescribed low dialysate potassium concentrations should be reviewed more frequently [47].

Conclusion

Should the patient in the case scenario have been managed differently? Firstly, the patient should probably not have been treated with a 1 mmol/L potassium dialysate despite the pre-dialysis hyperkalemia. Secondly, longer dialysis time would have provided smaller ultrafiltration volumes per hour and improvement in hyperphosphatemia. He may have benefited from more frequent dialysis sessions. He was receiving an angiotensin converting enzyme inhibitor but not a B-blocker at the time of his death, an appropriate decision, as there was no indication for this drug.

In conclusion, sudden cardiac death occurs when a vulnerable myocardium is subjected to systemic stressors. Each patient with CKD and ESRD is very unique with differing degrees of cardiomyopathy, coronary artery disease and predisposing cardiac risk factors. Individualized risk factor intervention must be given to patients with CKD and those on dialysis.

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Anticoagulation in CKD

4

Kathleen Quinn, Alistair John Ingram,
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Clinical Case Scenario

A 68-year-old male presents to hospital with shortness of breath and palpitations. He has a past medical history of hypertension, type 1 diabetes mellitus, and diabetic nephropathy. He was recently started on hemodialysis, which adequately removes 1.0–1.5 L of fluid per session and maintains a stable ideal body weight. Despite the adequacy of dialysis, the patient continues to have recurrent admissions to hospital for shortness of breath and palpitations. An echocardiogram done during this current admission shows a left ventricular ejection fraction of 50 % and a severely enlarged left atrium. His cardiac monitor shows episodes of paroxysmal atrial fibrillation. At this time, the medical team is considering whether there is a role for anticoagulation in this patient, as well which anticoagulant is most appropriate for a patient with chronic kidney disease.

Indications for Anticoagulation in Chronic Kidney Disease

There are several potential indications for anticoagulation in chronic kidney disease (CKD), however evidence to guide clinicians in both the advisability of initiating anticoagulation and the choice of anticoagulant is limited. Patients with stage 3 or greater CKD, defined as an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 for a minimum of 3 months, have an increased risk of atrial fibrillation compared to the general population. Data from the Chronic Renal Insufficiency Cohort (CRIC) study shows that up to 18 % of patients with stage 3 CKD (eGFR <60 ml/min) have atrial fibrillation by electrocardiographic evidence, or self-report [1]. In patients greater than 70 years of age with concomitant CKD, the prevalence of atrial fibrillation increased to 25 % [1]. The prevalence of atrial fibrillation in ESRD is between 7 and 12 % with an annual incidence of 2.7 % per year in patients on dialysis [2–5]. While it is well established that patients with CKD have a higher incidence of atrial fibrillation, the inverse is also true (Fig. 4.1). In a study involving CKD patients with an eGFR 30–50 ml/min, the development of incident atrial fibrillation was independently associated with worsening renal failure and declining GFR necessitating renal replacement therapy, although the mechanism of this effect is unknown [6].

Another common scenario in which the question of anticoagulation arises in CKD patients is acute coronary syndrome. The risk of incident myocardial infarction in middle-aged patients with CKD is increased (HR 1.67; 95 % CI 1.07–2.61 for women and HR 1.51; 95 % CI 1.09–2.10 for men) and the risk continues to rise with competing comorbidities and age [7]. Prosthetic valve placement necessitates anticoagulation, but in individuals with CKD, the evidence is again limited in this area and much of current clinical practice is extrapolated from studies that included a small number of CKD patients and excluded patients with end-stage renal disease (ESRD).

Venous thromboembolism (VTE) is yet another indication for anticoagulation in patients with CKD. A pooled analysis of five cohort studies showed a hazard ratio of 1.54 (95 % CI 1.15–2.06) for VTE in patients with mild-moderate CKD compared with those without CKD [8]. Several hypotheses exist to explain the potential increased risk of VTE in CKD, including sedentary lifestyle, obesity, and loss of natural anticoagulant proteins (e.g. protein C and protein S) in patients with nephrotic range proteinuria.

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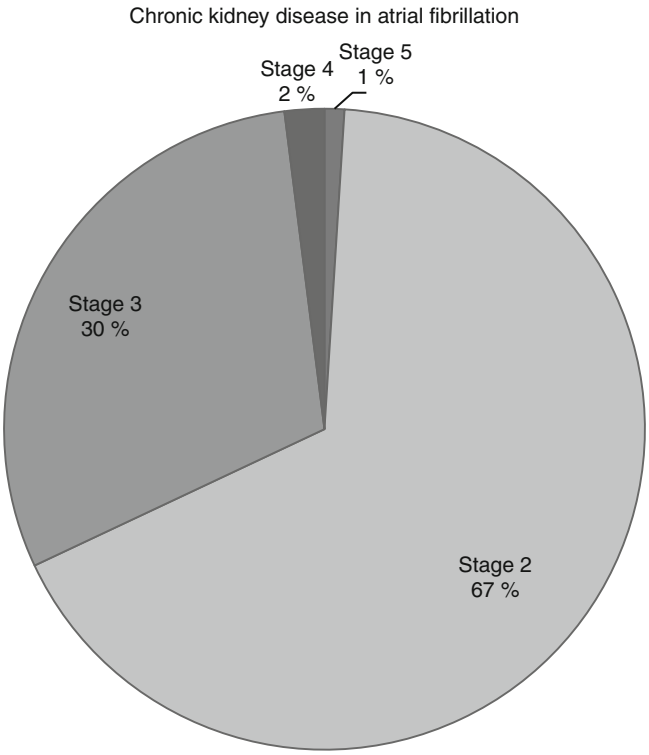

Fig. 4.1 Frequency of chronic kidney disease in patients with atrial fibrillation. Most patients with atrial fibrillation who have chronic kidney disease will have mild-moderate impairment of renal function, classified as stage 2 (67 %) and stage 3 (30 %) kidney disease. A small percentage of patients with atrial fibrillation will have more severe renal disease, classified as stage 4 (2 %) and stage 5 (1 %) CKD (Modified from: Hart et al. [58] with permission from Elsevier)

Stroke Risk in Patients with Chronic Kidney Disease

Both atrial fibrillation and CKD are independent risk factors for stroke. In patients without atrial fibrillation, CKD increases the risk of stroke by a factor of 3.7 [9]. In patients who require renal replacement therapy, the risk is increased by a factor of 5.8 [9]. Several studies have demonstrated that CKD is an independent risk factor for stroke in patients with atrial fibrillation. After adjustment of other risk factors for stroke, the hazard ratio (HR) is approximately 1.5 [10–12]. The increased risk of stroke in patients with CKD and atrial fibrillation was further highlighted in a study of 132,372 patients from the Danish National Registry, which found a significant increase in stroke in both patients with CKD without dialysis and those with end-stage renal disease requiring dialysis [13]. The AnTicoagulation and Risk factors In Atrial fibrillation (ATRIA) study also found CKD to be an independent predictor of thromboembolism in patients with atrial fibrillation [10]. In this study, there was a 54 % increase in the risk of systemic embolism in patients with proteinuria, which was defined as a protein value of ≥1+ on urine dipstick. Patients with more severe renal impairment (eGFR <45 ml/min) had a higher risk of stroke than those with an eGFR of >45 ml/min [10].

Determining the Risk of Stroke

Typically, clinicians use the validated $CHADS_2$ score to assess the risk of stroke in patients with atrial fibrillation [14]. The $CHADS_2$ score assigns 1 point for each of congestive heart failure, hypertension, age ≥75, and diabetes. An additional 2 points are added if the patient has a history of previous stroke, or transient ischemic attack. A score>1 suggests that the patient is at a high risk of stroke and should receive oral anticoagulation [14]. Another stroke prediction tool, CHA_2DS_2VASc is used when the $CHADS_2$ score is 0–1 and adds additional points for age 65–74 years, as well as for a history of vascular disease, or female sex. Both male and female patients ≤65 years old with lone atrial fibrillation are at relatively low risk of stroke. All other atrial fibrillation patients with an overall CHA_2DS_2VASc score of greater than, or equal to 1 point, should be considered for oral anticoagulation [15].

With increasing evidence that renal disease may be an independent predictor of stroke risk in patients with atrial fibrillation [10–12], a new stroke prediction model, R_2CHADS_2 was derived using data from the ROCKET-AF study and validated in the ATRIA study population [16]. This is similar to the $CHADS_2$ score, but assigns an additional 2 points when estimated creatinine clearance is<60 ml/min, calculated using the Cockroft-Gault formula. In the derivation and validation studies, the R_2CHADS was better able to predict stroke than either the $CHADS_2$ or CHA_2DS_2VASc scores [16]. This finding again highlights the importance of recognizing CKD as an independent risk factor for stroke. In our view, patients with stage 3–4 CKD should be considered to have at least a moderate risk of stroke, independent of other predictive factors. However, it is less clear which type of anticoagulation is safest in patients with impaired renal function, or indeed whether the benefits of anticoagulation outweigh the bleeding risks.

Warfarin in Patients with Chronic Kidney Disease

Warfarin antagonizes the action of vitamin K epoxide reductase, preventing the hepatic production of vitamin K dependent factors II, VII, IX, and X. It also inhibits the synthesis of anticoagulant proteins C and S. Warfarin is rapidly absorbed from the gastrointestinal tract, but the anticoagulant effect is typically not seen until 24–36 h post-dose, since circulating factors must be cleared before peak effect is reached. The anticoagulation effect of warfarin is monitored using the

international standardized ratio (INR) with a recommended therapeutic range of 2–3 for stroke reduction in atrial fibrillation and 2.5–3.5 for stroke reduction in patients with mechanical heart valves. The average half-life of warfarin is 44 h, however, this varies depending on genotype differences in cytochrome P450 subtypes, as well as in the gene for vitamin K epoxide reductase. While 99 % of warfarin undergoes oxidative metabolism in the liver, a lower dose of warfarin is recommended for patients with CKD, as they have been shown to have increased bleeding and supratherapeutic INR values on warfarin [17].

In the general population with atrial fibrillation, warfarin reduces the risk of stroke by approximately two-thirds [18]. There has not been randomized controlled trials to directly examine the efficacy of warfarin in patients with CKD, however, an analysis of 516 patients with stage 3 CKD (defined as an eGFR 30–59 ml/min) in the Stroke Prevention in Atrial Fibrillation (SPAF) III trials, indicated that therapeutic level warfarin decreased the incidence of stroke or systemic embolism by 76 % compared to low dose warfarin and aspirin [18]. Unfortunately, there were not enough bleeding events to accurately assess the risk of major hemorrhage for stage 3 CKD patients on warfarin. Further evidence of the benefit of warfarin comes from a retrospective analysis of patients from the United States Renal Data System (USRDS) Dialysis Morbidity and Mortality Study (DMMS), which found that there was a mortality reduction in patients who were taking warfarin at the time of hospitalization for atrial fibrillation [19]. A recent analysis of 24,317 patients from SWEDEHEART registry data calculated eGFR using the CKD-EPI equation and found that 51.7 % of patients included in the registry had an eGFR <60 ml/min. Regardless of CKD stage, patients using warfarin had a reduction in outcomes of death, stroke, and myocardial infarction. When analyzed by stage of CKD, there was no increase in bleeding risk for patients on warfarin [20].

Despite some evidence demonstrating a benefit of warfarin in patients with CKD, there have been some reservations about the use of warfarin in this population. Concerning is evidence paradoxically showing that the annual risk of stroke was doubled to 2.6 % for patients with atrial fibrillation and hemodialysis-dependence who were taking warfarin [21]. There has also been evidence showing that warfarin increases the risk of stroke among hospitalized hemodialysis patients with atrial fibrillation, compared with no anticoagulation (HR 1.93; 95 % CI 1.29–2.90) [22]. A recent retrospective cohort study found that, after adjusting for confounders, warfarin did not reduce the risk of stroke in dialysis patients, but did increase the bleeding risk by 44 % [23]. Reflecting the uncertainties alluded to above, recent guidelines do not recommend routine use of warfarin anticoagulation for hemodialysis patients with atrial fibrillation for primary prevention of stroke [24].

Aside from an increased risk of stroke and bleeding, patients with ESRD are at high risk of vascular calcification secondary to diabetes, dysfunctional mineral metabolism, inflammation, and uremia [25]. This risk may be amplified by warfarin, which is postulated to inhibit the action of vitamin K dependent matrix G1a protein (MGP) [26]. The inhibition of MGP has been shown to accelerate vascular calcification in animal models, and has been postulated to be a precipitant for calciphylaxis (calcific uremic arteriolopathy) in ESRD patients [25].

Direct-Acting Oral Anticoagulants (DOACs) in Chronic Kidney Disease

Direct-acting oral anticoagulants (previously termed novel oral anticoagulants, but no longer novel), are those that interact directly with their coagulation protein target for their anticoagulation effect, in contrast to warfarin's indirect mechanism (Table 4.1, Fig. 4.2). There have been several randomized controlled trials to examine the benefits and harms of these anticoagulants in atrial fibrillation (Tables 4.2 and 4.3).

Table 4.1 Pharmacological characteristics of direct-acting oral anticoagulant medications

Characteristic	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mechanism of action	Thrombin inhibitor	Factor Xa inhibitor	Factor Xa inhibitor	Factor Xa inhibitor
Atrial fibrillation Dose and frequency	150 mg BID 110 mg BID	20 mg daily	5 mg BID	60 mg daily 30 mg daily
Half-life (hours)	12–17	9–13	8–15	9–11
Drug interactions	P-gp inhibitor	P-gp/CYP3A4 inhibitor	P-gp/CYP3A4 inhibitor	P-gp/CYP3A4 inhibitor
Renal clearance	80 %	33 %	25 %	35 %
Dose adjustment for stage 3 CKD	No	Reduce dose to 15 mg daily if eGFR <50 mL/min	Reduce dose to 2.5 mg BID if Cr ≥133 umol/L and age ≥80 years, or weight ≤60 kg	Reduce dose to 15 or 30 mg daily if eGFR 30–49 ml/min
Approval for ESRD	No	No	No	No

Modified from: (1) Gong and Kim [60] with permission from Elsevier, (2) Eikelboom and Weitz [61] with permission from Wolters Kluwer Health
P-gp p-glycoprotein, *CYP3A4* cytochrome 3A4, *BID* twice daily

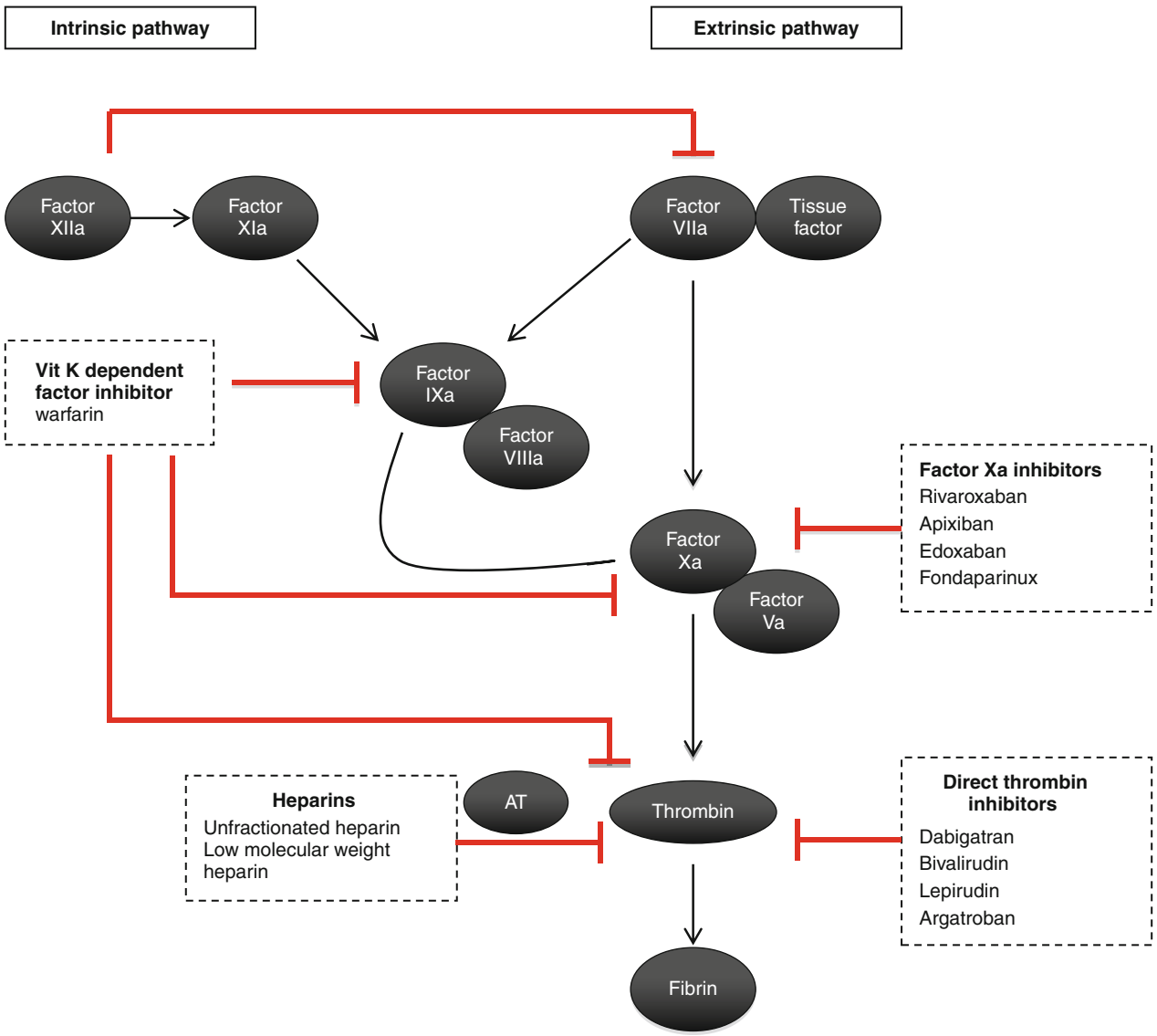

Fig. 4.2 Target sites for direct acting oral anticoagulants (DOACs). Warfarin is an inhibitor of vitamin K dependent factors (VII, IX, II, X). Therapeutic levels of warfarin will increase markers of anticoagulation in both the intrinsic pathway (INR/PT) and the extrinsic pathway (aPTT). Factor Xa inhibitors work on the common pathway to inhibit coagulation. Direct thrombin inhibitors target the common pathway even further upstream to prevent fibrin clot formation. Heparins act with antithrombin (AT) to inhibit thrombin (Modified from: Melnikova [59] with permission from Nature Publishing Group, Macmillan Publishers Ltd)

Dabigatran

Dabigatran etexilate is an oral direct thrombin inhibitor. It is converted by a serum esterase to its active form. Rapidly absorbed from the GI tract, dabigatran has an onset of action of approximately 2–3 h and a half-life of 12–17 h and does not require routine monitoring to determine drug function or dosage. Since up to 80 % of dabigatran is cleared by the kidneys, a dose reduction is necessary due to altered pharmacokinetics. An open-label, single-center pharmacology study found that the half-life of dabigatran was 28 h in patients with an eGFR <30 ml/min [27].

The RE-LY study was a large, randomized controlled trial, which compared dabigatran with warfarin in 18,113 patients with atrial fibrillation [28]. The results showed that dabigatran 150 mg twice daily significantly reduced the rate of stroke or systemic embolism compared to warfarin (1.11 % per year vs 1.69 % per year, RR 0.66; 95 % CI 0.53–0.82; $P<0.001$) with similar bleeding risk (3.11 vs 3.36 %,

Table 4.2 Study design and main outcomes from randomized trials in patients with CKD

	RE-LY	ROCKET-AF	Aristotle	Engage
Patients	18,113	14,264	18,201	21,105
DOAC	Dabigatran 150 or 110 mg BID vs warfarin	Rivaroxaban 20 mg daily vs warfarin	Apixaban 5 mg BID vs warfarin	Edoxaban low dose (30 mg), or high dose (60 mg) daily vs warfarin
Exclusion criteria related to CKD	eGFR <30 mL/min	eGFR <30 mL/min	Serum creatinine >2.5 mg/dL (221 umol/L) or eGFR <25 mL/min	eGFR <30 ml/min
Dose adjustment related to CKD	None	Reduce dose to 15 mg daily if eGFR <50	If creatinine ≥1.5 mg/dL (133 umol/L) and age ≥80 years and weight ≤60 kg, reduce dose to 2.5 mg BID	If eGFR 30–50 ml/min, dose was halved in high and low dose groups to 30 and 15 mg respectively
Stage III CKD	19 % with eGFR 30–49 mL/min	21 % with eGFR 30–49 mL/min	15 % with eGFR 30–50 mL/min	19 % with eGFR 30–50 ml/min
Outcomes in CKD patients	3,505 with eGFR 30–49 mL/min	2,950 with eGFR 30–49 mL/min	3,017 with eGFR 25–50 mL/min	4,074 with eGFR 30–50 mL/min
	Stroke/non-CNS embolism rate 2.8 % per year with warfarin, 2.2 % with dabigatran 110 mg BID (non-significant), and 1.5 % per year with dabigatran 150 mg BID ($P<0.01$)	Stroke/non-CNS embolism rate 3.4 % per year with warfarin, 3.0 % per year with rivaroxaban (non-significant)	Stroke/non-CNS embolism rate 2.7 % per year with warfarin, 2.1 % per year with apixaban (non-significant)	No subgroup analysis available
Major hemorrhage	No significant difference	No significant difference	Reduced ($P<0.001$)	No subgroup analysis available
Intracranial bleeding	Not reported	No significant difference	Reduced ($P<0.001$)	No subgroup analysis available
Mortality	Not reported	No significant difference	No significant difference	No subgroup analysis available

Modified from: Hart et al. [51] with permission from Nature Publishing Group, Macmillian Publishers Ltd
BID twice daily, *eCrCl* estimated creatinine clearance using Cockroft-Gault formula, *CNS* central nervous system, *NS* non-significant

Table 4.3 Oral anticoagulants for patients with CKD

CKD Stage[a]	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban[b]
eGFR[c] ≥60 ml/min	INR 2–3	110 or 150 mg BID	20 mg daily	5 or 2.5 mg[d] BID	30 or 60 mg daily
Stage 3 CKD					
eGFR 50–59 ml/min	INR 2–3	110 or 150 mg BID	20 mg daily	5 or 2.5 mg[d] BID	30 or 60 mg daily
eGFR 30–49 ml/min	INR 2–3	110 or 150 mg BID	15 mg daily	5 or 2.5 mg[d] BID	15 or 30 mg daily
Stage 4 CKD					
eGFR 25–29 ml/min	No data	No data[e]	No data[f]	5 or 2.5 mg[d] BID	No data
eGFR 15–24 ml/min	No data	No data	No data[f]	No data	No data
Stage 5 CKD/End-Stage renal disease					
eGFR <15 ml/min (not on dialysis)	No data	No data	No data	No data	No data
Hemodialysis	No data	No data	No data	No data	No data
Chronic peritoneal dialysis	No data	No data	No data	No data	No data

Modified from: (1) Hart et al. [58] with permission from Elsevier; (2) Skanes et al. [62] with permission from Elsevier
No data no data from suitably powered randomized controlled trials, *CKD* chronic kidney disease, *eGFR* estimated glomerular filtration rate, *BID* twice daily
[a]Stages of CKD defined according to National Kidney Foundation Classification; conventionally, stage 3 CKD defined as eGFR 30–59 ml/min and stage 4 CKD as 15–29 ml/min
[b]Approved for use in Japan
[c]GFR defined by the Cockroft Gault formula in the large, phase 3 clinical trials
[d]2.5 mg BID if creatinine ≥1.5 mg/dL (133 umol/L) and age ≥80 years and weight ≤60 kg
[e]US FDA has approved dabigatran 75 mg BID based on pharmacodynamic studies
[f]US FDA and European Medicines Agency has approved rivaboxaban 15 mg daily for patients with stage 4 CKD

p = 0.31). Furthermore, a reduced dose of 110 mg twice daily was non-inferior to warfarin in terms of rate of stroke or systemic embolism, but did significantly decrease major bleeds (2.71 vs 3.36 %, p < 0.003) [28]. For both doses of dabigatran, there was a significant reduction in intracranial bleeding. Patients with an estimated creatinine clearance < 30 ml/min were excluded from the study, but 3,505 patients with an estimated creatinine clearance of 30–50 ml/min and 8,766 patients with an estimated creatinine clearance of 50–79 ml/min were included. Subgroup analysis did not show an interaction between renal function and the effects of dabigatran. As well, a separate analysis of RE-LY data showed that both dabigatran 150 and 110 mg twice daily reduced the risk of stroke or systemic embolism regardless of renal function. Despite these efficacious results, there was increased major bleeding with declining renal function (1.98 % in GFR > 80, 3.30 % for GFR 50–79, and 5.48 % for GFR < 50). There was a similar increase in risk of intracranial hemorrhage as renal function declined. Life threatening bleeding was 3.2 times higher for patients using dabigatran with a GFR < 50 ml/min compared with a GFR > 80 ml/min [29]. Despite this evidence, RE-LY can give no guidance for those with CKD stages 4 or 5.

Rivaroxaban

Rivaroxaban is an oral direct Xa inhibitor with a rapid onset of action of 2–4 h. The half-life of the drug is between 11 and 13 h. Typically, rivaroxaban is highly absorbed by the gastrointestinal tract with 80–100 % bioavailability and the absorption is not impaired by concomitant food intake. The kidneys eliminate approximately 66 % of the active drug [30]. Currently, rivaroxaban is approved for prophylaxis of venous thromboembolism (VTE) in orthopedic patients following hip, or knee replacements. It has also been approved for treatment of VTE or pulmonary embolism, as well as for stroke prevention in patients with non-valvular atrial fibrillation.

The ROCKET-AF trial was a large, multicenter, randomized controlled trial that compared rivaroxaban with warfarin in 14,264 patients with atrial fibrillation [31]. Rivaroxaban was found to be non-inferior to warfarin for reducing the rate of stroke, or systemic embolism (1.7 % per year in the rivaroxaban group vs 2.2 % per year in the warfarin group, HR 0.79; 95 % CI 0.66–0.96; P < 0.001). The rivaroxaban group had a similar rate of bleeding overall compared to the warfarin group, but a significantly reduced rate of intracranial hemorrhage. This trial included only patients with a calculated creatinine clearance > 30 ml/min, with the dose of rivaroxaban reduced to 15 mg daily if estimated creatinine clearance was 30–49 ml/min [31]. The subgroup analysis did not find any interaction between renal function and efficacy of rivaroxaban, nor bleeding rates. Of 2,950 patients with eGFR 30–49 ml/min, the annual rate of stroke or systemic embolism was 3.5 % for patients on warfarin, compared with 3.0 % for those on rivaroxaban (HR 0.86; 95 % CI, 0.63–1.2) [26]. Overall, bleeding rates for stage 3 CKD patients were similar in the rivaroxaban group (15 mg daily) and the warfarin group, but fatal bleeds were more rare in the rivaroxaban group. However, since patients with a calculated creatinine clearance <30 ml/min were excluded from the study, no guidance can be given for patients with stage 4 or 5 CKD. It is important to note, however, that despite results from the above study, several countries approve the use of rivaroxaban 15 mg daily for patients with eGFR 15–30 ml/min based purely on plasma concentration studies.

Apixaban

Apixaban is a direct factor Xa inhibitor. The onset of action is approximately 2–3 h and the half-life of the drug is 12 h [32]. Renal excretion is responsible for 25 % of drug clearance. Similar to the other direct acting oral anticoagulants, apixaban does not require routine monitoring. ARISTOTLE was a large, double-blind trial, which randomized 18,201 patients to either oral apixaban 5 mg twice daily, or warfarin dose-adjusted to an INR 2–3 [33]. The dose of apixaban was reduced to 2.5 mg twice daily in patients with creatinine ≥ 1.5 mg/dL (133 umol/L), age ≥ 80 years, or weight ≤ 60 kg. Patients with an estimated creatinine clearance < 25 ml/min were excluded from the trial. Apixaban significantly reduced the rate of stroke, or systemic embolism compared to warfarin; 1.27 vs 1.60 % (HR 0.79; 95 % CI 0.66–0.95, P < 0.001). The apixaban group also had a significant decrease in major bleeding compared to the warfarin group, including gastrointestinal bleeds 0.24 vs 0.47 % (HR 0.51; 95 % CI, 0.35–0.75; P < 0.001) [33]. Of the 3,017 patients with eGFR 25–50 ml/min, subgroup analysis did not show a difference in the treatment effect compared to those without significant renal impairment. With the inclusion of patients with mild-moderate renal impairment (to a GFR of 25 ml/min), we are able to infer that the benefit of apixaban seen in this trial should be similar in patients with a GFR of at least 25 ml/min.

AVERROES, compared apixaban to aspirin in 5,599 patients that were unable to take a vitamin K antagonist [34]. This study excluded patients with a creatinine > 2.5 mg/dL, or a calculated creatinine clearance < 25 ml/min [34, 35]. Median follow-up was 1.1 years and the study was stopped early due to clear benefit of apixaban compared to aspirin for reduction in stroke or systemic embolism. The event rate was 1.6 % per year in the apixaban group and 3.7 % per year in aspirin group (HR 0.45; 95 % CI 0.32–0.62; P < 0.001) [35]. A separate analysis of the AVERROES data looked at safety and efficacy of apixaban versus aspirin in patients with stage 3 CKD. It found that apixaban significantly reduced the risk of stroke and systemic embolism by 68 % compared with aspirin (1.8 vs 5.6 % annually) and that the risk of major

hemorrhage was not increased in stage 3 CKD patients taking either apixaban, or aspirin [36]. These trials support the idea that apixaban may be efficacious and safe in patients with estimated creatinine clearance values >25 ml/min. Recently, the US FDA approved apixaban 5 mg twice daily for patients with all stages of CKD, including those on hemodialysis. This approval is based on pharmacokinetic and pharmacodynamics studies, however, given the lack of randomized controlled trial evidence in this patient population, we do not endorse the use of full dose apixaban in patients with GFR < 25 ml/min and would encourage caution when prescribing to patients with a propensity to develop acute kidney failure resulting in impaired renal function for prolonged periods of time.

Edoxaban

Edoxaban is the newest oral anticoagulant studied for the reduction of stroke risk in non-valvular atrial fibrillation. Edoxaban is an oral direct Xa inhibitor that is rapidly absorbed by the gastrointestinal tract and has 62 % oral bioavailability [37]. Similar to the other available direct oral anticoagulants, edoxaban has a short half-life of 8–10 h. The kidneys eliminate approximately 35–50 % of edoxaban [37, 38]. The ENGAGE TIMI 48 study was a double-blind randomized controlled trial, which enrolled 21,105 patients with non-valvular atrial fibrillation [39]. In the primary analysis, both high dose edoxaban (60 mg daily) and low dose edoxaban (30 mg daily) was non-inferior to warfarin in reducing systemic thromboembolism and stroke. Edoxaban also significantly reduced the annual rate of major bleeding compared to warfarin, except for gastrointestinal bleeding, which was increased in the high-dose edoxaban group. Patients with end-stage renal disease, defined as an estimated creatinine clearance <30 ml/min were excluded from the study. 4,074 patients with estimated creatinine clearance 30–50 ml/min were included in the study, but received half of the study dose of edoxaban to prevent drug accumulation [39]. The treatment effect was not impacted by renal disease, which is encouraging for the use of edoxaban in patients with CKD, but again, does not provide any information for patients with stage IV or V CKD.

Low Molecular Weight Heparins in Chronic Kidney Disease

Both unfractionated heparin and low molecular weight heparin (LMWH) bind to antithrombin and facilitate its inactivation of factor Xa and factor IIa. LMWH has a smaller mean molecular weight than unfractionated heparin and cannot bind to both antithrombin and thrombin at the same time. This limits its ability to inactivate thrombin as effectively as unfractionated heparin, but does not impair its action against factor Xa [40]. Unfractionated heparin undergoes hepatic clearance and a dose reduction is not necessary for patients with CKD [41]. Patients who are receiving therapeutic doses of unfractionated heparin for acute coronary syndrome, or for treatment of venous thromboembolism, should have activated partial thromboplastin time (aPTT) values measured 6 h after the first dose and continuously according to a standardized nomogram. Unlike unfractionated heparin, LMWH is cleared primarily by the kidneys and the American College of Chest Physicians (ACCP) guidelines suggest reducing the dose of drug for patients with an estimated GFR ≤ 30 ml/min [42].

When bleeding rates are compared in patients with moderate CKD (stage 3, eGFR 30–50 ml/min) and those without renal failure who are taking enoxaparin, there is an adjusted odds ratio of 3.9 (95 % CI 0.97–15.6, P = 0.055) suggesting increased bleeding risk with moderate renal impairment [43]. The risk of bleeding in patients with on LMWH with renal insufficiency may depend on the size of the anticoagulant molecule. Tinzaparin is the largest LMWH with a molecular weight of 6.8 kD, followed by dalteparin (5.6 kD), enoxaparin (4.5 kD), and fondaparinux (1.7 kD) [44]. Larger molecules are able to accumulate more negative charges, which promotes non-renal clearance. They are also able to bind more effectively to thrombin, which promotes hepatic clearance [44]. Indeed, there is some data to support less accumulation of tinzaparin in patients with stage 3 CKD in comparison to other LMWH [45, 46].

Anticoagulation for Patients with Atrial Fibrillation on Peritoneal Dialysis

In patients with ESRD on peritoneal dialysis, the prevalence of atrial fibrillation is approximately 7 % [47]. There are few studies that examine the benefit and risk profile for oral anticoagulation in this population of patients. Shah et al. included both hemodialysis and peritoneal dialysis patients in their recent study, which showed that warfarin did not significantly reduce the risk of stroke in dialysis patients, although it did significantly increase the risk of major bleeding compared to non-dialysis patients [23]. Unfortunately, there are no randomized controlled trials specifically designed to examine the role for anticoagulation in peritoneal dialysis patients with atrial fibrillation, which limits our ability to make recommendations in this area.

Anticoagulation for Atrial Fibrillation in Renal Transplant Patients

Using data from the US Renal Data System, the incidence of atrial fibrillation in patients hospitalized after renal

transplantation was 5.8 per 1,000 person years. Select associated risk factors included older age at time of transplant, obesity, and graft rejection or loss [48]. In another 62,706 post-renal transplant patients identified from the US Renal Data System, 3,794 (6.4 %) had a diagnosis of atrial fibrillation within the year prior to transplantation. Patients with atrial fibrillation were older (60 years old compared to 50 years old) and had more cardiovascular comorbidities including congestive heart failure, hypertension, diabetes, and prior cerebrovascular disease [49]. This study found that transplant patients with atrial fibrillation had worse outcomes, including death, graft failure, death-censored graft failure, and ischemic stroke compared with those that did not have atrial fibrillation pre-transplant [49]. Despite the prevalence of atrial fibrillation and poor outcomes in transplant patients with atrial fibrillation, there are no randomized controlled trials to describe the benefits of oral anticoagulation, or bleeding risk in this population.

Assessing Risk of Bleeding in Patients with Chronic Kidney Disease

While patients with stage 3 CKD and atrial fibrillation benefit from anticoagulation to reduce the risk of thromboembolism, particularly stroke, they also have a higher risk of bleeding than patients without renal disease [13]. In a study of 5,912 patients with non-valvular atrial fibrillation, decreased eGFR was associated with an increased risk of ischemic stroke or systemic embolism, as well as major bleeding, regardless of whether patients were taking warfarin or no anticoagulation [50]. Atrial fibrillation patients with stage 3 CKD have about twice the rate (about 5 %/year) of major bleeding during warfarin anticoagulation compared to those without CKD, but it is not clear whether this is accounted for by age differences, other associated disease, or renal dysfunction [51]. Increased bleeding rates appear to be particularly concerning in patients on dialysis; at baseline [52], with antiplatelet agents [53], or with warfarin [54].

The HAS-BLED risk score is a validated tool from 0 to 9 to determine the risk of major bleeding for patients with atrial fibrillation [55]. Hypertension, abnormal liver or renal function, stroke, bleeding, labile INR, elderly patients >65 years, and drugs or alcohol use are the component parts of the risk score [55]. Unfortunately, the HAS-BLED score has yet to be validated in patients with severe renal impairment or those requiring renal replacement therapy. The $HEMORR_2HAGES$ score is another tool used to calculate bleeding risk in patients with atrial fibrillation [56]. This score is slightly more arduous than the HAS-BLED score, as it requires genetic testing for CYP2C9 polymorphisms. The component parts of the $HEMORR_2HAGES$ score are hepatic or renal disease, ethanol abuse, malignancy, older age (>75 years), reduced platelet count or function, rebleeding risk, hypertension, anemia, genetic factors, excessive fall risk, and stroke [56]. Again, this score has not yet been validated in severe CKD and dialysis-dependent patients and is rarely used.

Another decision tool for bleeding risk was derived from the ATRIA study. This score includes five components: anemia (3 points); severe renal disease, defined as eGFR <30 mL/min, or dialysis-dependent (3 points); age >75 years (2 points), prior bleeding (1 point), and hypertension (1 point). Low risk for major bleeding is 0–3 points (0.8 % rate of major hemorrhage), moderate risk is 4 points (2.6 % rate of major bleeding), and high risk is 5–10 points (5.8 % rate of major hemorrhage) [57]. Since this study included patients with varying stages of CKD, as well as those on dialysis, it may be more applicable to assessment of bleeding risk in renal patients.

Conclusions

Despite the high prevalence of atrial fibrillation in patients with CKD, there is limited evidence to guide therapeutic decision-making. Warfarin is the only oral anticoagulant that is not dependent on renal clearance, however recent guidelines do not recommend using warfarin for patients with ESRD due to bleeding risk and vascular calcification. The available direct acting oral anticoagulants, dabigatran, rivaroxaban, apixaban, and edoxaban, depend on renal clearance in varying degrees. Subgroup analyses from the large phase III randomized trials shows that these anticoagulants are likely effective and safe for patients with stage 1–3 CKD, but there is no evidence supporting the efficacy or safety of these drugs in patients with stage 4 CKD (with the possible exception of apixaban to a GFR of 25 ml/min), or dialysis-dependent patients. The risk of stroke, as well as bleeding risk needs to be carefully considered in CKD patients and decisions regarding anticoagulation should be made in collaboration with patients and multi-disciplinary teams. Until more evidence becomes available regarding anticoagulation in CKD patients, there will continue to be an element of uncertainty in anticoagulant choice. Frequent assessment of CKD patients on oral anticoagulants, including ongoing reassessment of individual thromboembolism and bleeding risks will continue to be at the core of treatment decisions (Fig. 4.3).

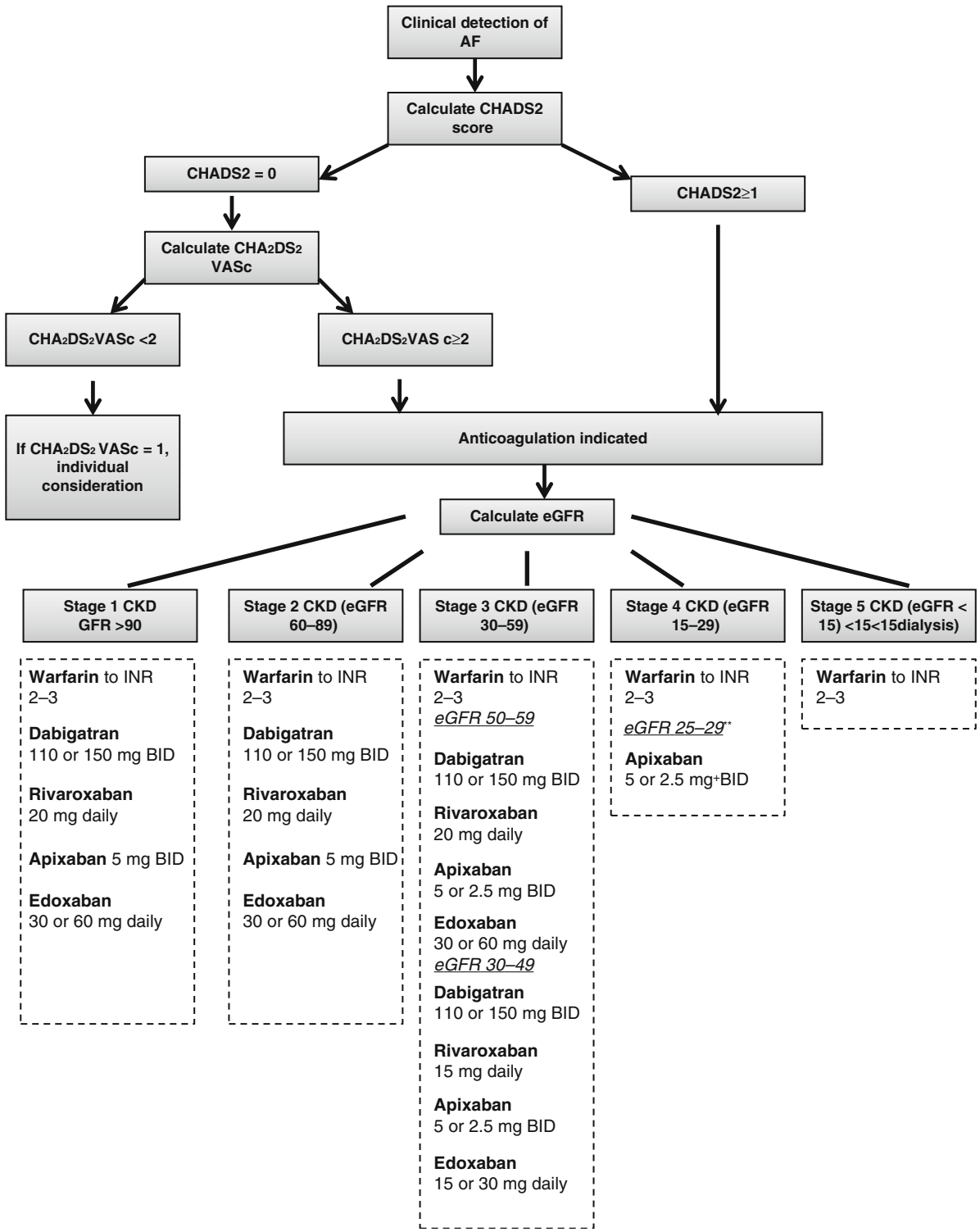

Fig. 4.3 Clinical recommendations for anticoagulant choice in patients with atrial fibrillation and CKD. *AF* atrial fibrillation, *CKD* chronic kidney disease, *eGFR* estimated glomerular filtration rate, *INR* international standardized ratio, *BID* twice daily. +2.5 mg BID if creatinine ≥1.5 mg/dL (133 umol/L) and age ≥80 years and weight ≤60 kg. **Apixaban should be used with caution and frequent clinical assessment of bleeding risk required

Back to the Clinical Case

Our 68-year-old male patient with type 1 diabetes mellitus, hypertension and hemodialysis-dependence has a CHA2DS2VASc score of 2 (1 point for hypertension and 1 point for diabetes). He has an R_2CHADS_2 score of 4 and a HAS-BLED score of 1. When the risks of stroke were measured against the risks of bleeding, the medical team opted to start anticoagulation. Despite controversial evidence in hemodialysis patients, warfarin was started for stroke prevention. Over the next 2 years, the patient continues to be carefully monitored and has not had an event (stroke, or bleeding) since commencing treatment.

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MRA Inhibition in CKD: More Than Salt and Water

5

Christina Gant, Gozewijn Dirk Laverman, and Gerjan Navis

Clinical Case Scenario

A 54 year old man suffering from CKD (eGFR 58 ml/min) was treated with the maximum dose of an ACE inhibitor. He had no primary glomerular disorder necessitating specific immunosuppressive treatment. However, proteinuria (4.8 g/day, target <1.0 g/day) and ambulatory blood pressure (155/96 mmHg) were insufficiently controlled. He was sent to a dietician and instructed to adhere to a moderate sodium restriction. He successfully changed his habits, reflected by a decrease in urinary sodium excretion from 245 mmol/day to 150 mmol/day, and a concomitant improvement of proteinuria (2.6 g/day) and blood pressure (145/88 mmHg), both typical for the amount of sodium restriction. As proteinuria and blood pressure were still above target, the decision was then made to add the MRA inhibitor spironolactone 25 mg once daily. The patient was extensively instructed to stop the drug in any circumstance of excessive water/sodium loss. The proteinuria (1.1 mmol/day) and blood pressure (132/81 mmHg) further decreased. There was an acceptable decrease in eGFR from 58 to 51 ml/min (reflecting the reversible effect of treatment on glomerular pressure) and renal function remained stable in three subsequent years. Based on the 24 h urine collections, he was reinforced to keep his sodium restriction of a few occasions. In the next summer he suffered from a severe gastroenteritis after having a barbecue. He immediately stopped spironolactone and promptly contacted the outpatient clinic for blood collection. The potassium concentration remained within acceptable limits. After recovery of his illness, spironolactone was started again.

Introduction

Chronic kidney disease (CKD) is characterized by prolonged (≥3 months) structural and functional abnormalities of the kidneys. CKD is defined by a decreased renal function, that is glomerular filtration rate (GFR) <60 mL/min/1.73 m^2, and/or urinary loss of protein. The latter, proteinuria, may also be measured as albuminuria.

CKD is one of the major causes of morbidity and mortality worldwide and it is closely related to cardiovascular disease. CKD prevalence has been steadily increasing over the last decades, leading to a large global disease burden. The most important causes of CKD in developed countries are diabetic nephropathy and renovascular disease/hypertension. Deterioration of renal function into end stage renal disease (ESRD) leads to a requirement for renal replacement therapy, i.e. dialysis or kidney transplantation. Unfortunately, the possibility for transplantation is limited by donor shortage, and dialysis is associated with a poor quality of life, partly caused by an extremely increased risk of cardiovascular complications. Prevention of renal function loss in the earlier stages of CKD is therefore of utmost importance.

The so-called renoprotective treatment aims to halt kidney damage and thus progressive renal function loss with blood pressure and proteinuria as important intermediate outcome measures. Therapy of choice is blockade of the renin-angiotensin-aldosterone system (RAAS), with either angiotensin converting enzyme inhibitors (ACEi), or angiotensin II receptor blockers (ARB). Despite a proven favorable effect

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of RAAS blockade on short-term parameters (blood pressure, proteinuria) as well as long term outcome (slower decline of GFR), progression of CKD to ESRD still occurs in many patients. In the search for additional treatment options, combination therapy by ACEi and ARB, or combination of either ACEi or ARB with direct renin-inhibitor, unfortunately do not improve long term renal outcome, and may even worsen it.

Mineralocorticoid receptor activation (MRA) inhibition is currently being studied as a new therapeutic approach to CKD. Although this therapy is not new, there is new attention, fuelled by striking new insights that have been obtained in the understanding of aldosterone and its (patho) physiological effects. Next to the classic anti-diuretic and potassium wasting effects, aldosterone has been shown to directly impact the heart, central nervous system, vasculature and kidneys, promoting inflammation, fibrosis and tissue remodeling, independently of its effect on sodium status and blood pressure. Furthermore, it has been shown that during prolonged RAAS blockade treatment, aldosterone levels return to normal only in 10–50 % of cases, suggesting a window of opportunity for intervention. Here we will review the role of MRA inhibition as an added treatment option in the management of chronic kidney disease.

Aldosterone

Classic Effects and Regulation of Aldosterone Release

Aldosterone, primarily synthesized in the zona glomerulosa of the adrenal cortex, is a steroid hormone with mineral corticoid activity. In addition, aldosterone is also locally synthesized in the blood vessels, brain, heart and adipocytes. Adrenal release of aldosterone is stimulated by an increase in angiotensin II, by hyperkalemia and by the adrenocorticotropic hormone (ACTH). Circulating aldosterone levels are higher in men than in women, but the clinical significance of this difference is so far unknown.

The classic role of aldosterone is homeostatic volume control by promoting sodium and fluid reabsorption in the kidneys, thus providing a main contribution to the body's defense against sodium/volume depletion. Furthermore in hyperkalemia aldosterone promotes potassium excretion in the kidneys and colon. These classical effects are achieved by binding to the mineralocorticoid receptor (MR), which is located in the cortical collecting ducts in the distal nephron. The MR is a cytosolic receptor which migrates to the cell nucleus when ligand-activated. Here it attaches to the hormone regulatory part of target genes, enhancing transcription and translation of these genes, and thus stimulating the synthesis of aldosterone-induced proteins. The subsequent molecular pathway leads to an increased expression of the Na+/K+ pump in the apical epithelial membrane of the cell, increasing sodium reabsorption and potassium wasting. Furthermore, it increases expression of the basolateral Na+/K+ ATPase, stimulating sodium extrusion out of the cell and potassium entry into the cell. Lastly it increases the expression of apical renal outer medullary potassium channels which are involved in passive excretion of potassium. The MR has equal affinity to both mineral corticosteroids and glucocorticosteroids. While glucocorticoid plasma levels greatly exceed aldosterone plasma levels, the enzyme 11-beta-hydroxysteroid dehydrogenase-2 metabolizes intracellular glucocorticosteroid levels from 100 to 10-fold that of aldosterone, rendering aldosterone the major activator of the MR.

Non-classic Effects of Aldosterone

In the last decades new renal and extra-renal effects of aldosterone have been found, which can be reversed by MRA inhibition (Fig. 5.1). It has become known that aldosterone not only leads to genomic effects through activation of the MR, but can also lead to rapid non-genomic effects which do not require the transcriptional pathway described earlier [1, 2]. These non-genomic effects consist primarily of pro-fibrotic and pro-inflammatory changes and are mediated through (an interplay of) the cytosolic MR and aldosterone receptors in the cell membrane (Fig. 5.2). Aldosterone exerts these effects on not only renal targets, such as podocytes, mesangial cells and renal vasculature, but also on extra-renal targets where the MR has been found, primarily cardiomyocytes, endothelial cells, vascular smooth muscle cells, adipocytes, and macrophages [3].

Aldosterone is pathophysiologically involved in kidney damage through multiple mechanisms in addition to the effects of elevated systemic blood pressure [4, 5] (Fig. 5.2). Firstly, glomerular damage is induced by the increased production of reactive oxygen species (ROS) by mitochondria [6, 7]. Furthermore, aldosterone increases expression of the pro-inflammatory serine/threonine-protein kinase and activates NFkB, which ultimately lead to mesangial inflammation, fibrosis, and glomerular injury [8]. Also macrophage infiltration into the renal cortex is stimulated by aldosterone, which promotes inflammation [9]. Lastly increased local renal aldosterone production has been shown to induce apoptosis in podocytes, through mechanisms which are not completely elucidated [10]. These local effects were larger in rats with diabetes mellitus, which was associated with increased MR and aldosterone levels. All the mechanisms listed above may contribute to renal damage and consequent deterioration of kidney function. Indeed, an increased proteinuria has been found in patients with excess aldosteronemia, independent of blood pressure [4, 5]. As proteinuria is a bad prognostic sign for CKD, this adds to the rationale for aldosterone inhibition as a new promising approach in halting disease progression.

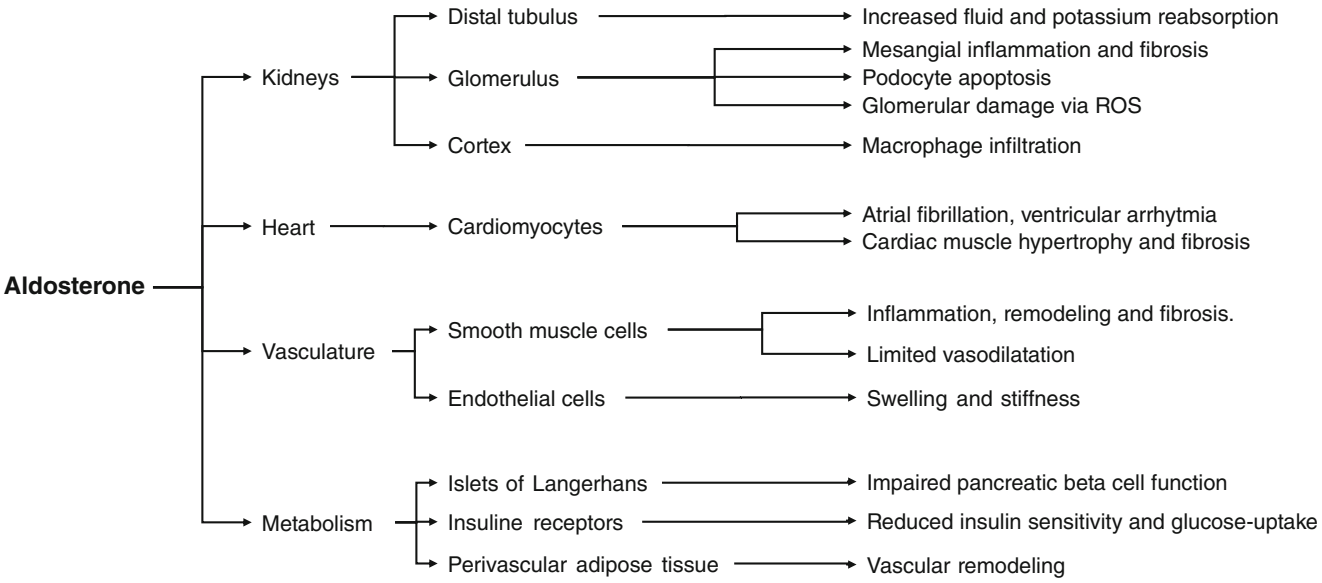

Fig. 5.1 Aldosterone exerts effects in the kidney, the heart, the vasculature and on the metabolism. It binds to the mineralocorticoid receptor in various target cells to induce different effect mechanisms

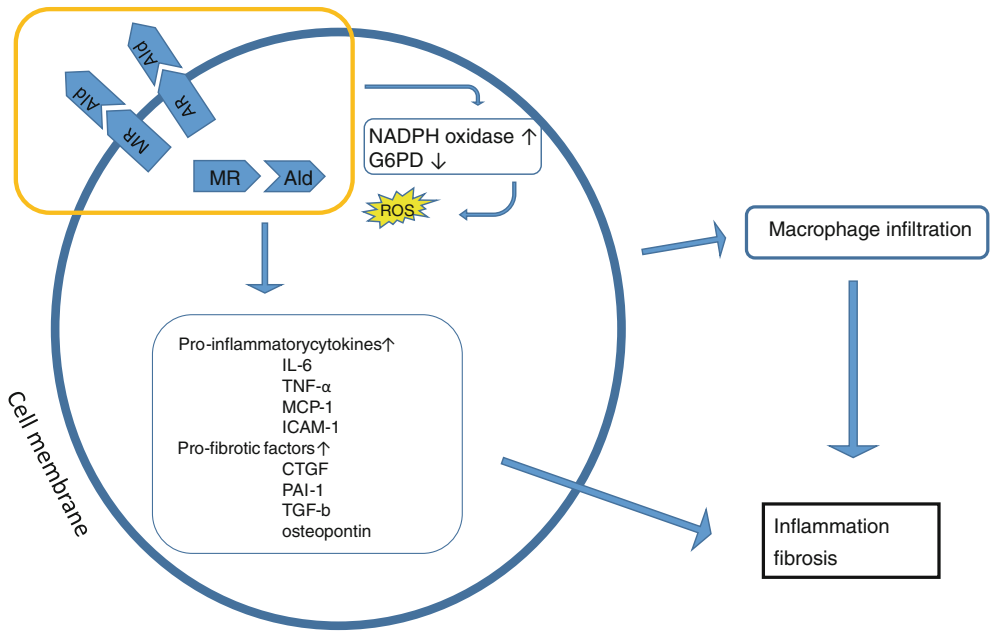

Fig. 5.2 Stimulation of cytosolic and membrane MRs by aldosterone in combination with stimulation of aldosterone receptors in the cell membrane lead to pro-inflammatory and pro-fibrotic effects [2]. In the mitochondria NADPH oxidase activity is increased, while G6DP activity is reduced, stimulating ROS generation [3]. Furthermore aldosterone upregulates pro-inflammatory and pro-fibrotic cytokines, and induces macrophage infiltration [4]. Ultimately these changes lead to tissue inflammation and fibrosis. *MR* mineralocorticoid receptor, *Ald* aldosterone, *AR* aldosterone receptor, *G6PD* glucose-6-phosphate dehydrogenase, *ROS* reactive oxygen species; *IL-6* interleukin; *TNF-α* tumor necrosis factor, *MCP-1* monocyte chemoattractant protein, *ICAM-1* intercellular adhesion molecule, *CTGF* connective tissue growth factor, *PAI-1* plasminogen activator inhibitor, *TGF-b* transforming growth factor

The heart was the first extra-renal organ where mineralocorticoid receptors were found. Here aldosterone has been shown to promote electrophysiological remodeling, leading to atrial fibrillation and ventricular arrhythmias [3]. Remodeling takes place through modulation of T-type, potassium L-type and ryanodine receptor calcium channel activity [11–14]. Furthermore through pro-inflammatory processes cardiac hypertrophy and cardiac fibrosis are propagated, resulting in a reduced cardiac function. The blood vessels are a target for aldosterone through MRs in the

vascular smooth muscle cells and endothelial cells. Here too hyperaldosteronism can lead to tissue inflammation, remodeling and fibrosis. MRA leads to endothelial swelling and stiffness by promoting the insertion of the epithelial sodium channel (ENaC) into the cell membrane [15]. Due to a simultaneous decreased ability to form nitric oxide, vasodilatation is limited. There is evidence that this is a main pathophysiological event leading to hypertension caused by hyperaldosteronism, rather than excess fluid retention.

Excess aldosterone levels are associated with the cardiometabolic syndrome, which is characterized by insulin resistance, central obesity, dyslipidemia and hypertension [3, 16]. Aldosterone impairs pancreatic beta cell function by promoting inflammation and oxidative stress in the islets of Langerhans [17, 18]. Also aldosterone degrades insulin receptor substrate proteins, reducing insulin sensitivity and glucose-uptake [19]. Furthermore, aldosterone promotes the release of inflammatory cytokines from adipose tissues resulting in systemic inflammation and impaired glucose tolerance [18]. The MR is found in adipocytes and perivascular adipose tissue (PVAT). Adipocytes and PVAT can produce local levels of aldosterone which exert paracrine and autocrine effects, influencing not only adipose tissues but also the vasculature and thus promoting vascular remodeling. In line, aldosterone blockade has been shown to be particularly effective to reduce blood pressure in obesity–related hypertension [20].

The Interaction Between Salt Status and Aldosterone Effects

The activity of the RAAS depends on what is denoted to as the "salt status", the RAAS being suppressed in state of sodium/fluid excess and being activated in a state of sodium depletion. Interestingly, an interaction between salt status and the pro-fibrotic, pro-inflammatory effects of aldosterone has been described, which is independent of blood pressure [21]. While in rats on a high or normal salt diet, high levels of aldosterone are associated with development of substantial end organ damage, high levels of aldosterone do not have such target organ effects during a low salt diet. Furthermore, the hypertrophic effects observed in high-salt, high-aldosterone rats can be completely reversed by the addition of MRA inhibitors, underlining the causal role of the mineralocorticoid receptor in the pathophysiological process. Salt excess has a role in sensitizing cardiovascular tissue for damage caused by an excess in aldosterone through mechanisms currently unknown. Interestingly new research shows that in CKD patients urinary salt excess is a significant predictor of urinary excretion of the mineralcorticoid metabolites tetrahydroaldosterone and tetrahydrocorticosterone, suggesting an alternative regulatory mechanism for aldosterone [22]. Whereas this novel insight may provide a missing link between CKD, high salt-status, and increased target organ damage, further research regarding this topic is warranted.

MRA Inhibition

MRA Inhibition in Heart Failure

After publication of the results from the large randomized controlled trials RALES and EPHESUS, MRA inhibition has been adopted as part of the standard treatment of chronic heart failure [23, 24]. These studies showed that MRA inhibition with spironolactone or eplerenone reduces morbidity and mortality in patients with severe chronic heart failure (NYHA functional class III and IV; Table 5.1). The EMPHASIS-HF study showed that eplerenone was also effective in patients with mild symptoms of heart failure (NYHA functional class II) [25]. This is supported by a meta-review published in 2009 which showed a reduction in all-cause mortality and an increase in ejection fraction in patients with left ventricular failure on spironolactone therapy [30]. However, in a recent observational study spironolactone was shown not to have a significant effect on risk of hospitalization and death, suggesting that the benefits of MRA inhibition that has been found in randomized trials may not be true in clinical practice [26]. However, in this study outcome was not adjusted for baseline disease severity and spironolactone use may have been more often applied in patients with a worse clinical condition. Currently the ACCF/AHA recommends MRA inhibition therapy in patients with NYHA class II to IV heart failure and a left ventricular ejection fraction of ≤35 %, unless contraindicated [31].

The Role of MRA Inhibition in CKD Treatment

Current treatment of CKD aims to prevent progressive renal function loss and its associated cardiovascular complications. Treatment of hypertension and proteinuria is the cornerstone of renoprotection. Inhibition of the RAAS by either ACEi or ARB has been proven to be an effective treatment option in CKD, reducing proteinuria as well as the rate of renal function loss. However, additional treatment options are necessary as progression of kidney disease still occurs in many patients. Combined blockade of the RAAS at different levels has been tested in several combinations, mostly ACEi combined with ARB [32]. Whereas dual blockade, with either ACEi plus ARB, or ACEI plus a renin-inhibitor is associated with a better efficacy on short term (i.e. proteinuria), hard outcome studies show that dual RAAS blockade does not confer better reno- and cardio-protection, but to the contrary, is associated with worse outcome [33].

Table 5.1 Long term effects of MRA inhibition in several types of disease

Author	Study type	Studied population	No of patients	Baseline medication	MRA	Follow up	Endpoints	Results	Hyperkalemia
Heart failure									
Pitt et al. [23]	Randomized controlled trial	NYHA III and IV heart failure	1,663	ACEi, loop diuretic	Spironolactone 25 mg daily	24 months	Death from any cause	RR of death, 0.70; 95 % CI 0.60–0.82, P<0.001; RR of hospitalization, 0.65; 95 % CI 0.54–0.77, P<0.001	Minimal incidence of serious hyperkalemia
Pitt et al. [24]	Randomized, double-blind, placebo-controlled trial	Acute myocardial infarction complicated by LV dysfunction and heart failure	6,632	Optimal treatment	Eplerenone 25–50 mg daily	16 months	Death from any cause	RR of death, 0.85; 95 % CI 0.75–0.96, P=0.008	Serious hyperkalemia, 5.5 vs 3.9 % in the placebo group (P=0.002)
Zannad et al. [25]	Randomized, double-blind placebo-controlled, parallel-group trial	NYHA II heart failure	2,737	ACEi, ARB, or both, and a beta-blocker	Eplerenone up to 50 mg daily	21 months	Death from CV causes or a first hospitalization for HF	HR of death from CV cause or first hospitalization for HF, 0.63; 95 % CI 0.54–0.74, P<0.001	Serious hyperkalemia, 11.8 vs 7.2 % in the placebo group P<0.001
Lee et al. [26]	Prospective cohort study	Newly diagnosed heart failure, LVEF <40 %	2,538	ACEi, ARB, beta-blocker, loop diuretic and/or calcium channel blocker	Spironolactone	36 months	Death from any cause, hospitalization	Adjusted HR of death, 0.93, 95 % CI 0.60–1.44; adjusted HR of hospitalization 0.91, 95 % CI 0.77–1.08	Severe hyperkalemia 4.8 per 100 person-years vs 1.6 per 100 person-years with nonuse, p<0.001
Chronic kidney disease									
Navaneethan et al. [27]	Cochrane systematic review	CKD patients	845	ACEi or ARB	Spironolactone	2–12 months	Proteinuria, GFR, BP	24 h proteinuria, 7 studies, 372 patients; MD −0.80 g, 95 % CI −1.23 to −0.38. eGFR, 5 studies, 306 patients: MD −0.70 mL/min, 95 % CI −4.73 to 3.34. Systolic BP, 7 RCTs, 372 patients: MD −3.40 mmHg, 95 % CI −5.13 to −1.68. Diastolic BP, 6 studies, 336 patients: MD −1.79 mmHg, 95 % CI −2.99 to −0.59	Hyperkalemia, 8 studies, 436 patients: RR 3.06, 95 % CI 1.26–7.41

(continued)

Table 5.1 (continued)

Author	Study type	Studied population	No of patients	Baseline medication	MRA	Follow up	Endpoints	Results	Hyperkalemia
Mavrakanas et al. [28]	Systematic review	Diabetic nephropathy	404	ACEi or ARB	Spironolactone 25 mg daily or eplerenone 50–100 mg daily	2–12 months	Proteinuria, GFR, BP	Reduction of albuminuria by 23–67 %. GFR slightly decreased. Significant drop in BP	Increased incidence hyperkalemia
Boesby et al. [29]	Open randomized cross-over trial	Non-diabetic chronic kidney disease	40	ACEi or ARB	Eplerenone 25–50 mg daily	2 months	Albuminuria, creatinine clearance, BP	Urinary albumin excretion was 22 % lower, CI: 14,28, $P<0.001$; creatinine clearance 5 % lower, CI: 2,8, $P=0.005$; mean systolic BP 4 mmHg lower, CI: 2,6, $P=0.002$; diastolic BP 2 mmHg lower, CI: 0,4, $P=0.02$	Potassium 0.1 mEq/L higher, CI: 0.1, 0.2, $P<0.001$

Another strategy to improve the efficacy of RAAS-blockade, is in manipulating the salt status: correction of the volume overload in patients on monotherapy RAAS-blockade, by either diuretics, a low sodium diet or their combination, considerably potentiates the efficacy of monotherapy RAAS-blockade [34, 35, 36]. Post-hoc analyses suggest that moderate dietary sodium restriction is also associated with better long-term outcome of RAAS-blockade [37], but prospective studies, so far, are unfortunately lacking. Observational data have shown a worse long term outcome in subjects that consume very low (<5 g/day) amounts of salt [38]. Whereas this might be related to underlying conditions associated with poor intake and malnutrition, it has also been pointed out that reactive hyperreninemic hyperaldosteronism might exert an adverse effect in such subjects [39] (Fig. 5.3). Of note, despite interference with the renin-angiotensin axis, a low sodium diet during ACEi or ARB is associated with secondary hyperreninemic aldosteronism that is particularly marked during the combination of diuretics and low sodium, demonstrating that the feedback loop between volume status and aldosterone is not disrupted by the current modes of inhibition of the RAAS by ACEi or ARB.

It has long been known that while under RAAS inhibition treatment with ACEi or ARB, aldosterone levels initially decrease, but can thereafter gradually increase to pretreatment, or even exceed pretreatment levels, a phenomenon that has been called "aldosterone breakthrough" or "aldosterone escape" [40] (Fig. 5.3). Whereas this so-called escape is usually associated with long term treatment, detailed assessment of the early effects of RAAS-blockade on aldosterone levels demonstrate that, actually, aldosterone displays an early partial return towards its baseline values even during the first week of treatment, possibly in response to the negative sodium balance induced by the RAAS-blockade, again demonstrating the preservation of aldosterone's role in volume homeostasis, despite ACE-inhibition [41].

Keeping in mind the deleterious effects of aldosterone on the kidneys, MRA inhibition is a promising new therapeutic approach in CKD. Studies in experimental animals, in proteinuric models and in CKD patients support a renoprotective effect of MRA inhibition. As monotherapy RAAS-blockade is therapy of choice for CKD, in particular the added effects of MRA to ACEi or ARB are of clinical interest. These could be due to interference with classic effects of aldosterone (i.e. a diuretic effect of MRA) as well as due to interference with the non-classic effects of aldosterone. A Cochrane review dating from 2009 has shown that MRA antagonism in addition to an ACEi or ARB, can in small doses significantly reduce proteinuria while only slightly influencing renal function or blood pressure, with the adverse effect of an increased incidence of hyperkalemia (Table 5.1) [27]. Long term clinical endpoints such as cardiovascular

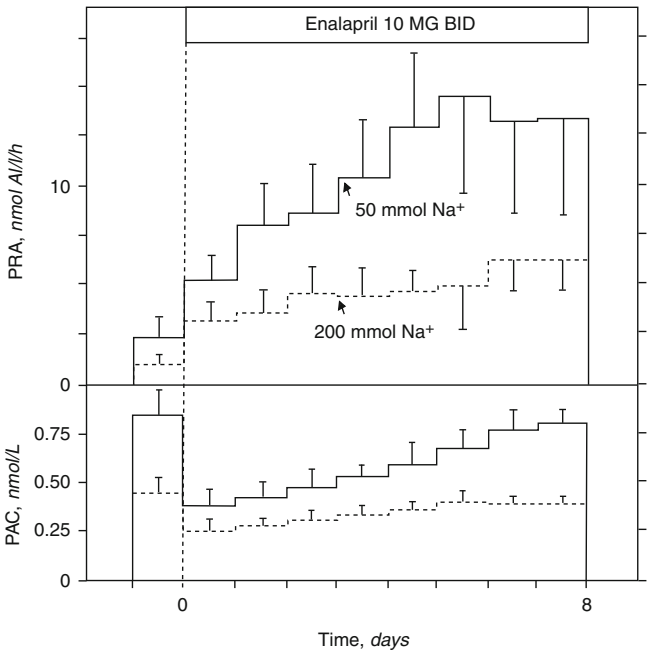

Fig. 5.3 Effects of enalapril on PRA and PAC (mean ± SEM) on liberal (*broken lines*) and low (*continuous lines*) sodium diet. *PRA* plasma renin activity, *PAC* plasma aldosterone concentration (Reprinted by permission from Macmillan Publishers Ltd: Navis et al. [39])

events or renal function were not available in the included studies. A recent systematic review concerning the effect of MRA inhibition in addition to RAAS inhibition on diabetic nephropathy confirmed these effects on proteinuria, blood pressure, glomerular filtration rate and potassium levels, however data on long term cardiovascular and renal outcome were still not available [28]. In non-diabetic patients with CKD, long term effects of MRA inhibition in addition to RAAS inhibition are also unavailable, while short term effects are comparable to that in patients with diabetic nephropathy [29]. In patients with mild CKD, treatment with MRA inhibitors was shown to have a beneficial effect on left ventricular mass and arterial stiffness [42]. In summary, the short-term effects of spironolactone and eplerenone are beneficial for CKD patients and these agents are also safe, provided that potassium levels are being monitored. However, there is a lack of data concerning the long term clinical outcome of dual treatment with an ACE-inhibitor or ARB and a MRA inhibitor, as well as lack of data on the mechanism of the added effect of MRA to ACEi or ARB. The treatment can be considered in individual patients who otherwise have an unacceptable poor (renal) prognosis, given that these patients are extremely well instructed with regards to stopping the MRA inhibitor in circumstances of volume/sodium depletion. It is obvious that more research is needed to determine the definite role of MRA inhibition in CKD treatment, in particular whether the risks outweigh te benefits.

Aldosterone Breakthrough and Sodium Status Intervention in CKD

The importance of aldosterone breakthrough during RAAS blockade treatment on clinical endpoints is currently unknown. While a low salt diet is associated with higher aldosterone levels, the deleterious effects of aldosterone on end organs are generally absent during low salt-status. In contrast, in patients with a high salt intake, however, aldosterone breakthrough may be associated with an increase in target organ damage. Better elucidation of the interrelationships between salt status and the renoprotective effects of aldosterone blockade in CKD is therefore needed. This could also contribute to a better understanding of the mechanisms of the added effects of MRA to ACE-inhibition or ARB. In a best-case scenario MRA inhibition could be an add-on therapy that allows to combine ACE-inhibition or ARB with low sodium diet potentiating its renoprotective effects, without the possible adverse effects of a reactive rise in aldosterone. Several studies on the renoprotective effects of MRA inhibition are currently ongoing, including long term intervention for prevention of diabetic nephropathy (PRIORITY) [43] and a short-term intervention analyzing the role of sodium status, and comparison with conventional diuretic during RAAS-blockade (http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=2133). These results may provide insight in the complex interplay between aldosterone breakthrough, salt status and MRA inhibition and thus delineate the optimal use of MRA for renoprotection.

Effects on Vascular Fibrosis and Hypertension

Spironolactone and eplerenone are anti-hypertensive agents used in patients with resistant essential hypertension. The rationale behind the use of MRA inhibitors for treating hypertension is derived from the classical genomic effects of aldosterone. By blocking the MR, slow onset volume and sodium loss occurs, and thusly blood pressure is lowered. However, in the absence of activation of the MR in vascular tissues, also arterial stiffness induced by aldosterone can be prevented. In 2008 a study has shown that treatment with eplerenone can reduce the media collagen/elastin ratio, reducing vascular stiffness [44]. Also, in low-renin hypertensive patients eplerenone was shown to be more effective than the ARB losartan in lowering blood pressure [45]. Possibly, in a low-renin state the MRA inhibitor is more efficient in reducing the non-classical effects of aldosterone than ARB. However, in diabetic patients spironolactone was shown not to influence endothelial function, while effectively reducing blood pressure [46]. While MRA inhibitors are effective in reducing blood pressure, more research is needed to clear up the physiological mechanisms.

MRA Inhibition and PTH

Primary hyperparathyroidism is a known risk factor for developing cardiovascular disease. Recent findings have suggested a bilateral interplay between aldosterone and parathyroid hormone levels. Aldosterone secretion in the zona glomerulosa of the adrenal gland is regulated by Ca^{2+} channels [47]. There is evidence PTH levels can up-regulate aldosterone by increasing plasma calcium [48]. On the other hand, relative hyperaldosteronism stimulates urinary and fecal Ca^{2+} excretion in the presence of excess dietary salt intake, and thusly stimulates PTH secretion [49]. Recently the MR was also identified in parathyroid cells [50]. It is unknown, however, whether activation of these MRs also lead to increased PTH excretion. The combination of relative hyperaldosteronism and elevated PTH levels can increase target organ damage, as well as have deleterious skeletal effects. Research has shown that patients with congestive heart failure treated with spironolactone have a reduced fracture risk compared with patients without MRA inhibition treatment [51]. Recently the relationship between the RAAS and the PTH level in humans, without primary hyperaldosteronism has been studied, and it was shown that spironolactone treatment can slightly but statistically significantly reduce plasma PTH levels [52]. However in this study aldosterone infusion did not directly increase PTH levels, suggesting a more long term gradual effect of aldosterone on PTH levels. As secondary hyperparathyroidism often occurs in both CKD and congestive heart failure patients, the interplay between PTH and aldosterone may be relevant [53]. Future research will have to determine the role of PTH on end organ damage, and the effect of MRA inhibitors on PTH and calcium metabolism.

Adverse Effects of MRA Inhibition

The most important adverse events associated with MRA inhibition therapy are hyperkalemia and hemodynamically mediated renal function loss. Most trials concerning MRA inhibitor usage show an increase in hyperkalemic events in patients treated with mineralocorticoid receptor antagonists, however, this was not associated with an increased risk of hospitalization or death in patients with heart failure or CKD [26, 54]. Furthermore, significant or irreversible renal function loss was not seen. Still, long-term studies on the effect of MRA inhibition in CKD patients on renal function and cardiovascular events are currently lacking.

Conclusion

New insights in the non-genomic effects of aldosterone on multiple target organs render MRA inhibition a promising approach in CKD treatment. The role of aldosterone breakthrough during RAAS blockade therapy is under

investigation. While salt restriction is associated with higher aldosterone levels during ACEi or ARB, low salt intake could prevent the non-classical pro-fibrotic pro-inflammatory effects of aldosterone. Future studies will have to answer the question whether there is a role for MRA inhibition in CKD treatment in addition to current evidence-based renoprotective treatment (RAAS blockade with ACEi or ARB, salt restriction). Furthermore, upcoming data on the efficacy of MRA inhibition as compared to conventional diuretics, and the optimal combination with dietary salt targeting in CKD will allow the understanding needed to use MRA inhibition for optimal therapeutic benefit in CKD patients.

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Vascular Effects of Inflammation and Oxidative Stress in CKD

6

Michal Chmielewski, Bengt Lindholm, and Peter Stenvinkel

Clinical Case Scenario

Eric Johnson is a 78 year old male. Eric quit smoking at age 64, used to be moderately obese but lost 18 kg in the last year and now has a BMI of 20. He suffered a myocardial infarction 6 years ago and has since then been taking aspirin (75 mg), metoprolol (100 mg) and candesartan (16 mg). He generally avoids health-care contacts but knows he has "some problems" with the kidneys.

You becomes involved in this case as a nephrology consultant when the resident on-call contacts you a Wednesday evening at 6 pm. Eric has been referred acutely to the ER by his GP due to anaemia with Hb 7.5 g/dL and general wasting since "some time". The resident is concerned by the patients estimated GFR of 18, potassium 6.4 mmol/L, serum bicarbonate of 15 mmol/L and CRP 34 mg/L. The patient receives oral resonium, sodium bicarbonate (intravenous, then oral) and finally a blood transfusion. He is shown to be mildly iron deficient. Post-renal obstruction and acute nephritis are excluded, and during the following week he is evaluated for GI bleed, malignancy, infections and inflammatory diseases. Nothing but signs of advanced generalised atherosclerosis are found.

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Introduction

Chronic kidney disease (CKD) affects about 10 % of the general population [1] and, with disease progression, increasingly associates with excessive mortality risk, mainly due to cardiovascular complications [2]. Evidence suggests that CKD is associated with premature aging [3]. In end-stage renal disease (ESRD) patients on dialysis, the annual mortality rate, 10–20 % depending on the country/region, is comparable to that of patients with some common forms of metastatic cancer [4]. Even a slight decrease in glomerular filtration rate (GFR) predicts cardiovascular risk [5]. Although traditional (*i.e.*, Framingham) risk factors, such as age, smoking, dyslipidemia, hypertension, and diabetes mellitus are common and predict cardiovascular mortality in CKD patients, especially in patients with mild to moderate CKD, so called novel risk factors, such as inflammation and oxidative stress, are also highly prevalent in these patients and are major driving forces for the uremic phenotype, which commonly includes both premature cardiovascular disease and protein-energy wasting (PEW) [6]. The risk factor profile is markedly different in the uremic milieu and chemical alterations of molecules in the uremic milieu may transform them and change their pro-atherogenic potential. This chapter focuses on the impact of inflammation and oxidative stress on cardiovascular complications in CKD population.

Inflammation

Inflammation appears as an inherent complication of CKD and the strong links between chronic inflammation, protein-energy wasting (PEW), and atherosclerosis in ESRD were described more than 15 years ago [7], and since then have been confirmed and widely acknowledged [8]. The prevalence of inflammation, as assessed on the basis of elevated laboratory markers, may exceed 75 % in dialysis patients [9]. Although the causes of inflammation are evident in some

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patients, the exact mechanisms are often not clear. Bioincompatibility of dialysis membranes in hemodialysis (HD) and of dialysis fluids in peritoneal dialysis (PD), and their interaction with circulating monocytes, have been postulated as primary factors in dialysis patients [10, 11]. However, elevated pro-inflammatory biomarkers are also frequently found in CKD patients not yet on dialysis, indicating that the dialysis procedure *per se* is not the leading cause of inflammation [7, 12]. Toxicity of uremic solutes, overhydration, altered gut microbiota, and co-morbidities, all seem to be major contributors to the "uremic inflammation".

Whatever the cause, inflammation seems to be a strong predictor of poor outcome in CKD. Numerous studies have shown that even a single measurement of an inflammatory biomarker can predict mortality in this patient population [7, 13–19]. The following sections will briefly describe the most important inflammatory markers, disturbances in their metabolism in the course of CKD, their possible impact on vascular complications, and, as a consequence, their detrimental effect on the renal and general outcome of CKD patients. Their potential contribution to vascular injury is summarized in Table 6.1.

C-Reactive Protein (CRP)

In the clinical setting, C-reactive protein (CRP) is the molecule that is most often used as a marker to monitor inflammation. Synthesis of CRP in the liver occurs during a wide range of acute and chronic inflammatory conditions, but also in malignancies or tissue injuries. With its 19-h half-life, CRP is easy to detect in the circulation. The average CRP level ranges from 1 to 3 mg/l in the general adult population [20] while it is typically twice as high in dialysis patients [21, 22]. Similarly, patients with CKD not yet on dialysis display CRP concentrations higher than those observed in the general population and the probability of having an increased CRP rises as GFR decreases [9]. The exact mechanisms that lead to increase in CRP are still not clear. However, apart from well-established clinical causes such as intercurrent illnesses, especially infections, the most probable factors responsible include: retention of circulating cytokines, advanced glycation end-products (AGEs), pro-oxidants, sympathetic overactivity, and the impact of the dialysis procedure itself [23–25].

Studies *in vitro* suggest that CRP is involved in vascular processes contributing to atherosclerosis. CRP is found in lipid-laden plaques [26] where its ability to facilitate monocyte adhesion has been documented [27]. Moreover, CRP inhibits endothelial nitric oxide synthase, and, hence, impairs vasoreactivity [28]. The concept that inflammation in general, and/or specifically the CRP may contribute to vascular risk was further strengthened by the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) [29]. In this trial, decrease in hsCRP following rosuvastatin administration was associated with a substantially lower cardiovascular risk, even though cholesterol concentration was normal in the studied subjects.

However, a growing body of evidence seems to negate a causative role of CRP in vascular pathology [30]. Experimental animals overexpressing CRP do not show features of accelerated atherosclerosis [31, 32]. Similarly, injections of large doses of CRP have no or minimal effect on atherosclerosis progression [33]. In the general population, large-scale Mendelian randomization studies have demon-

Table 6.1 Biochemical inflammatory markers and their potential contribution to vascular injury in CKD

Molecule	Molecular weight (kDa)	Normal levels	Concentration in advanced CKD	Potential contribution to vascular injury
Adiponectin	30	<11 mg/L	>15 mg/L	Low levels associated with vascular injury, high concentrations may reflect weight loss [46]
CRP	115	1–3 mg/L	>3 mg/L	Probably none, rather a marker than a causative risk factor [34–36]
Interleukin-6	24.5	<4 ng/L	>10 ng/L	Increase in platelet count, impaired insulin sensitivity, increased fibrinogen synthesis, release of adhesion molecules in the endothelium [41, 44, 45]
Leptin	16	<10 µg/L	>100 µg/L	Controversial, possibly sympathetic nerve activity, endothelial dysfunction, platelet aggregation and vascular smooth muscle cell proliferation [46]
Pentraxin-3	40.2	<5 ng/mL	>10 ng/mL	Endothelial dysfunction [50]
Resistin	12.5	<15 µg/L	60 µg/L	Controversial, sympathetic nerve activity, endothelial dysfunction, platelet aggregation and vascular smooth muscle cell proliferation [46]
SAA	12	2–5 mg/L	>5 mg/L	Activation of monocytes, reversal of the anti-inflammatory properties of HDL [53]
Visfatin	55	1–2 ng/ml	10 ng/ml	Controversial, possibly endothelial damage, inflammation, plaque destabilization [46]

CKD chronic kidney disease, *CRP* C-reactive protein, *SAA* serum amyloid A

strated that even marked elevations in CRP concentrations do not increase the risk of cardiovascular disease (CVD) [34, 35]. Similarly, there was no association between CRP haplotypes and cardiovascular risk in dialysis patients [36]. On the basis of these and other studies, CRP is currently regarded as a risk marker but not a risk factor for CVD.

Interleukin-6 (IL-6)

Intereleukin-6 (IL-6) is a 24.5 kDa molecule that promotes the activation and proliferation of lymphocytes, differentiation of B cells, leukocyte recruitment, and the induction of the acute phase protein response in the liver [23]. The concentration of IL-6, one of the most potent drivers of CRP production, is typically elevated in CKD [37]. The mechanisms for IL-6 increase in the course of CKD are far from being clarified but the most probable are similar to the ones responsible for CRP elevation described above. The concentration of IL-6 has been shown to independently predict cardiovascular complications and mortality both in the general population [38] and in CKD patients [39, 40]. Several mechanisms by which IL-6 could influence the vascular system have been put forward such as an increase in platelet count, impaired insulin sensitivity, increased fibrinogen synthesis, and release of adhesion molecules in the endothelium [41]. It has been postulated that the potential role of *Chlamydia pneumonia* on atherosclerosis progression is mediated by increased IL-6 synthesis [42]. Indeed, CKD patients in whom atherosclerosis progresses show increased prevalence of anti-chlamydia antibodies, and, at the same time, enhanced IL-6 concentration, which independently predicts atherosclerosis progression (Fig. 6.1) [43]. A direct role for IL-6 in vascular complications is further strengthened by Mendelian randomization studies showing that functional variants of *IL-6* gene affect the risk of CVD, both in the general population [44] and in CKD [45]. These results support a causative role of IL-6 in atherosclerosis progression and suggest it might be a target for future interventional studies.

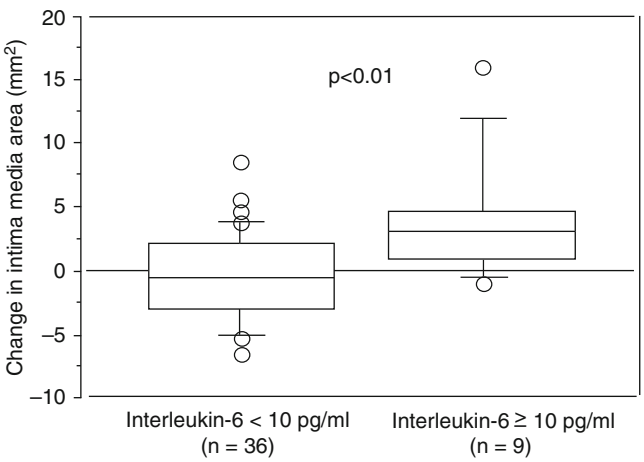

Fig. 6.1 Box plot showing a significant difference in changes of the calculated carotid artery area over 12 months between nine patients with IL-6 levels >10 pg/mL and 36 patients with IL-6 levels <10 pg/mL before start of dialysis treatment [43] (Reprinted from Yao et al. [19] with permission from Elsevier)

Adipokines

Adipokines are a group of bioactive proteins, such as leptin, adiponectin and resistin that are synthesized and released by adipocytes. They are believed to mediate the well-established association between obesity and increased cardiovascular risk. Their concentration in CKD it typically increased, possibly due, at least in part, to impaired renal clearance [46]. Experimental studies have documented the presence of adipokine receptors in atherosclerotic plaques. Moreover, their role in sympathetic nerve activity, endothelial dysfunction, platelet aggregation and vascular smooth muscle cell proliferation has been postulated [46]. As clinical studies evaluating the abovementioned associations have brought conflicting results [46] more studies are needed to establish whether adipokines could be considered as true risk factors for CVD.

Other Inflammatory Markers/Mediators

Pentraxin 3

Pentraxin 3 (PTX3) is a multifunctional soluble receptor modulating the immune-inflammatory response. It belongs to the same superfamily of acute-phase reactants as CRP and serum amyloid A. Concentrations of PTX3 have been found to be elevated in CKD, and to independently predict cardiovascular complications, both in dialysis and pre-dialysis patients [47, 48]. Elevated PTX3 may reflect endothelial dysfunction and be involved in adipose tissue-orchestrated mechanisms that modify inflammation and vascular complications in CKD.

Soluble TNF-Like Weak Inducer of Apoptosis (sTWEAK)

Soluble TNF-like weak inducer of apoptosis (sTWEAK) is a member of the tumor necrosis factor (TNF) superfamily. It is a glycoprotein with a molecular weight of 18 kD, which concentration tends to decrease in inflammatory conditions [49, 50]. Its levels have been shown to directly correlate with GFR, i.e. the lowest sTWEAK concentration has been reported in ESRD patients [51]. In this context, it is of interest that low sTWEAK has been shown to independently predict endothelial dysfunction in CKD subjects [52]. The mechanisms are still poorly understood, as for now it is difficult to discern whether sTWEAK has some protective role in endothelial functionality or merely is a

marker of endothelial dysfunction and risk for cardiovascular complications.

Serum Amyloid A (SAA)

Serum amyloid A (SAA) is a member of a family of apolipoproteins associated with high-density lipoproteins (HDL) in plasma. Since uremia impairs the atheroprotective properties of HDL, the role of this acute-phase protein has been evaluated. Indeed, in experimental studies, SAA induces inflammatory reactions in human monocytes and may reverse the anti-inflammatory properties of HDL [53]. As SAA has failed to independently predict mortality in HD patients [54], its exact role in promoting atherogenesis in CKD remains to be established.

Other Inflammatory Markers

Obviously, the abovementioned inflammatory markers do not fulfill the whole list of molecules and conditions that are associated with inflammatory processes and that are dysregulated in uremia. One of the most important abnormalities involving both inflammation and vascular injury in CKD include the disordered calcium-phosphate balance, where calcium-phosphate deposits induce inflammatory response, and at the same time lead to vascular calcification, one of the most potent risk factors for cardiovascular mortality in CKD [55]. Recently, calciprotein particles (CPPS) have emerged as a possible novel link between calcium-phosphate disorders, inflammation and vascular calcification [56].

Anemia in CKD, primarily caused by deficiencies in erythropoietin and iron, is exacerbated by inflammation, and may contribute to CVD. Metabolic acidosis, another inherent feature of CKD, can be aggravated by inflammation, and contributes to atherogenesis through enhanced protein catabolism, insulin resistance and bone resorption. The limited size of this chapter does not allow for a thorough description of these, and other, important risk factors.

Oxidative Stress

Oxidative stress can be defined as an imbalance between the generation of free radicals and the anti-oxidative capacity of surrounding tissues. Oxidative stress results in oxidation of macromolecules, including proteins, lipids, and carbohydrates, and is a widely acknowledged contributor to vascular disease in the general population. It is also an important feature of CKD, as increased levels of oxidative stress markers have been constantly demonstrated in uremic plasma [57]. Actually, oxidative stress starts early with renal function decline, and increased levels of oxidative markers have been documented already in CKD stage 3 [58]. Low-density lipoproteins (LDL) tend to be smaller and more dense in the course of CKD, and as such are more prone to oxidative modifications [59]. Indeed, numerous studies have shown that CKD, both at early stages and when dialysis-dependent, is associated with lipid and lipoprotein peroxidation [57]. Similarly, oxidatively modified plasma proteins and amino acids have also been documented in renal patients [57]. The exact mechanisms for oxidative stress in CKD are still poorly understood but are definitely associated with inflammation and PEW. As both these processes are prevalent in CKD, leading to hypoalbuminemia, it should be stated that the most important antioxidant capacity in plasma is provided by the thiol groups, which are largely located on the albumin molecule [57]. Therefore, patients with inflammation and/or PEW have a significantly diminished plasma antioxidant capacity. Other factors potentially responsible for increased oxidative stress in CKD have also been described (Fig. 6.2) [60]. Moreover, the uremic toxemia *per se* is postulated to augment oxidative stress, and, on the other hand, oxidative modifications of retained uremic solutes may potentiate their

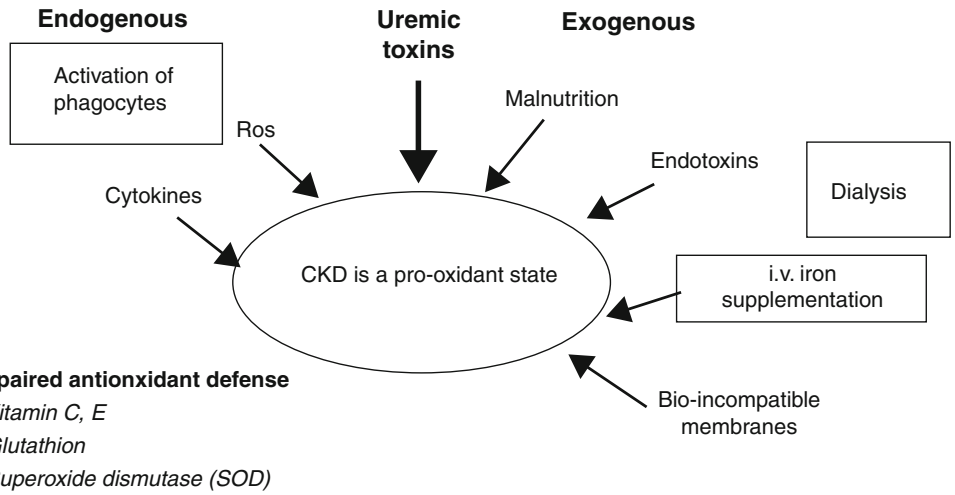

Fig. 6.2 Potential factors responsible for oxidative stress in CKD [60] (Reproduced from Stenvinkel et al. [43] with permission from John Wiley & Sons, Inc)

pathogenicity [57, 61]. As an example, recent evidence shows that HDL-cholesterol (regarded as anti-atherogenic) is transformed by symmetric dimethylarginine in the uremic milieu and paradoxically induces endothelial dysfunction via activation of toll-like receptor-2 [62]. In the clinical setting, few studies in CKD patients demonstrate associations between the intensity of oxidative stress and cardiovascular outcome [7, 63]. The impact of oxidative stress on hypertension and anemia, acknowledged cardiovascular risk factors, has also been postulated in CKD [64, 65]. Moreover, functional polymorphisms in genes encoding proteins involved in the antioxidant capacity have been shown to be associated with atherosclerosis, pointing to a casual role of oxidative stress in vascular complications in CKD [66, 67].

Therapeutic Possibilities of Anti-inflammatory and Anti-oxidative Treatment in CKD

The close relationships between inflammation, oxidative stress and atherosclerosis have led to studies evaluating drugs that would target inflammation and oxidative stress to diminish the cardiovascular risk. The current strategies are described below and summarized in Table 6.2. However, since inflammation and oxidative stress in CKD are driven by numerous factors, it has to be stated that we may never find a single silver bullet to tame these disorders. Instead, we may need a holistic approach involving among others: adequate dialysis prescription, use of biocompatible membranes and solutions, avoidance of central dialysis catheters, exercise implementation, adequate nutrition, efficient treatment of co-morbidities, and perhaps, on top of that, targeted anti-inflammatory and anti-oxidative medications.

Anti-cytokine Therapies

Given the potential of inflammatory molecules to directly modify the vascular risk, as described above, the hypothesis that by decreasing concentrations of these inflammatory markers one could improve the cardiovascular outcome is solid. However, only a few studies have tested anti-cytokine drugs in CKD patients. Administration of the TNF-receptor antagonist etanercept improved albumin and pre-albumin concentrations in HD patients [68]. In a similar cohort, treatment with a recombinant human IL-1 receptor antagonist resulted in a marked reduction in CRP and IL-6 levels as well as an increase in pre-albumin concentration [69]. Pentoxifylline is another drug with interesting anti-inflammatory effects, as it has been shown to improve protein breakdown along with an incremental anabolic effect [70, 71]. In the general population we are now witnessing an outbreak of studies focusing on targeted inhibition of IL-1, IL-6, phospholipase A2, CCR-2, and leukotrienes [72, 73]. Whether these therapies prove useful also in CKD patients, remains to be determined.

Anti-oxidative Therapies

Although, as described above, oxidative stress is enhanced in CKD, studies on anti-oxidative therapies show conflicting results. While some demonstrate no effect of treatment with tocopherols and alpha-lipoic acid in CKD stage 3–4 patients [74], nor in HD subjects [75], others show that supplementation with gamma-tocopherol, docosahexaenoic acid, or N-acetylcysteine has the potential to decrease IL-6 levels [76, 77]. Clearly, larger prospective trials are needed to verify these findings and to establish their impact on surrogate markers of vascular function and outcome.

Table 6.2 Therapeutic possibilities of anti-inflammatory and anti-oxidative treatment in CKD

Intervention	CKD population	Results
Anti-cytokine therapies		
Etanercept	HD	Increase in albumin and prealbumin concentration [68]
IL-1 receptor antagonist	HD	Reduction in CRP and IL-6 levels, increase in pre-albumin concentration [69]
Anti-oxidative therapies		
Gamma-tocopherol	HD	Decrease in inflammatory markers concentration [76]
Docosahexaenoic acid	HD	Decrease in inflammatory markers concentration [76]
N-acetylcysteine	PD	Decrease in inflammatory markers concentration [77]
Bardoxolone	Pre-dialysis	Decrease in inflammatory markers, retardation of CKD progression; however increased risk of cardiovascular events [78–80]
Nonspecific immunomodulatory approach		
Statins	Pre-dialysis	Reduction in CRP, and in mortality risk [83]
Cholecalciferol	HD	Reduction in inflammatory cytokines, and in left ventricular mass [88, 90]
Sevelamer	HD	Reduction in CRP and increase in getuin-A, improvement of endothelial function [92]

CKD chronic kidney disease, *HD* hemodialysis, *PD* peritoneal dialysis, *CRP* C-reactive protein, *IL-6* interleukin 6

The Nrf2 transcription system, which regulates genes involved in antioxidant and cytoprotective responses, may be an attractive target for intervention studies. Bardoxolone methyl, which acts by inhibiting pro-inflammatory transcription factors (such as NF-kB and STAT3), has shown promising results in CKD as it, in a small study, did slow down the progression of the CKD [78, 79]. However, a subsequent larger trial on bardoxolone was terminated prematurely due to an increased risk of cardiovascular events [80]. The reason for this unexpected result remains obscure, but potential hypotheses include: fluid retention, increased afterload, higher heart rate, and direct toxic effects. Since bardoxolone methyl activates a central transcription factor peroxisome proliferator–activated receptor γ, other, as yet unknown, mechanisms leading to volume retention and/or heart failure are also possible [81]. As various nutritional interventions may have weaker, but still meaningful, stimulatory effects on Nrf2, studies to evaluate if nutritional interventions may have an impact on inflammation and oxidative stress should be conducted [82].

Nonspecific Immunomodulatory Approach

In a secondary analysis of the JUPITER, rosuvastatin has been shown to reduce cardiovascular events and all-cause mortality among patients with moderate CKD and elevated CRP level [83]. In dialysis patients, the effect of statins is more controversial. While the SHARP (Study of Heart and Renal Protection) trial has demonstrated cardiovascular benefits of combined therapy with ezetimibe and simvastatin [84], other trials have shown no effect of statins on cardiovascular outcome, despite some impact on inflammatory markers [85, 86].

Vitamin D appears to play a special role in delaying atherosclerosis progression. Vitamin D receptors are present in all cells implicated in atherosclerosis, including endothelial cells, vascular smooth muscle cells, and immune cells. Experimental studies have revealed that vitamin D is involved in nitric oxide production and modulation of the vascular tone [87]. It significantly represses gene expression of prostaglandins, thromboxane A2, and of intercellular adhesion molecule-1, platelet endothelial cell adhesion molecule-1, and IL-6 in endothelial cells [87]. Following some promising results of *in vitro* studies, the anti-inflammatory potential of cholecalciferol supplementation has been evaluated. Indeed, cholecalciferol therapy was found to reduce circulating levels of inflammatory cytokines, including IL-8, IL-6, and TNF in HD patients with vitamin D deficiency [88, 89], as well as left ventricular mass index [90]. Moreover, administration of paricalcitol, a selective activator of the vitamin D receptor, was associated with a significant reduction in serum concentrations of CRP, TNF and IL-6, as well as a significant decrease in the mRNA expression levels of TNF and IL-6 in uremic peripheral blood mononucleated cells [91].

Sevelamer, probably through its lipopolysaccharide (LPS) binding potential, has been associated with a reduction in CRP and endotoxin levels [92] as well as higher fetuin-A levels [93], accompanied by an amelioration of endothelial dysfunction. Finally, it should be mentioned that several non-pharmacological interventions, such as short daily dialysis, exercise training, modification of nutrition (such as plant food, free fatty acids, probiotics etc.) may have impact on the smoldering uremic inflammation [94].

Conclusions

The risk of cardiovascular complications in CKD exceeds the one observed in the general population multifold. Current studies demonstrate that along with the traditional risk factors for CVD, inflammation and oxidative stress play a significant role in promoting atherosclerosis and vascular events. Both are highly prevalent in the course of CKD and seem not only to associate with cardiovascular risk but also to directly and causatively augment it. Although smaller studies show promising results of anti-inflammatory and anti-oxidative therapies in attenuating these complications, much larger trials are needed to verify their potential and clinical usefulness.

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Uric Acid, Allopurinol: The Cardio-Renal Silver Bullet?

7

Adrian Covic and Luminita Voroneanu

Clinical Case Scenario

A 67 years old Caucasian man with chronic kidney disease (eGFR 35.8 ml/min) presented with symptoms characteristic to new onset heart failure. He had a history of diabetes mellitus and hypertension for almost 20 years, and CKD due to diabetic nephropathy. The laboratory investigation revealed stationary renal function and stationary asymptomatic hyperuricemia (8.9 mg/dl), without any treatment.

In this case, hyperuricemia could be associated with new onset HF? Does he require medication for hyperuricemia? Is uric acid a prognostic factor for cardiac events and death in this case? Uric acid would be also a risk factor for ESRD?

Introduction

Elevated uric acid concentration is a common laboratory finding in subjects with metabolic syndrome/obesity, hypertension, kidney failure and cardiovascular events. Uric acid is the end product of purine metabolism that circulates in the plasma at concentrations varying from 2 to 10 mg/dl or higher. Purine nucleotides are derived from both exogenous (alimentary intake, especially animal proteins) and endogenous sources (*de novo* molecule synthesis and nucleic acid breakdown in the liver, intestines and other tissues – muscles, kidneys and the vascular endothelium). Purine catabolism involves several intermediate products (inosine, hypoxanthine, xanthine), and as a final step, xanthine oxidase catalyzes oxidation of xanthine to uric acid. Under normal conditions, the kidneys eliminate two-thirds of the uric acid production while the biliary tree removes the remaining one-third [1]. In the kidney, uric acid is filtered by the glomerulus and subsequently reabsorbed by the proximal tubes. Normal fractional excretion of uric acid is ~10 % [2].

Recently, four protein complexes that may act as urate transporters across the tubular cell membranes have been identified: human urate transporter 1 (URAT1) – the main protein responsible for tubular reabsorption – located at the apical membrane of the proximal tubular cells; urate transporter/channel (UAT) and OAT1 and OAT3 – two members of organic anion transporters family [3]. These two organic anion transporters OAT1 (*SLC22A6*) and OAT3 (*SLC22A8*) are found on the basolateral side of the epithelial cells from the proximal tubule [4]. Additionally, other multispecific anion transported have been identified: OAT4 (encoded by the *SLC22A11* gene), involved in luminal urate reabsorption by a mechanism that is transactivated by intracellular dicarboxylates but not by the antiuricosuric agents and OAT10 (*SLC22A13*), expressed in brush border membrane vesicles from proximal tubules [4].

In the proximal convoluted tubules, uric acid reabsorption is facilitated by URAT1 encoded by the *SLC22A12* gene and by GLUT 9 – a member of the glucose transporter family, encoded by the *SLC2A9 gene* [5]. The enzyme URAT1 is inhibited by probenecid, benzbromarone and by losartan [6]. It is not associated with gout. In contrast, GLUT9 is a glucose, fructose and uric acid transporter, with the highest affinity for uric acid [7]. It reabsorbs urate from the proximal renal tubes, but is also expressed in the distal nephron. It is responsible for almost 4 % of the variance in uric acid serum levels and is associated with gout. Mutation of this enzyme could determine severe hereditary renal hypouricemia type 2 [8, 9]. Hereditary renal hypouricemia type 1 is secondary to loss or functional mutations in URAT1 and is relatively common in Japan [10].

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Epidemiological Data

The incidence and prevalence of hyperuricaemia are not commonly studied. In a relatively recent study of the US population (in 2007–2008), prevalence rates for hyperuricaemia were reported to be 21.4 % (men: 21.2 %, women: 21.6 %) compared to 3.9 % for gout (men: 5.9 %, women: 2.0 %) in the same study [11]. A recent systematic review conducted in China has estimated the prevalence of hyperuricaemia to be similar to the US rate for men (21.6 %) but not for women (8.6 %) [12]. Hyperuricaemia is also very common in Europe: a prevalence of hyperuricaemia up to 15–20 % has been reported in UK population-based studies [13]. However, the prevalence appears different in several specific cohorts: 25~40 % in patients with untreated hypertension; 50 % in patients with hypertension on diuretics; 70~100 % in patients with malignant hypertension [13]; ~ 50 % in patients with CKD at the onset of renal replacement therapy [14, 15].

Pathophysiology

Hyperuricaemia may occur because of decreased excretion (underexcretors), increased production (overproducers), or a combination of these two mechanisms. Overproduction can be exogenous, due to a diet rich in purines, or endogenous due to accelerate purine degradation secondary to: (i) rapid cell proliferation and turnover (leukemias); (ii) cell death (rhabdomyolysis, cytotoxic therapy) or (iii) glycogenoses types III, IV, and VII – from excessive degradation of skeletal muscle ATP [16]. A small percentage of hyperuricaemia is derived from enzymatic defects: (i) complete deficiency of hypoxanthine guanine phosphoribosyltransferase (HGPRT) as in Lesch-Nyhan syndrome [17]; (ii) partial deficiency of HGPRT (Kelley-Seegmiller syndrome) [18]; (iii) increased production of 5-phospho-alpha-d-ribosyl pyrophosphate (PRPP) activity. Underexcretion accounts for most causes of hyperuricaemia. Hyperuricaemia can be secondary to (i) decreased GFR; (ii) decreased tubular secretion in patients with acidosis; – the organic acids compete with urate for tubular secretion; (iii) superior reabsorption of uric acid distal to the site of secretion (in association with diuretic therapy or in diabetes insipidus) [19]. The most common cause of combined mechanisms (underexcretion and overproduction) is alcohol consumption, which results in accelerated hepatic breakdown of ATP and the generation of organic acids that compete with urate for tubular secretion [20]. Other causes of combined mechanisms are the enzymatic defects such as glycogenoses type I and aldolase-B deficiency.

Uric Acid and Metabolic Syndrome/ Type 2 Diabetes

Metabolic syndrome is a state of insulin resistance associated with elevated blood pressure (BP), elevated plasma glucose and triglyceride levels, decreased high-density lipoprotein cholesterol levels and abdominal obesity, according to The National Cholesterol Educational Program Adult Treatment Panel III (NCEP ATP III) criteria [21]. These criteria were updated in 2005 to correspond to the new American Diabetes Association (ADA) standard of a normal fasting glucose level of less than 100 mg/dl. The metabolic syndrome describes a collection of modifiable risk factors occurring in the same individual and associated with an increased risk of developing cardiovascular disease and type 2 diabetes. Hyperuricaemia is already recognized as an important feature. In patients with metabolic syndrome, mean serum urate levels are approximately 0.5–1.0 mg/dl higher compared with controls [22]. Although hyperuricaemia is strongly associated with metabolic syndrome, a cause and effect relationship has not been established yet. It has been suggested that hyperuricaemia could be a simple consequence of the increased absorption in the proximal tubule secondary to hyperinsulinaemia; on the other hand, there are data showing that uric acid may predict the development of metabolic syndrome, obesity and diabetes [23]. The analysis of the NHANES III data have showed a higher prevalence of metabolic syndrome in patients with serum uric acid higher than 10 mg/dl (70.7 % (95 % CI 51.4–89.9 %) compared with 18.9 % (95 % CI 16.8–21.0 %) for urate levels less than 6.0 mg/dl [24]. Similarly, the prevalence of the metabolic syndrome was more than two-fold greater in patients with gout. A cross-sectional analysis of 1,370 adolescents aged 12–17 years showed a high prevalence in the highest quartile of uric acid serum levels (21.2 %) compared with < 1 % in the lowest quartile [24]. It was also demonstrated that the correlation between hyperuricaemia and metabolic syndrome is independent of kidney function. The renal status does not provide justification for the observed association between hyperuricaemia and metabolic syndrome.

The potential pathophysiological mechanisms by which uric acid contribute to metabolic syndrome are being clarified. The most probable is related to fructose rich diets; uncontrolled fructose metabolism determines intracellular ATP depletion, increased uric acid production, endothelial dysfunction, oxidative stress, and increased lipogenesis [25]. High fructose consumption induces insulin resistance and other manifestations of metabolic syndrome in a series of animal and human studies. Nakagawa et al. used rats fed with a high rich fructose diet with or without uric acid lowering drugs (allopurinol or benzbromarone) [26]. The group of rats that did not receive drugs developed hyperinsulinaemia, hypertriglyceridaemia, systolic hypertension and increased body weight. In children with primary fructose malabsorption the proportion of obese patients was lower compared with non-fructose malabsorption children. Logistic regression analysis with inclusion of various covariates showed that fructose malabsorption was negatively associated with obesity (OR = 0.35) [27]. In contrast, fructose from natural sources is less harmful possibly because of the presence of additional nutrients and

antioxidants. Pure fruit juice consumption among USA adults is associated with lower insulin resistance and lower odds of obesity and metabolic syndrome, although partly explained by demographics and life-style factors [28]. Additionally, it has been demonstrated that hyperuricaemia may stimulate hepatic fat accumulation and metabolic syndrome [29]. The mechanism appears to be mediated by mitochondrial oxidative stress. Uric acid stimulates NADPH oxidase, which translocates to mitochondria and generates free species radicals or may directly inactivate nitric oxide. This induction of oxidative stress in the mitochondria determines a decrease in the activity of aconitase in the Krebs cycle; the aconitase substrate – citrate – accumulates and is released to the cytosol, where it acts as substrate for fatty acid synthesis; additionally, uric acid stimulates B fatty acid oxidation, and ultimately, fat accumulation in the hepatocyte [29].

An essential link between uric acid, metabolic syndrome and type 2 diabetes is insulin resistance. Hyperuricaemia can induce insulin resistance through several mechanisms: (i) increased mitochondrial oxidative stress; (ii) endothelial dysfunction via inhibition of nitric oxide bioavailability [30]. Because insulin depends on NO for stimulation of glucose uptake, this may result in decreased glucose uptake. Therefore, it can be hypothesized that hyperuricaemia plays an important role in the development or worsening of insulin resistance. Nagakawa showed that uric acid block acetylcholine mediated vasodilatation, and can impair endothelial dysfunction, leading to subsequent hyperinsulinaemia [26]. Furthermore, a direct effect on adipocytes has been suggested. Recent studies have described the pro-oxidative capacity of uric acid in the differentiation of preadipocytes to adipocytes, an increase in reactive oxygen species (ROS) by activation of the NADPH oxidase, and sustained inflammation, mechanisms that may further promote insulin resistance and impaired insulin secretion [31]. In mouse adipocytes, uric acid induces a proinflammatory state, whereas lowering uric acid levels in obese mice resulted in reduced insulin resistance via direct effects on antiinflammatory markers produced by adipocytes [32]. Additionally, hyperinsulinaemia could amplify uric acid reabsorption in the proximal tubules, leading to hyperuricaemia. Thus, hyperuricaemia and insulin resistance share a bidirectional cause effect relationship [33].

Numerous studies have demonstrated an association between hyperuricaemia and insulin resistance even among normal fasting glucose and normal glucose tolerance patients. In a study involving 9,000 non-diabetic participants from the Atherosclerosis Risk in Communities Study, Carnethon et al. reported a higher risk of developing hyperinsulinaemia with increased baseline uric acid (odds ratio = 1.3, 95 % confidence interval (CI): 1.2–1.4; per 1.4 mg/dl) [34]. In a recent paper, Krishnan et al. analysed 15-year follow-up data on 5,012 persons in 4 US cities who were aged 18–30 years and diabetes-free at the time of enrolment [35]. They found that patients with hyperuricaemia have 1.36 times the risk of developing insulin resistance during 15-years of follow-up.

Several investigators have described the link between uric acid and type 2-diabetes. However, not all studies have found a strong association between the two. Because numerous diabetes risk factors also closely associate with uric acid (lifestyle factors – alcohol intake in particular, high values of body mass index, fasting plasma glucose, triglycerides etc.), it is difficult to definitely conclude about an independent relationship. In the Finnish Diabetes prevention study, elevated baseline uric acid and its increase overtime predicted a two-fold increase in the probability of developing type 2 DM [36]. A meta-analysis of 11 cohort study including almost 43,000 participants showed that serum uric acid had a positive correlation with the development of type 2 DM, despite of various study characteristics [37]; the authors reported an overall 17 % increased diabetes risk per 1 mg/dL (59.5 μmol/L) uric acid raise. In analyses limited to studies that corrected for at least three metabolic confounders (such as BMI), the association was attenuated to 11 %, but remained significant; this suggests an independent association. In a case-cohort analysis nested in the European Prospective Investigation into Cancer and Nutrition-Netherlands study, including 2,318 members and 845 incident diabetes cases, with a mean follow-up of 10 year, Sluijs et al. found almost identical directions and magnitudes of associations, with a 20 % increased diabetes risk per 59.5 μmol/L uric acid increase in an obesity-adjusted model, which attenuated to 13 % after further adjustment for metabolic risk factors in additional analyses [38]. In a recent analysis of the data from the Atherosclerosis Risk in Communities (ARIC) Study, Juraschek et al. showed that uric acid level was associated with diabetes even after adjustment for recognised risk factors (hazard ratio = 1.18 per 1 mg/dL) and the association remained significant after adjustment for fasting glucose and insulin levels [39]. Additionally they found that uric acid concentration rises prior to diagnosis of diabetes and then declines with diabetes duration; every additional 5 years' duration of diabetes was associated with a 0.10 mg/dL lower uric acid level after adjustment [39].

In contrast, a recent study found no evidence for a causal link between uric acid and diabetes using a Mendelian randomization approach [40]. However, the genetic loci used in this study explain only 5 % of uric acid variation and there may be other still-unidentified loci associated with uric acid as well as type 2 diabetes. In a prospective cohort study in Japan, involving 6,356 Japanese men, uric acid was not associated with an increased risk of type 2 diabetes [41].

Uric Acid and Cardiovascular Diseases

High uric-acid levels are correlated with cardiovascular risk, but it is as yet unclear whether uric acid is a culprit, a risk factor, or just a surrogate marker of disease.

Uric Acid and Hypertension

Serum uric acid was originally linked with hypertension in the 1870's. The pathogenic role of uric acid may be mediated by several mechanisms such as: inflammation, endothelial dysfunction, vascular smooth muscle cell proliferation (of the renal microcirculation), and activation of the renin – angiotensin – aldosterone system [42]. Furthermore, as discussed above, the intracellular pro-oxidative effects of uric acid, mediated through the NADPH dependent pathway are well described [43]. In endothelial cells, uric acid blocks nitric oxide release, inhibits endothelial proliferation and stimulates CRP production [44]. Mazzali et al. demonstrated that hyperuricaemia induces NO reduction in the macula densa, which in addition to stimulation of the renin-angiotensin system, generates hypertension [45]. Rat and human models suggest two phases in the development of hypertension [46]: an initial phase driven by uric acid and mediated by endothelial dysfunction, oxidative stress and the activation of the rennin-angiotensin system and a second one – which is no longer dependent on uric acid levels, and is mainly driven by pathological microvascular and inflammatory changes in the kidney. In a landmark study by Mazzali et al., pharmacologically induced hyperuricaemia was associated with the development of hypertension [45].

There is still a lack of consensus between authors regarding a direct causal relationship uric acid – hypertension. Numerous clinical studies since the early 1990s have persistently shown that increased uric acid precedes the development of hypertension. Cannon et al. reported that hyperuricaemia was present in 25–40 % of untreated hypertensives and 75 % of malignant hypertension subjects [47]. Feig et al. showed that 90 % of adolescent with newly diagnosed primary hypertension had an elevated uric acid (over 5.5 mg/dl) [48]. Moreover, administration of allopurinol has been shown to reduce both uric acid and blood pressure in several smaller studies [49–51].

Despite of these arguments, numerous authors do not consider hyperuricaemia a pertinent etiologic risk factor for hypertension [52]. Uric acid is well known as an antioxidant and the infusion of uric acid in humans *actually acutely improves* endothelial function [53]. Furthermore, the benefit of lowering uric acid with xanthine oxidase inhibitors may in fact be attributable to blocking xanthine oxidase-generated oxidants rather than to lowering uric acid. In fact, various uric acid lowering therapies have different effects on endothelial dysfunction, despite equivalent reductions in serum uric acid [52, 54]. Finally, genome wide association studies provided an additional counterargument: the presence of the genetic polymorphisms in various genes can explain only 5–7 % of the variance in serum uric acid levels – which may be associated with an increased risk for gout but not for hypertension.

Uric Acid and Coronary Heart Disease

Prospective studies analysing the predictive role of uric acid in the development of ischemic heart disease also report contradictory results [55]. Bickel et al. showed that the patients with angiographically confirmed coronary artery disease and serum uric acid levels in the upper quartile are five times more likely to die than those in the lowest quartile [56]. Also, 1 mg/dL increase in serum uric acid levels was associated with a 26 % increase in mortality. In contrast, plasma uric acid was not associated with coronary heart disease or ischaemic heart disease in two large cohort studies. In the Framingham study, during 117,376 person-years of follow-up, elevated serum uric acid level was not associated with an increased risk for adverse outcomes, after adjustment for established cardiovascular risk factors [57]. Strasak et al. reported similar results in a prospective study including 83,683 Austrian men [58]. Finally Palmer et al. analysing data from two large prospective cohort studies (58,072 participants from the Copenhagen General Population Study and 10,602 from the Copenhagen City Heart Study, comprising 4,890 and 2,282 cases of ischaemic heart disease, respectively) and using variation of the specific genes SCL2A9 as a marker for uric acid, found no evidence for supporting a causal relationship between uric acid or hyperuricaemia and risk of ischaemic heart disease [59].

Two meta-analyses concluded that hyperuricaemia was associated with only modest risk increases for cardiovascular outcomes, independently of other established risk factors. The most recent one, including 26 eligible studies with 402,997 adults described a modest association between hyperuricaemia and CHD events, independent of traditional CHD risk factors [60]. The overall risk of CHD death increased by 12 % for each increase of 1 mg/dL in uric acid levels. In subgroup analyses, hyperuricaemia appeared to significantly increase the risk of CHD deaths in women (by approximately 70 %), but not in men. A previous meta-analysis including 16 observational studies showed a pooled relative risk of 1.13 (95 % confidence interval [CI] 1.07–1.20), but with significant heterogeneity ($p=0.02$) [61]. In subgroup analyses, the relative risk for CHD was 1.12 (95 % CI: 1.05–1.19) in men and 1.22 (95 % CI: 1.05–1.40) in women.

Uric Acid and Heart Failure

Elevated uric acid is a constant feature of metabolic imbalance in heart failure (HF) pathophysiology [62]. In patients with HF, hyperuricaemia has been associated with reduced exercise capacity, diastolic dysfunction and endothelial dysfunction [63]. Moreover, a strong association between serum uric acid, HF severity and the risk of mortality has been described, suggesting that uric acid plays an independent role in the pathophysiology of CHF [64]. The potential

mechanisms involved are: (i) increase xanthine oxidase pathway activity and oxidative stress; this pro-oxidative effect may account for a variety of damaging processes relevant for HF pathophysiology, such as endothelial dysfunction, inflammation, metabolic impairment [65]; (ii) vascular smooth muscle cell proliferation – effect mediated by mitogen activated protein kinases, cyclooxygenase-2 and platelet derived growth factor [66]. The debate is again if uric acid itself is actively involved in these processes or whether it merely functions as an indicator of xanthine oxidase activity.

In numerous CHF studies, inhibition of xanthine oxidase with allopurinol was found to improve endothelial dysfunction and peripheral blood flow [67], hospitalization [68], B-type natriuretic peptide levels [69], metabolic imbalance [70], left ventricular ejection fraction and NYHA functional class [71–73].

Uric Acid and Stroke

The link between uric acid and stroke is less clear. Some authors have suggested that elevated uric acid levels are closely associated with stroke risk factors (hypertension, insulin resistance/metabolic syndrome) and therefore hyperuricaemia is a marker for patients at high risk for stroke [74]. Others suggest that uric acid is indeed an independent risk factor for stroke, directly inducing arterial stiffness, endothelial dysfunction and pro-oxidative effects and therefore, is directly involved with the pathophysiology of cerebrovascular disease [75]. Still others believe that the antioxidant properties of uric acid may in reality provide some protection against ischemic damage, in the brain [76]. Currently, the role uric acid plays in cerebrovascular disease is a matter of ongoing debate [77].

Nevertheless, there are several studies showing that elevated uric acid is associated with poor long-term outcomes in patients with stroke. In a recent, population-based, prospective cohort study, including 5,700 men and women from the general population, an 1-SD (87 μmol/L) increase in serum uric acid was significantly associated with 31 % increased risk for ischemic stroke in men [78]; additionally, the all-cause mortality risk was increased in both genders (by 11 % in men, and 16 % in women). In contrast, Chamorro et al. report a 12 % increase in the odds of a good recovery from ischemic stroke for each 1 mg/dL increase in uric acid [79]. Based on these results the same group has actually suggested *giving* uric acid as a therapeutic agent, in patients with acute ischemic stroke. Indeed, recently, Wang et al. showed in 1,452 patients with acute ischemic stroke that lower serum uric acid levels independently predicted poor functional outcomes at 1 year after stroke onset (odds ratio 0.335, 95 % CI: 0.164–0.684, $P=0.003$), also concluding that serum uric acid may be neuroprotective for acute ischemic stroke patients [80].

Uric Acid and Endothelial Dysfunction/ Vascular Stiffness

Increased arterial stiffness has been associated with an increased risk of CVD and mortality [81, 82]. The association between uric acid and arterial stiffness remains unclear. Studies of postmenopausal women [83] or unselected Japanese populations [84] describe a correlation between serum uric acid levels and increased arterial pulse-wave velocity, in multivariate-adjusted analyses that include conventional risk factors. Similarly, in a large cohort from China (n = 3,772), hyperuricaemia was associated with increased arterial stiffness independent of conventional cardiovascular risk factors [85]. In contrast, a cross-sectional evaluation of the ARIC cohort, including 6,522 women (74 % white) and 4,966 men (79 % white) showed a significant association between uric acid and intimal media thickness in women and white men (but not in black men). However, when known risk factors for atherosclerotic disease were controlled in multivariate analysis, the association became negligible in white women and much weaker and not statistically significant in black women and white men [86]. In 292 subjects with never-treated hypertension, serum uric acid was found to be associated with high sensitivity C-reactive protein but not pulse-wave velocity, suggesting that uric acid reflects low-grade inflammation within affected vessels rather than arterial stiffness itself [87].

Uric Acid and Chronic Kidney Disease

Mechanisms of Action

Increased serum uric acid is driven by numerous mechanisms [87]. Uric acid is primarily excreted by the kidney and consequently a decline in renal function is unavoidably escorted by a rise in the serum uric acid level. Sanchez-Lozada et al. showed in rats that hyperuricaemia induces oxidative stress, endothelial dysfunction, and secondary glomerular hypertension, in association with elevated renal vascular resistance and reduced renal blood flow [88, 89]. Additionally, hyperuricaemia had direct effects on the tubular cells, being able to induce an epithelial to mesenchymal transition [90]. These effects were more pronounced in animals with pre-existing renal disease. The specific mechanisms are complex – many described previously. Uric acid has a pro-oxidant intracellular effect, inducing stimulation of NAPDH oxidases and mitochondrial dysfunction. Moreover, uric acid can stimulate vascular smooth-muscle cells with overproduction of chemotactic factors and oxidants and activation of the RAS. Hyperuricaemia can also stimulate the release of alarmins from endothelial cells by mechanisms that involve calcium mobilization, the MEK/Erk pathway and activation of Toll-like receptor pathways [87, 91]. This

pathway stimulate the release of HMGB1, and once released, HMGB1 promotes its own further cellular release operating in a feedback loop mechanism and also activates NF-κB activity upregulating angiotensin-II expression and release [91]. In conclusion, HMGB1 promotes its own further cellular release while acting as an autocrine and paracrine system to activate a systemic inflammatory response [91].

Uric Acid and CKD Progression

For many years, it was thought that having elevated uric acid levels was only a risk for the development of gout or nephrolithiasis. In fact, the observation that uric acid can function as an antioxidant led many experts to consider an elevated uric acid as a rather beneficial host response, with possible protection from the oxidant stress associated with ageing, cancer and cardiovascular disease [92, 93]. However, in the last years, numerous experimental studies demonstrated an independent detrimental role for uric acid in the development and progression of CKD. The association of hyperuricaemia and CKD progression has been supported by some studies, but not by all. Hsu et al. showed in a large cohort (177,570 participants, with a 25 years follow-up) that increased serum uric acid level was associated with increased risk of end-stage renal disease independently of age, race, sex, body mass index, educational level, blood pressure, diabetes status, serum creatinine level, haemoglobin level, and proteinuria [14, 94]. Patients with the highest quartile of serum uric acid level had a more than two-fold higher adjusted risk of developing ESRD compared with those in the lowest quartile (adjusted hazard ratio 2.14; 95 % CI, 1.65–2.77). Chonchol et al. in 5,808 participants of the Cardiovascular Health Study found only a modest association between quintiles of uric acid levels and CKD progression [95]. In contrast, in 840 patients with CKD stage 3–4, participating in the Modification of Diet in Renal Disease (MDRD) prospective Study, hyperuricaemia was an independent risk factor for overall and CV survival, but not for kidney failure, despite a 10 years follow-up [96]. A potential explanation for these contradictory results may be that uric acid clearance is impaired in CKD, and as such, serum uric acid level is increased early on in kidney disease [14]. The MDRD Study adjusted for measured GFR, in this context it is possible that uric acid acted as a sensitive indicator of compromised kidney function and adjustment for accurate measurement of GFR did offset a potential positive association [14].

Hyperuricaemia in Kidney Transplantation

After kidney transplantation hyperuricaemia is frequent, and it is associated with cyclosporine therapy, use of diuretics, and the high prevalence of metabolic syndrome and diabetes [97]. Uric acid is associated with oxidative stress, inflammation, endothelial dysfunction and microvascular injury. In this context, uric acid may be associated with graft dysfunction, or chronic allograft nephropathy [98].

Armstrong et al. found in a small study, including only 90 patients that hyperuricaemia was associated with renal allograft dysfunction, even after correction for baseline renal function [99]. Hirirrian et al. provided similar results [100]. In a larger transplant cohort, including 212 patients, mean uric acid level during the first 6 months post-transplant was an independent predictor of short-term and long-term graft survival (hazard ratio 1.92; 95 % CI, 1.1–3.4; P = 0.029). Kim et al. recently reported their review of patients transplanted between 1990 and 2009, where they observed that hyperuricaemia conferred a 1.45 ($P < 0.001$) hazard ratio for graft loss [101]. In contrast Akgul et al. was not able to find an impact for baseline uric acid on (the incidence of) chronic allograft nephropathy [98]. Similar data are provided by the SYMPHONY Study, in which a cohort of 1,645 was followed-up for 3 years. Baseline serum uric acid levels were not associated with 3-years renal function (P = 0.62) [102].

Recently published data from a systematic review and meta-analysis including twelve cohort studies showed that hyperuricaemia was a risk factor of chronic allograft nephropathy (hazard ratio 1.65, 95 % CI 1.02 ~ 2.65) and graft loss (hazard ratio 2.01, 95 % CI 1.39 ~ 2.94) [103].

Allopurinol

Allopurinol is the pro-drug of oxypurinol, a xanthine oxidase inhibitor that reduces xanthine oxidase activity by almost 90 % and efficiently blocks uric acid generation. Febuxostat, a non-selective xanthine oxidase inhibitor, has recently been shown to be effective and safe in lowering serum uric acid levels in 1,072 hyperuricaemic individuals with and without impaired renal function, in a 28-week, phase III, randomized, double-blind, parallel-group trial, and may offer a viable, yet expensive alternative to treat symptomatic hyperuricaemia in those allergic, or otherwise intolerant, to allopurinol [104]. Pegloticase, a PEGylated mammalian recombinant uricase/urate oxidase, may be another treatment option [105, 106].

The key effects of allopurinol are: (i) to reduce superoxide anions and other free radicals and therefore oxidative stress [107]; (ii) to improve endothelial dysfunction in several studies; this effect is secondary to reduced oxidative stress and not due to changes in serum uric acid [54]; (iii) to block xantin oxidase activity; thus allopurinol increases hypoxanthine and oxygen, the substrates of xantin oxidase; it is well known that ATP is broken down to hypoxanthine and,

in theory, increasing hypoxanthine might increase ATP and, thus, energy. Indeed, allopurinol does increase ATP in the hypoxic rat heart (by 32 %) and also increases ATP energy delivery in the failing heart in man [107, 108] (iv) to reduce the myocardial oxygen consumption; Noman et al. showed a significant improvements in time to ST segment depression and increase in exercise tolerance following high dose of allopurinol for 6 weeks [109, 110].

Multiple studies have investigated the impact of allopurinol treatment on uric acid, hypertension, heart failure, stroke, myocardial infarction or CKD progression, as already mentioned in this chapter.

Allopurinol and Hypertension

The most promising study, which showed a significant systolic and diastolic blood pressure reduction after allopurinol was reported by Feig et al. in adolescents with hypertension or prehypertension [48]. In a recent systematic review and meta-analysis including 10 studies and a mixed cohort of patients, with mean age ranged between 15.1 and 78 years, Agarwal et al. found a small, but significant decrease in systolic (3.3 mmHg) and diastolic blood pressure (1.3 mmHg) in patients treated with allopurinol [111]. The same results were reported when the analysis was restricted to higher quality randomised controlled trials. However, the design of this review was criticized – Agarwal et al. included heterogeneous studies as well as trials with poor methodological quality; in contrast, in a Cochrane systematic review, with more rigorous entry criteria, the authors found that, to date, there is only one study designed to adequately answer whether allopurinol treatment has a positive effect on blood pressure in hypertensive individuals – i.e. the study mentioned above by Feig et al. [112]. In this context, there are no sufficient data to support the conclusion that allopurinol may be used to treat hypertension [113].

Allopurinol and Ischemic Heart Disease

The capacities of allopurinol to improve endothelial function and to decrease oxidative stress recommend a possible role for allopurinol in coronary artery disease [106]. In a RCT performed in patients with myocardial infarction, 18 individuals received a single oral dose of 400 mg allopurinol prior to percutaneous transluminal coronary angioplasty (PTCA) and experienced improved coronary flow after reperfusion, higher left ventricular ejection fraction, as well as an improved cardiac index 6 months after intervention, as compared to 20 control patients with standard PTCA [114]. In a randomised controlled crossover trial, allopurinol in increasing dosing regimens from 100 to 600 mg over 6 weeks improved time to angina, as well as total exercise time [115]. Finally, a RCT performed in 15 patients with coronary artery disease showed that a 4-week treatment with the angiotensin II receptor blocker losartan and allopurinol reduced endothelial xanthine oxidase activity and improved vasodilatation [116].

Allopurinol and Chronic Heart Failure

By reducing myocardial oxygen consumption and increasing ATP level, allopurinol was a reasonable addition in heart failure treatment [110]. In this context, the OPT-CHF study was designed to test the hypothesis that oxypurinol, when added to the best conventional therapy, would improve clinical outcomes in patients with symptomatic heart failure due to systolic dysfunction [71]. The study failed to achieve its primary endpoint. However, a post-hoc analysis suggested that benefits occur in patients with markedly elevated serum uric acid levels (>9.5 mg/dl) in a manner correlating with the degree of uric acid reduction. This led to the OPT-CHF trial, which was mostly neutral [71]. A major problem with this trial was the low dose of xanthine oxidase inhibition used (equivalent to 85 mg allopurinol only), whereas, there are good data showing that dosing is crucial when using xanthine oxidase inhibitors.

In chronic heart failure, a 3-month therapy with 300 mg of allopurinol versus placebo in a single-centre cross-sectional RCT performed in 44 patients, reduced brain natriuretic peptide levels, but there was no improvement in physical performance. Notably, haemoglobin levels dropped from 138.4 to 134.9 g/L in the treatment group [69]. In 20 patients with ischemic cardiomyopathy grades NYHA III and IV, with highly increased end-systolic and end-diastolic volumes, and severely suppressed left ventricular function, a single intravenous dose of 400 mg of oxypurinol led to a reduction in end-systolic volume and an increased left ventricular ejection fraction as compared to placebo [117].

Allopurinol and CKD Progression

Several small studies, with a short duration of follow-up showed a beneficial effect of allopurinol treatment on CKD progression. In a small-randomized trial by Siu et al. 54 hyperuricaemia patients with mild to moderate CKD were assigned to allopurinol (100–300 mg/day with the goal of normalizing serum uric acid levels) versus no therapy (control) and followed up for 12 months [14, 112]. An improvement in renal function was reported in the treatment group. More recently, a larger study conducted by Goicoechea et al. included 113 hyperuricaemia patients with CKD randomly assigned to either allopurinol (100 mg/d) or a control group (no therapy) [118]. At the end of the 2-year follow-up,

estimated GFR decreased by 3.3 ± 1.2 mL/min/1.73 m^2 in the control group; in the allopurinol group, estimated GFR increased by 1.3 ± 1.3 mL/min/1.73 m^2 (P = 0.018). Another recent open-label randomised controlled trial conducted by Shi et al. evaluated allopurinol treatment in 40 patients with immunoglobulin A nephropathy [119]. After 6 months of treatment, allopurinol did not significantly alter kidney disease progression or proteinuria, although it significantly improved blood pressure.

A systematic review including eight trials and 476 participants summarizes the available evidence concerning the effect of uric acid-lowering therapy on renal outcomes [120]. In five trials, there was no significant difference in change in glomerular filtration rate from baseline between the allopurinol and control arms. In contrast, allopurinol therapy lowered serum creatinine concentration in 3 trials with 130 participants. In this context is insufficient evidence to currently recommend widespread use of allopurinol therapy to slow the progression of CKD.

Although it is generally safe, allopurinol treatment could be associated with hypersensitivity reactions ranging from mild cutaneous eruption (morbilliform rash/pruritic erythematous maculopapular rash [121]), to more severe clinical manifestations such as allopurinol hypersensitivity syndrome or Steven-Johnson syndrome and lethal toxic epidermal necrolysis [122]. Risk factors associated with allopurinol hypersensitivity are concomitant diuretic use, pre-existing renal impairment and recent initiation of allopurinol [123]. Recent studies have demonstrated the association between human leukocyte antigen (HLA) B*58:01 allele and allopurinol-induced severe cutaneous adverse reactions in a dose-dependent manner [124]. Both the presence of HLA-B*58:01 allele and high concentration of drug are important for the generation of drug-specific T cells [124]. In contrast, a recent meta-analysis including 802 patients with severe allopurinol hypersensitivity revalidate HLA-B*5801 status as an essential risk factor for hypersensitivity [123]; this was especially relevant in Asian populations where there is a higher carriage rate of the allele. However, the high allopurinol dose, previously suggested to be a risk factor, was not confirmed in this meta-analysis [123].

In conclusion, it is becoming clear that role of the uric acid is no longer restricted exclusively to gout or nephrolithiasis. Increasing evidence now points to a significant, but still controversial relation of uric acid to different disorders (hypertension, obesity, metabolic syndrome, type 2 diabetes, cardiovascular diseases, and renal disease). Hyperuricaemia can arbitrate these effects by provoking oxidative stress, inflammation, endothelial dysfunction or activation of the rennin-angiotensin system. However, despite considerable progress, more compelling evidence is needed before ultimately labelling uric acid as a causative factor is these disorders.

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FGF23 and Phosphate: Two Cardiovascular Toxins with Distinct Toxicity Profiles?

8

Tobias E. Larsson and Hannes Olauson

Clinical Case Scenario

Eva Svensson is a 69 year old woman, still active as part-time politician. Eva has never smoked, she is slightly over-weight and takes metoprolol (100 mg) for the past 8 years for her blood pressure. She is referred to you for moderate kidney dysfunction developing the last years with eGFR decreasing from 50 to now 31 mL/min. The work-up before her appointment shows nothing remarkable besides from kidney size in the lower range, microalbuminuria, and phosphate 1.7 mmol/L (normally 0.8-1.5). At the visit, her blood pressure measure 152/68 mmHg, and the ECG shows signs of left ventricular hypertrophy later confirmed by echo. You prescribe ramipril and follow her BP. At a follow-up visit she shows a copy of her lab-results and an article from internet procurred by her son, a leading lawyer, indicating that Sevelamer is "the best" medication to help treat high phosphate levels. She asks you in a somewhat irritated manner why you have not already prescribed her this?

Introduction

The type 4 cardiorenal syndrome (CRS-4) addresses the pathological consequences of chronically impaired renal function on the cardiovascular system. An integral element of CRS-4 is dysregulated mineral metabolism including altered serum levels of calcium and inorganic phosphorus (Pi). Downstream biochemical consequences entail remarkable elevations in the principal hormones regulating serum calcium and Pi, including parathyroid hormone (PTH), and the more recently discovered Fibroblast growth factor-23 (FGF23).

Pi is a generally endorsed uremic toxin that promotes cardiovascular risk, particularly vascular calcification. Recent evidence implies that the Pi-regulating hormone FGF23 is another culprit driving cardiovascular risk in CRS-4. Current mechanistic insights into the link between FGF23 and cardiovascular risk are limited, however, ongoing research gradually unravel FGF23 as an independent cardiovascular risk factor, perhaps with a toxicity profile distinct from serum Pi.

In this chapter, we aim to summarize the principal clinical, epidemiological and experimental evidence linking serum Pi and FGF23 to adverse cardiovascular outcomes. Further, we delineate important research questions aimed to close the gaps between theory and practice, and the need for robust randomized clinical trials (RCTs) to ultimately assess the importance of Pi and FGF23 in promoting the incremental cardiovascular risk associated with renal dysfunction.

Disturbances in Mineral Metabolism and Cardiovascular Disease Across the Spectrum of Chronic Kidney Disease

It is widely known that the frequency of mineral disturbances and cardiovascular disease (CVD) rises in parallel with declining renal function, and dysregulated mineral metabolism is considered a principal pathogenic element in CRS-4 [1]. The osteocyte-derived hormone FGF23 appears to be a highly sensitive biomarker for imbalances in the homeostatic systems that control mineral metabolism. In chronic kidney disease (CKD) the rise in FGF23 precedes all clinical measures that are routinely monitored such as hyperphosphatemia and secondary hyperparathyroidism (sHPT) [2]. The concept of FGF23 as an early phase biomarker of imbalances in renal handling of mineral metabolites is also supported by clinical and experimental situations of acute kidney injury (AKI) in which FGF23 elevations are detected within a few hours after onset of the renal

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insult [3]. The underlying presumed renal-bone signal responsible for the rapid systemic rise in FGF23 in AKI, and to some extent in early CKD, is still unidentified. It may include humoral factors secreted from the deceased kidney and/or activation of FGF-receptors in the bone.

The two main physiological functions of FGF23 are to promote phosphaturia by decreasing the activity of the renal sodium-dependent phosphate co-transporters NPT2a and c, and to decrease availability of 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) by suppressing its activating enzyme (CYP27B1) and stimulate its catabolic enzyme (CYP24A1) [4]. In addition, FGF23 suppresses PTH synthesis and release, at least in the short-term, by directly targeting the parathyroid glands [5, 6]. In a sense, FGF23 can therefore be regarded as an anti-vitamin D and calciotropic hormone which ultimately protects against the detrimental consequence of an elevated calcium-Pi (Ca-Pi) product.

The rise in FGF23 triggered by renal dysfunction is generally viewed as a compensatory mechanism to maintain normal serum levels of Pi (and to some extent calcium) with a decreased number of functioning nephrons. Indeed, extracellular Pi, calcium and PTH are considered to, directly or indirectly, stimulate FGF23 expression in bone [7]. However, this adaptation comes at the expense of decreased circulating $1,25(OH)_2D$, and thus indirectly contribute to the development of sHPT [8]. As CKD progresses there is a striking increase in FGF23, reaching extreme concentrations in many patients with end-stage renal disease (ESRD) [9]. Typically, serum calcium and Pi are kept normal by the compensatory hormonal changes in FGF23, $1,25(OH)_2D$ and PTH until entering CKD stage 4 or 5 (glomerular filtration rate (GFR) less than 30 mL/min) where onset of hyperphosphatemia is noted in some, but not all, CKD patients. The dynamics and frequency of mineral disturbances as a function of GFR is graphically depicted in Fig. 8.1.

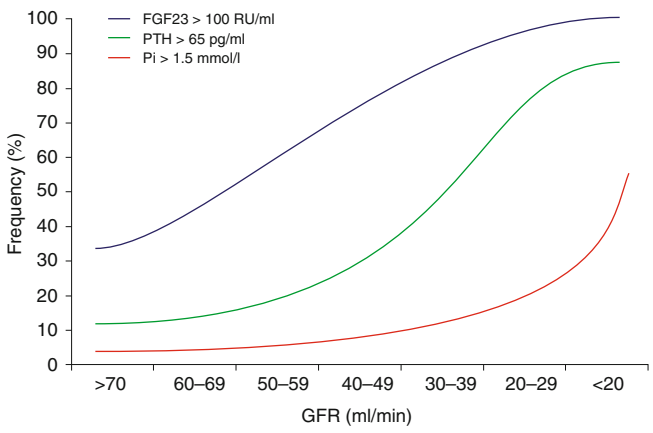

Fig. 8.1 Estimated prevalence of elevated Pi, PTH and FGF23 across the strata of chronic kidney disease. FGF23 is an early biomarker of renal dysfunction, and its increase precedes the development of secondary hyperparathyroidism. Hyperphosphatemia is usually prevented by these homeostatic mechanisms until CKD stage 4 or 5 (GFR < 30 ml/min/1.73 m^2). Adapted from the CRIC cohort

In addition to stimulation by Pi, calcium and PTH, a decline in Klotho, a membrane-bound co-receptor for FGF23, is likely contributing to excessive FGF23 production in advanced CKD due to end-organ (i.e. renal) FGF23 resistance. This is analogous to high insulin concentrations observed in type 2 diabetic patients to overcome peripheral insulin resistance. The residual expression of Klotho is markedly reduced in CKD with less than 10 % of normal levels in many ESRD subjects [10]. In the context of mineral metabolism, this accelerates and aggravates the typical biochemical profile of high FGF23, sHPT, low $1,25(OH)_2D$ and hyperphosphatemia.

A key question is whether these biochemical abnormalities should be considered merely as cosmetic defects, or if they actively contribute to mechanisms of CVD. A wealth of clinical and epidemiological data supports the latter. Even mild renal dysfunction is independently associated with increased CVD risk, and cardiovascular mortality is 10–30 times higher in ESRD patients on dialysis treatment compared to the general population [11]. A more descriptive and complete discussion of cardiovascular pathology in relation to CKD are provided elsewhere in this book, yet we herein want to emphasize two dominant CVD features in the context of serum Pi and FGF23: vascular calcification with stiffening of the arteries and left ventricular hypertrophy/congestive heart failure.

Hyperphosphatemia and Cardiovascular Risk

Over the last decades a link between serum Pi and cardiovascular risk has gradually been uncovered. This relationship was noted early by Block and colleagues in ESRD patients, which is the most common clinical situation of severe hyperphosphatemia [12]. With adjustment for case mix they found a graded relationship between increasing serum Pi levels and mortality risk and cardiovascular hospitalization, which remained significant after multivariate adjustment for other confounding CVD risk factors. Another hallmark study conducted by Tonelli and co-workers demonstrated a similar graded relationship between serum Pi levels and cardiovascular risk in individuals free of CKD [13]. It is noteworthy that this association held true in a setting of Pi levels within the defined normal reference range. Similar findings have subsequently been corroborated in various CKD studies, in renal transplant recipients and in community-based cohorts as well as in the general population [14–17].

Due to the complex interplay and dynamics of mineral metabolism in relation to CKD, and the large risk for residual confounding in epidemiological settings, some concerns about true causality have been voiced. Yet, there is an overall consensus that serum Pi is a considerable risk factor in CKD, not at least due to the consistency of data pointing to serum Pi as an independent cardiovascular risk factor, and because the association between hyperphosphatemia and mortality appears stronger than for other components of mineral metabolism. Indeed, a recent meta-analysis comprising more

than 300,000 CKD patients demonstrated that a 1 mg/dL increase in serum Pi was associated with an 18 % higher risk of death, whereas serum calcium and PTH were not associated to increased mortality risk [18].

What is then the mechanisms linking hyperphosphatemia to CVD and mortality? Several biologically plausible, and experimentally proven, pathways by which Pi promotes CVD have been proposed [19, 20]. First, under conditions of hyperphosphatemia the rate of Pi influx from extracellular fluids into various cell types, including vascular smooth muscle cells (VSMC), are augmented. This is accomplished by an active, sodium-dependent Pi transport of the ubiquitously expressed Pit-1 protein. Downstream consequences of augmented Pi uptake in VSMCs include cell death and osteochondrocytic differentiation. Osteochondrocytic differentiation is a maladaptive process where VSMCs transform to an osteoblast-like phenotype, associated with local production of bone proteins and release of precalcified membrane matrix vesicles. Under normal circumstances these vesicles contain mineralization inhibitors such as Fetuin A and matrix Gla protein, and are believed to protect the VSMC from calcium overload. In CKD these inhibitors are low or absent, thus turning the vesicles into foci for calcification. Vascular calcification is indeed a dominant feature in a majority of CKD patients [21], and the presence and severity of vascular calcification increases in parallel with serum Pi (Fig. 8.2) [22, 23]. Notably, the ability of Pi to induce vascular calcification diminishes drastically in the absence of calcium [24]. Inhibition of the formation of Ca-Pi crystals effectively prevent the progression of Pi-driven vascular calcification as well [25], supporting that Pi and calcium operate synergistically in the calcification process. This concept is also supported by several randomized clinical trials (RCTs) that typically demonstrate a relative decline in the progression rate of vascular calcification when using non-calcium based Pi binders compared to calcium-based treatment regimens [26, 27].

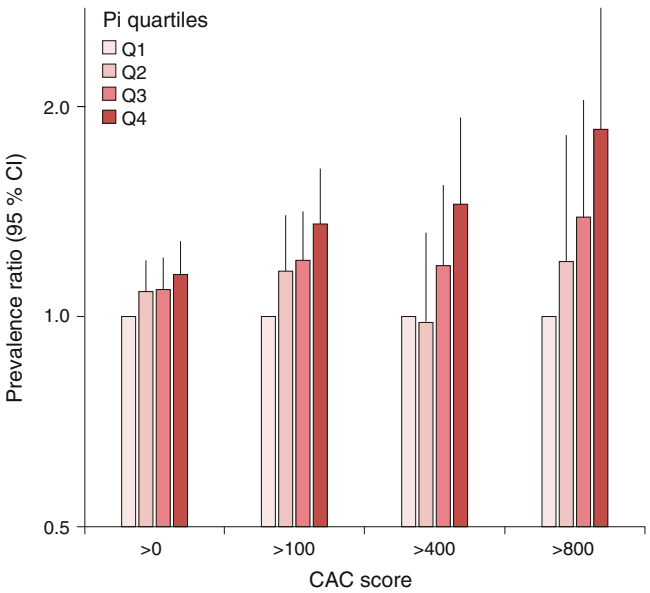

Fig. 8.2 Higher serum Pi is associated with the adjusted prevalence of increased coronary artery calcification (CAC) score. Adapted from the CRIC study.

It should be underscored that high serum Pi may have other detrimental consequences beyond vascular calcification. Rapid infusions of Pi in rodents and humans have shown an acute impairment in the endothelial response to other vasoactive substances, and epidemiological studies in CKD patients confirm an independent association between serum Pi and endothelial dysfunction, the latter being a well-established surrogate marker of long-term cardiovascular risk [28–30]. Similarly, hyperphosphatemia is associated with both static and dynamic measurements of cardiovascular function including impaired endothelium-dependent and endothelium-independent vasodilation, increased pulse-wave velocity (a measure of vascular stiffness), carotid artery intima-media thickness, as well as measurements of systolic and diastolic cardiac dysfunction [13, 16, 31, 32].

In experimental models, Pi loading has many detrimental consequences, both at the cellular and organ level. First, high Pi induces cellular senescence defined by telomere shortening and apoptosis [33]. Second, it induces fibrotic processes through several different pathways, and phenotypic abnormalities promoted by Pi can be ameliorated or reversed by dietary restriction of Pi and/or Pi binding therapy, strengthening the likelihood of causal relationships in epidemiological studies [34, 35]. Fibrosis is the end result of a chronically failing nephron, and a pro-fibrotic environment accelerates the underlying progression rate in CKD. It is intriguing that recent clinical data not only confirm a link between serum Pi and CVD but support an association between serum Pi and an accelerated CKD progression rate [36, 37]. Another organ-specific consequence of pro-fibrotic stimuli is cardiac fibrosis, frequently occurring in conjunction with development of left ventricular hypertrophy (LVH). LVH is a common complication in CKD patients and is a strong predictor of cardiac events and mortality in the general population as well as in CKD patients [38, 39].

Despite cumulative evidence favoring serum Pi as a cardiovascular toxin, few RCTs have properly examined whether Pi-lowering therapy improves long-term cardiovascular outcome. The largest RCT to date that addressed this hypothesis was conducted in dialysis patients and did not show any survival benefit in the primary analysis when comparing treatment with sevelamer (a non-calcium Pi binder) and calcium-based Pi binders [40]. Interpretation of data is hampered by several factors attributed to design and execution of this study, not at least the remarkable drop-out rate of approximately half of all subjects randomized to treatment. Subsequent head-to-head RCTs comparing sevelamer with Ca-based Pi binders have convincingly demonstrated a reduction in the progression rate of vascular calcification as measured by abdominal calcification score (ACS) or coronary artery calcification score (CAC) [26, 41]. Although less calcification is expected to translate into reduced long-term cardiovascular risk, this remains an open issue. A few small studies comparing sevelamer and Ca-based Pi binders supported a survival benefit for sevelamer, although these studies were not

adequately powered to assess the impact on mortality [42, 43]. A recent meta-analysis including more than 4600 patients from 11 different trials indicated a reduction in all-cause mortality by 22 % in favor of non-Ca Pi binding treatments [44]. As a note of caution, none of these studies were placebo-controlled, implying that the true advantage of Pi-lowering therapy remains unclear. A possibility is that the assumed survival benefit attributed to non-Ca Pi binders could be related to less Ca exposure rather than a reduction in intestinal Pi absorption. In this regard, a recent placebo-controlled RCT which explored the efficacy of various Pi binders for slowing progression of vascular calcification in non-dialysis normophosphatemic CKD patients demonstrated no benefit, but rather a trend towards harm, for Pi binders as compared to placebo [45]. Although this trend appeared primarily driven by Ca-based Pi binders, it is still possible that gastrointestinal Ca absorption (and thus systemic Ca exposure) is augmented by Pi binding therapies in this setting. The reason is because the intestinal fraction of free Ca increases when Pi is attached to the binder rather than forming fecally excreted Ca-Pi complexes. Nevertheless, this study underpins the need for more rigorous exploration of serum Pi as a modifiable cardiovascular risk factor.

FGF23 and Cardiovascular Risk

Considering the dynamics of serum FGF23 and Pi in CKD depicted in Fig. 8.1 (e.g. FGF23 rises in early CKD whereas Pi levels are maintained normal until advanced CKD or ESRD due to homeostatic mechanisms) the idea was planted that FGF23 may be a surrogate marker for time-averaged Pi exposure, analogous to Hb1Ac and glucose levels. This concept was fueled in a study from 2008 by Gutierrez et al. that provided the first clinical evidence for FGF23 as an independent predictor of mortality in incident hemodialysis patients [46]. The magnitude of this relationship was strong, with a nearly six-fold increased risk for mortality during the first year of hemodialysis in those individuals within the highest quartile of FGF23 compared to those in the lowest. Equally important, a relationship between FGF23 and mortality was confirmed irrespective of baseline serum Pi levels, and the predictive value of FGF23 was superior relative to serum Pi. This report was followed by a multitude of observational studies confirming FGF23 as a marker of mortality across the spectrum of CKD, including early and late stage CKD, incident and prevalent dialysis populations and renal transplant recipients [47–49]. Similarly as for serum Pi, several reports confirmed that FGF23 predicted mortality in community-based settings and in individuals free of CKD [50, 51].

Epidemiological studies do not prove causality, but they may shed light on potentially relevant mechanisms that drive observational findings. Subsequent data more specifically supports a link between FGF23 and CVD, and that FGF23 is more robustly linked to cardiovascular mortality than non-cardiovascular or total mortality. In an attempt to dissect which aspects of cardiovascular pathology FGF23 portrays, we initially measured FGF23 in the PIVUS study, which is a community-based, prospective, observational study in which all study participants have undergone careful evaluation of subclinical indices of cardiovascular function. In this study population, FGF23 was associated with impaired dynamic vasoreactivity and endothelial function, total atherosclerosis score, LVMI and risk for the presence of LVH [52–54]. All these associations remained significant after adjustment for relevant cardiovascular risk factors and for markers of mineral metabolism including serum Pi. Subsequent studies in various CKD populations have confirmed these findings and also demonstrated that FGF23 predicts new onset or aggravation of pre-existing conditions in longitudinal follow-up studies, in particular CHF and LVMI/LVH [55–58]. In the PIVUS study a 10 % increase in FGF23 corresponded to a 0.7 % increase in LVMI. Notably, this strength of relationship was observed in a setting of essentially normal renal function (mean eGFR 77 ml/min/1.73 m^2). In comparison, in patients from the CRIC study (average eGFR 42 ml/min/1.73 m^2) every unit increase in natural log-transformed FGF23 associated with a 5 $g/m^{2.7}$ increase in LVMI, translating to approximately 0.9 % increase in LVMI per 10 % increase in FGF23. In principle, this means that a reduction in FGF23 by 20–40 % that may be accomplished by cinacalcet or phosphate-binding treatment in some CKD patients potentially could result in a clinically significant reduction of LVMI, although not of the same magnitude as for anti-hypertensives (−6–13 %) [59]. In contrast to serum Pi, FGF23 is not consistently linked to vascular calcification. Recent data from the CRIC study showed that FGF23 were not associated with coronary artery or thoracic aorta calcium in a cohort of 1,501 CKD patients [23].

In principle, the current situation must be dealt with: serum Pi and FGF23 are both independent predictors of hard cardiovascular endpoints as well as intermediate/surrogate cardiovascular endpoints. There is no critical effect modification by any of the parameters, implying that both factors portray risk independent of the other. This leaves us with two questions, one being if FGF23 only is a biomarker of CVD? If the answer is no, is then serum Pi and FGF23 two cardiovascular toxins with similar or distinct toxicity profiles?

Is FGF23 a Biomarker or Contributor to CVD?

Based on elegant experimental work, it has been established that membrane-bound alpha-Klotho (Klotho) is a permissive co-receptor for FGF23 that allows its high-affinity binding to cognate FGF-receptors (FGFRs) [60]. According to the initial Klotho reports originating from 1997 onwards, its expression is largely confined to renal tubules, parathyroid glands and choroid plexus [61], but not within the cardiovascular system except the sinoatrial node of the heart [62]. Given the absence of its co-receptor in the cardiovascular system, the prevailing

assumption has been that FGF23 cannot directly contribute to CVD. However, this concept has recently been challenged by studies providing evidence for Klotho expression in the vasculature and the presence of alternative (Klotho-independent) FGF23 signaling pathways in the heart.

Lim et al. report that Klotho is expressed in human VSMCs, and that FGF23 attenuate vascular calcification in vitro [63]. Further, they show that vascular Klotho declines in parallel with renal function, which would explain the loss of FGF23's anticalcific effects in CKD. This report was later substantiated by other studies reporting on vascular Klotho expression in rodents and humans [64, 65]. Second, Faul et al. demonstrate that FGF23 induces LVH in mice, and that treatment with FGF23 directly stimulates growth of isolated cardiomyocytes in vitro [56]. Klotho is not expressed in cardiomyocytes and the effects of FGF23 on the heart were shown to be mediated via the non-canonical PLCγ-calcineurin pathway. Moreover, the effects of FGF23 on LVH were blocked by administration of an FGF-receptor inhibitor.

However, both these mechanisms remain controversial and subsequent studies have failed to replicate the findings. As previously mentioned, Scialla et al. did not see Klotho expression in human or mice VSMCs or in mouse aorta, nor any direct effects of FGF23 on the calcification process in vitro [23]. Similar data were also reported in a study by Lindberg et al., in which Klotho expression was very low or absent in major murine arteries, and FGF23 lacked effects on endothelial function and vascular calcification [66]. On the other hand, if FGF23 can signal via non-canonical pathways in the heart, cannot that also be the case in the vasculature? In the context of vascular effects of FGF23, the presence or absence of Klotho may perhaps be more of an academic discussion if FGF23 targets the vasculature through alternate signaling mechanisms. Regardless of which pathway FGF23 acts on, data on direct effects on the vasculature is scarce and conflicting, and further studies are warranted.

Concerning FGF23 and cardiomyopathy, a recent study by Agerwal et al. failed to confirm an association between elevated Fgf23, LVH and reduced ejection fraction in *Klotho* knockout mice, and only found a weak relationship between FGF23 and left ventricular ejection fraction in patients free of CKD [67]. Similarly, in a study by Shalhoub et al. treatment of uremic rats with neutralizing FGF23 antibodies had no effects on LVH or cardiac hypertrophy markers [8]. Another dilemma is that patients with certain endocrine disorders characterized by over-expression of FGF23, such as tumor-induced osteomalacia and X-linked hypophosphatemic rickets, do not suffer from overt LVH or higher risk for CVD. That does not however fully exclude the possibility that FGF23 is harmful, since its absolute levels are much higher in ESRD subjects and its detrimental effect may be potentiated in the uremic environment.

As a final remark on this topic, it should be noted that the current understanding of FGF23 in relation to CVD may be confounded by its co-receptor Klotho. Some studies have shown that soluble Klotho (a shedded form of membrane-bound Klotho) inhibits vascular calcification and progressive renal damage, at least partly through inhibition of TGF-β and Wnt signaling [68–70]. The inverse relationship between FGF23 and membrane-bound Klotho in CKD implies that Klotho deficiency, rather than FGF23 excess, may explain some of the aforementioned epidemiological findings. Unfortunately, methodological limitations in measuring soluble Klotho hamper clinical research in this field at present.

An Emerging Model of Serum Pi and FGF23 as Two Distinct Cardiovascular Toxins

Consolidating the rich flora of clinical and experimental data, we propose a model in which most definitely serum Pi, and quite likely FGF23, are to be considered cardiovascular toxins. Their toxicity profiles may overlap, yet a pattern can be discerned in which serum Pi at first hand promotes vascular calcification whereas FGF23 may drive LVH. This hypothesis is summarized in Fig. 8.3. The most severe clinical consequences of LVH are CHF and risk for arrhythmias and sudden death. In this context, a recent preliminary post-hoc analysis of the EVOLVE trial suggesting that individuals with a large reduction in serum FGF23 upon treatment with the calcimimetic cinacalcet had a markedly reduced event rate for CHF is of prime interest [71].

Summary and Conclusion

Epidemiological and RCT data consistently link hyperphosphatemia and high FGF23 to increased mortality risk and numerous long-term or surrogate cardiovascular endpoints. The link between hyperphosphatemia and vascular calcification seems straightforward based on the collective record of experimental and clinical data as well as biological plausibility. The acceptance of serum Pi as a surrogate for vascular calcification and cardiovascular outcomes is evidenced by the widespread use of Pi binders in the CKD population, especially in dialysis patients [72]. Nevertheless, further RCTs are warranted to fully delineate the benefit of lowering serum Pi for reducing CVD, particularly in the non-dialysis CKD population.

The link between FGF23 and CVD is largely of epidemiological nature and unravel FGF23 as a relatively stronger predictor of CVD than serum Pi across all ranges of kidney function, perhaps with a more distinct cardiac toxicity profile. The clinical use of FGF23 as a biomarker for identification of high risk individuals and enrichment strategies in RCTs deserves further exploration. Identification of Klotho-independent FGF23 signaling in the heart is illuminating and presents novel plausible explanations for causal relationships

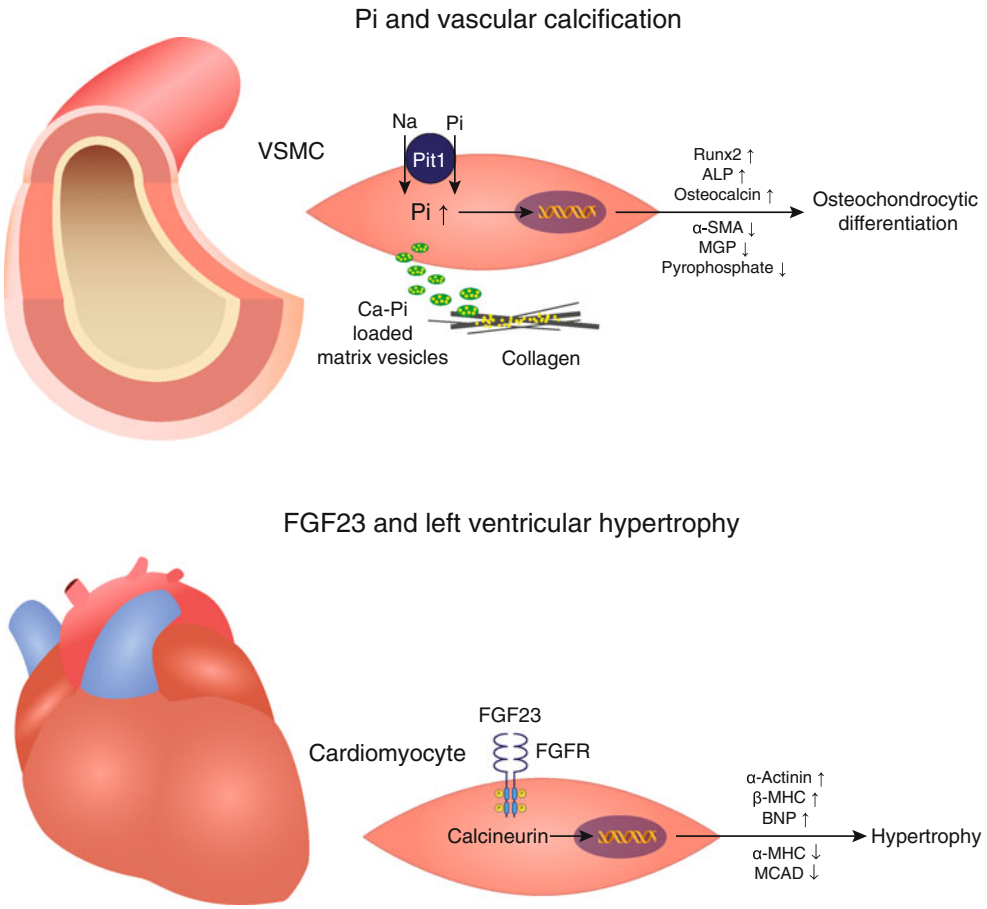

Fig. 8.3 Proposed model: FGF23 and phosphate – two cardiovascular toxins with distinct toxicity profiles. *Top*: A wealth of epidemiological and experimental data has implicated a direct role for Pi in cardiovascular pathology, particularly in the development of vascular calcification. Intracellular excess of Pi in vascular smooth muscle cells induces osteochondrocytic differentiation and release of calcified matrix vesicles. *Bottom*: Novel data suggest Klotho-independent effects of FGF23 on cardiomyocytes, resulting in cell growth and development of left ventricular hypertrophy

between FGF23 and LVH/CHF, yet the relevance of FGF23 "off-target" signaling remains unclear and future research efforts should explore the presence, magnitude and relevance of FGF23 signaling in the cardiovascular system.

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Renal Congestion in Heart Failure

9

Baris Afsar and Mehmet Kanbay

Clinical Case Scenario

Peter Anderson is now again admitted for decompensated heart failure, for the 3 rd time in the last 12 months. Peter is a 67 years old obese (BMI 38) previous smoker with two myocardial infarctions 5 and 8 years ago. He also suffers from type 2 diabetes with poor glucose control making him incapable of limiting his fluid intake. He was discharged 7 weeks ago on high doses of oral furosemide (250+120 mg) on top of his regular heart failure medications (full-dose ramipril, metoprolol and 25 mg spironolactone).

Peter was admitted last evening. His echocardiogram showed a surprisingly preserved EF of 45%, but an enlarged vena cava without respiratory change indicating a CVP >20 mmHg. He has already received an IV furosemide infusion of 250 mg during the night but this achieved little diuresis. His creatinine has increased from 185 to now 320 μmol/L, potassium to 6.0 mmol/L, and he is also severely constipated. You are contacted as consultant for a discussion on which of the heart failure medications to reduce/discontinue, and on how much more furosemide he should receive.

Introduction

Cardiorenal interactions in heart failure have become increasingly recognised, and achieving adequate control of congestion with simultaneous preservation of renal function has become a goal of good patient management. Renal congestion and deterioration of kidney function is common in patients with heart failure and associated with increased risk of hospital readmission and both in-hospital and post-discharge mortality [1]. The exact pathophysiologic mechanisms, prognostic markers and treatment options regarding renal congestion and deterioration of kidney function in heart failure are not known despite increased research. In the present discussion, the mechanisms, outcomes, prognostic markers and the treatment options related with renal congestion and deterioration of kidney function in heart failure is summarised.

The Pathophysiology of Renal Congestion in Heart Failure

The pathophysiology of renal congestion and deterioration of kidney function in heart failure is very complex and multiple pathways are involved simultaneously. Below, these mechanisms are summarized.

Firstly, age, hypertension, and diabetes may act as unifying factors that associate heart failure with renal dysfunction and their coexistence can be considered to be partly due to common effects of the process of atherosclerosis on the heart and the kidney [2].

Secondly, arterial underfilling was one of the mechanisms involved in this process. Indeed, traditionally this mechanism was accepted as a main cause of deterioration of kidney function. Regarding the hypo perfusion (as also called forward failure) when mean aortic pressure is reduced; the renal perfusion pressure may also be lowered to ≤80 mmHg that is the threshold of kidney autoregulation. This threshold is important since below this threshold renal perfusion becomes directly pressure dependent [3]. Additionally, the thresholds and responses probably depend on intact endothelial function and responses, which are deranged in CKD and heart failure. At this point a high degree of neural and humoral activation occurs. The reduction in perfusion pressure is sensed by baroreceptors that increase catecholamine release from the sympathetic nervous

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system and adrenal glands. This increase in sympathetic activity, and the reduced cardiac output itself, elicit release of renin from granular cells in the juxtaglomerular apparatus of the nephron. Renin cleaves angiotensinogen to angiotensin I, which angiotensin-converting enzyme (ACE) converts to angiotensin II (AngII). AngII elicits positive feedback on the sympathetic nervous system, facilitating further catecholamine release. Both AngII and catecholamines induce glomerular arteriolar vasoconstriction, decreasing renal plasma flow. Yet AngII has a disproportionate vasoconstrictive effect on the efferent arteriole, preserving the glomerular filtration rate (GFR) despite reduced renal plasma flow [4]. Thus initially the filtration fraction and glomerular filtration rate was preserved but when this activation progress (if AngII levels and/or catecholamine levels are very high), it causes more preglomerular vasoconstriction leading to decrease in GFR [5]. This in turn activates proximal tubular sodium and water reabsorption leading to more congestion [6, 7].

Thirdly, the other determinant of kidney function in heart failure is the tubuloglomerular feedback. In the tubuloglomerular feedback, distal chloride delivery is sensed by the loop diuretic–sensitive sodium/potassium/2 chloride co transporter (NKCC2) in the macula densa at the end of Henle's loop. The hairpin orientation of the loop of Henle allows for close proximity of the macula densa with the other elements of the juxtaglomerular apparatus, the afferent arteriolar smooth muscle cells and the renin-secreting granular cells at the glomerular vascular pole. When volume expansion or increased GFR results in increased chloride delivery to the macula densa, TGF mediates afferent arteriolar vasoconstriction and decreased renin release. This afferent vasoconstriction, with efferent arteriolar vasodilatation from the fall in AngII, decreases GFR. In heart failure, high AngII and catecholamine levels increase proximal tubular reabsorption of solute. This reduces distal chloride delivery and the opposite downstream events occur: the afferent arteriole vasodilates and renin release increases, leading to increased efferent arteriolar tone [4].

Fourthly, the role of increased intra abdominal pressure (IAP) must be mentioned. Abdominal congestion, i.e., splanchnic, venous, and interstitial congestion, manifests in a substantial number of patients with advanced congestive heart failure, yet is poorly defined, and current pathophysiological models unsatisfactorily explain the detrimental link between congestion and deterioration in renal function [8]. The normal IAP is usually <5–7 mmHg and a constant elevation of IAP >12 mmHg defines intra-abdominal hypertension [9, 10]. Renal blood flow is determined by the abdominal perfusion pressure, which is directly related to mean arterial pressure and inversely related to IAP [11]. From the 1940s and onwards, it was shown that abdominal compression and intra abdominal hypertension decreased renal plasma flow and GFR [12]. Those findings are consistent with reports of elevated plasma renin activity and aldosterone levels during elevated IAP [13]. There has been also a concern that some of the renal dysfunction with intra abdominal hypertension is due to hypotension and low cardiac output. Nevertheless, when cardiac output is corrected by volume expansion in intra abdominal hypertension dogs, renal blood flow and GFR were still <25 % of normal [14]. Compromised capacitance function of the splanchnic vasculature and deficient abdominal lymph flow resulting in interstitial oedema might both be implied in the occurrence of elevated cardiac filling pressures and deterioration of kidney function [15]. Additional data suggest that gut-derived hormones might influence sodium homeostasis, while the entrance of bowel toxins into the circulatory system- as a result of impaired intestinal barrier function secondary to congestion- might further depress cardiac as well as renal function. Those toxins are mainly produced by microorganisms in the gut lumen, and undergo important alterations in the case of advanced heart failure, especially when renal function is depressed [8]. In fact, until recently, little attention had been paid to the role of the intestine and its microbial flora in the pathogenesis of CKD-associated inflammation and oxidative stress. Almeida Duarte et al. demonstrated penetration of bacteria across the intestinal wall and their detection in the mesenteric lymph nodes in uremic rats [16]. In more recent studies, uremia induced loss of tight junction proteins (which play important role in barrier function of intestine) has been clearly shown [17]. Thus in bowel wall oedema and ischemia occurring in decompensated heart failure has been shown to increase intestinal permeability and result in endotoxemia, systemic inflammation, and even bacterial translocation. Therefore, when present, severe oedema and hypervolemia can further impair intestinal barrier function in CKD patients. Indeed, direct evidence comes from the fact that intestinal microflora changed in patients with CKD with the abundance of Brachybacterium, Cateni-bacterium, Enterobacteriaceae, Halomonadaceae, Moraxellaceae, Nesterenkonia, Polyangiaceae, Pseudomonadaceae, and Thiothrix families compared to healthy population [18].

Taken together all these evidence suggests that changes in the composition of the gut microbiome and disruption of its barrier structure/function may result in production and absorption of noxious by-products that can contribute to the uremic toxicity and inflammation which are further exaggerated in the presence of heart failure.

Lastly, as important as the decreased perfusion, the tubuloglomerular feedback and IAP; elevated central venous pressure (CVP) and renal congestion (the specific subject of this chapter) also plays a role in renal dysfunction in heart failure (as also called backward failure). Indeed, experimental evidence from classic experiments demonstrates that blood flow

through the kidney is reduced more by an increase in venous pressure than by an equivalent decrease in arterial pressure, and that there is a steeply graded relationship between change in renal venous pressure and reduction in urine flow [19]. These changes occur independently of reduction in cardiac output and mean arterial pressure, which occur much later in the progression of congestive heart failure [20]. In normal people without heart failure, the transient hypervolemic state leads to increased renal fluid and salt excretion and loss of extracellular fluid from the body becomes greater than fluid intake, and this decreases both blood volume and cardiac output, returning the pressure back to normal. However, in patients with heart failure despite an increase in blood volume (hypervolemic state) the elevated right atrial and central venous pressure causes reducing driving force of fluid and salt excretion in kidney and a vicious cycle of sodium retention, volume expansion and heart failure exacerbation occurs [21]. Indeed in patients with various cardiovascular disease, elevated CVP has been shown to reduce renal perfusion pressure and possible be associated to increased mortality [22, 23]. It was even suggested that that venous congestion (both with increased CVP on admission and inadequate decrease of venous pressure with treatment) is the strongest hemodynamic determinant of renal dysfunction and persistent reduction of cardiac output may not have a primary role in the development of the renal dysfunction. Mullens et al. studied the importance of CVP in advanced decompensated heart failure. In 145 patients with acute decompensated heart failure, worsening renal function had a greater CVP on admission (18 ± 7 mmHg vs. 12 ± 6 mmHg, $p < 0.001$). The development of deterioration of kidney function occurred less frequently in patients who achieved a CVP < 8 mmHg ($p < 0.01$). Furthermore, the ability of CVP to stratify risk for development of deterioration of kidney function was apparent across the spectrum of systemic blood pressure, pulmonary capillary wedge pressure, cardiac index, and estimated glomerular filtration rate. Besides, systemic blood pressures were similar between those with versus without deterioration of kidney function [24].

Thus as a combination, in decompensated heart failure defective renal perfusion pressure, tubuloglomerular feedback, elevated IAP and increased CVP and neurohumoral activation causes hypervolemia, renal congestion and renal dysfunction. The pathophysiologic mechanisms leading to renal congestion in heart failure are summarized in Fig. 9.1.

How Does Renal Congestion Lead to Worsening of Renal Function?

As suggested above venous congestion (including renal vein) is an important factor for kidney dysfunction. However, little is known regarding the mechanisms leading to deterioration of renal function in venous congestion. Some mechanisms such as reduced transglomerular pressure, increased interstitial pressure, interstitial fibrosis, tubular back leak probably play a role. Additionally, increased sympathetic renal nerve activity resulting in intrarenal arterial vasoconstriction and a fall in GFR play a role [25]. During renal venous hypertension there

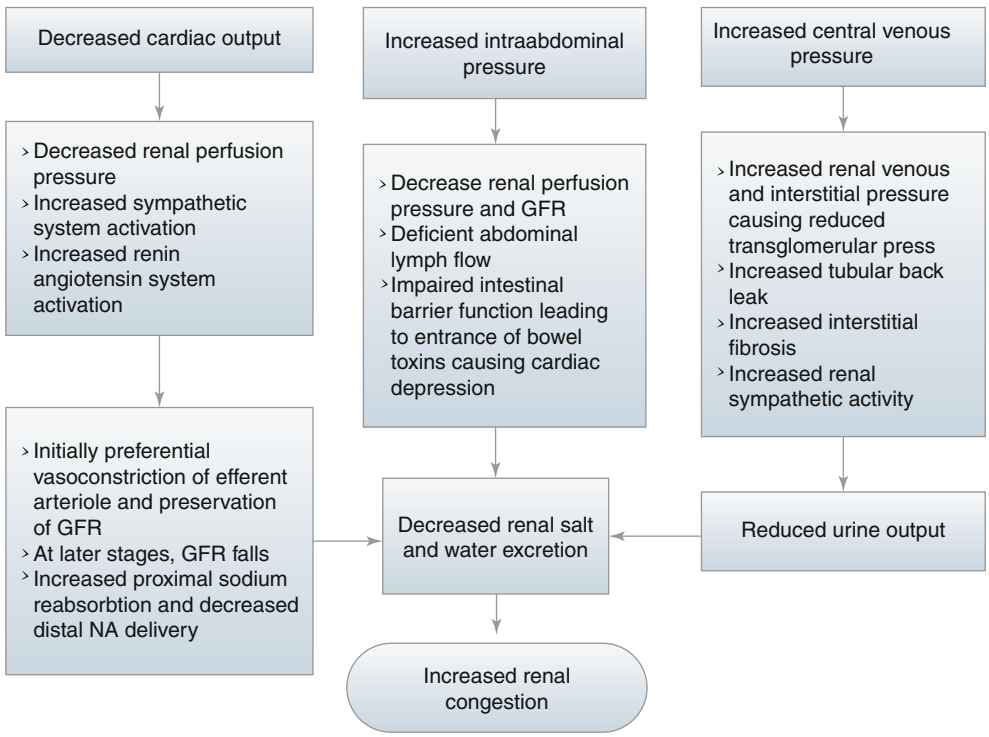

Fig. 9.1 Mechanisms involved in renal congestion in heart failure

would be a rise in renal interstitial pressure that would affect the entire capillary bed and the tubules, possibly also involving local hypoxia. Compression of the tubules raises the luminal pressure, further attenuates the transglomerular pressure gradient, and lowers the GFR. It is important to appreciate that a rise in renal interstitial pressure due to venous congestion is physiologically different than that caused by elevations in arterial pressure which is associated with a natriuresis [26].

The inflammatory process is another mechanism which is thought to be involved in venous congestion mediated deterioration of kidney function [27, 28]. Inflammation can beget vascular dysfunction via endothelial activation and enhanced arterial stiffness. Second, inflammation may reduce myocardial contractility either through functional suppression of the contractile apparatus or through increased myocardial cell death. Third, inflammation may cause progressive renal dysfunction and fibrosis. Finally, inflammation may increase the permeability of the endothelium allowing extravasation of fluids into the alveolar space of the lungs and absorption of pro-inflammatory endotoxin from the bowel [27]. In heart failure and venous congestion activation of renin angiotensin system (RAS) and sympathetic system promotes inflammatory reaction. However, accumulating evidence suggests that volume overload and venous congestion independent of RAS and sympathetic system, are independently accepted as an additional source of inflammatory mediators [27]. Thus evidence is accumulating that inflammation is related with congestion. However, the exact mechanisms related to venous congestion and inflammation are not solved completely although some mechanisms are speculated. In volume overload state mesenteric venous congestion leads to bowel wall oedema with translocation of gram-negative bacteria through the endothelial cells of the intestinal villi. Lipopolysaccharide is then released into the circulation, and activating the inflammatory response [28]. The proof of this assumption comes from recent studies [29, 30]. Similarly, in a recent prospective study, endotoxin levels were higher in chronic kidney disease (CKD) patients with signs of fluid overload compared to CKD patients without fluid overload [31].

The other speculated mechanism is the activation of endothelial cells during congestion. Venous congestion itself may switch the synthetic and endocrine profile of the endothelium from quiescent toward an activated state that is pro-oxidant, proinflammatory, and vasoconstricting. Once "activated," the endothelium can promote additional congestion through humoral, renal, and cardiac mechanisms, resulting in a deleterious positive feedback loop that leads, over time, more congestion [19].

Indeed it was clearly shown that during venous stretch endothelin-1 (ET-1), interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-alpha) can be secreted within hours of stretch exposure [32]. Besides, biomechanical signals such as stretch modulate endothelial production of reactive oxygen species [33]. Reactive oxygen species and cytokines may also trigger an inflammatory response through activation of nuclear factor (NF)-κB [34].

In summary, based on these reports, vascular stretch can activate endothelial pro-oxidant and proinflammatory programs. These results demonstrate that venous congestion and volume overload alone can promote an inflammatory state with elevations of inflammatory mediators in the circulation. Ultimately, the source of chronic inflammation in venous congestion syndrome is likely a combination of the several biologic mechanisms discussed (Fig. 9.2).

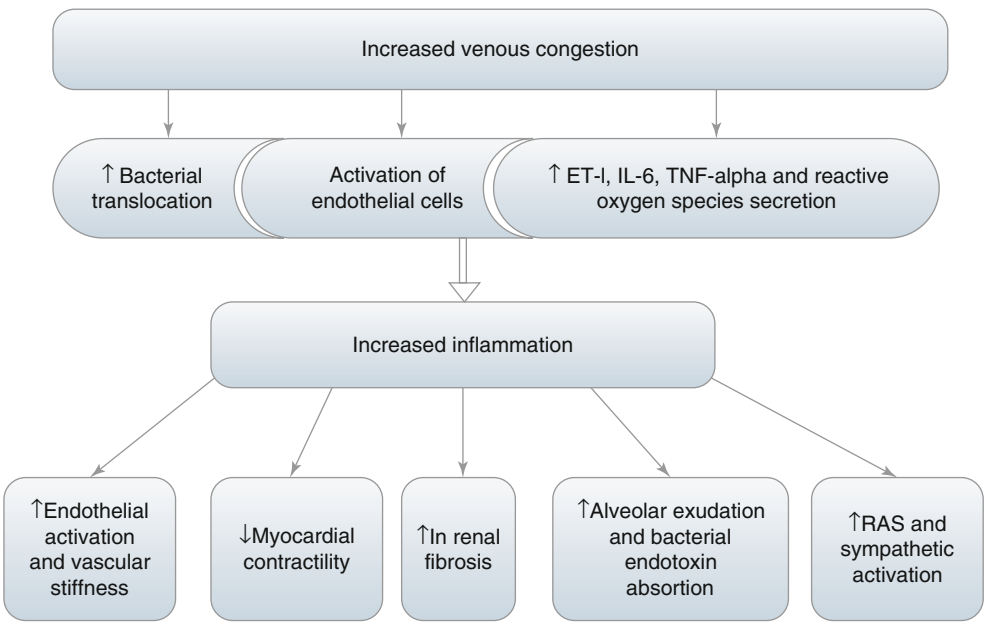

Fig. 9.2 Mechanisms of increased inflammation during venous congestion

Venous Congestion: An Important Cause of Renal Dysfunction in Heart Failure

Various studies have shown that venous and renal congestion may play more important role in kidney dysfunction. In the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) trial involved hospitalized decompensated heart failure patients in which kidney function did not correlate with cardiac index, pulmonary capillary wedge pressure, or systemic vascular resistance, but rather was associated with right atrial pressure [35]. In a retrospective analysis of 2,557 patients undergoing right heart catheterization, CVP was associated with low estimated GFR independently from cardiac index, and it predicted mortality [23]. Similarly, Guglin et al. described catheterization findings in 178 heart failure patients wherein low estimated GFR correlated with high CVP and low renal perfusion pressure but not the cardiac index or left ventricular ejection fraction [36]. Aranson et al. studied 475 patients with decompensated heart failure, of which 238 had right heart catheterization data available over the first 24 h. Net fluid loss was recorded in the first 24 h. Worsening renal function was defined as a >0.3 mg/dL increase in serum creatinine above baseline. The authors found that baseline right atrial pressure had a weak association with baseline renal function (r: −0.17, p: 0.009), but there was no association between baseline or change in right atrial pressure with the volume removed over the first 24 h, nor was there an association with the incidence of worsening renal function up to 14 days. The authors did, however, find a strong association between an increased volume of diuresis in the first 24 h of the hospitalization and a lower incidence of worsening renal function. The authors concluded that early net fluid loss is associated with worsening renal function [37]. Thus, as detailed below CVP may not be sensitive enough to detect subtle changes in volume status.

The role of haematocrit elevation (as a measure of extracellular fluid reduction) was also investigated in heart failure patients. In one study it was shown that 1,684 patients with heart failure were compared with respect to all cause mortality, cardiovascular mortality or heart failure depending on whether haemoconcentration (as a marker of decongestion) occurred or not. Haemoconcentration was defined as ≥3 % absolute increase in haematocrit. Haemoconcentration correlated with greater risk of in-hospital worsening renal function, but renal parameters generally returned to baseline within 4 weeks post-discharge. Patients with haemoconcentration were less likely to have clinical congestion at discharge and experienced greater in-hospital decreases in body weight and natriuretic peptide levels. They were also less likely to have dyspnoea, rales, and peripheral oedema at the time of discharge/day 7. After a median follow-up of 9.9 months and after adjustment for baseline clinical risk factors, every 5 % increase of in-hospital haematocrit change was associated with a decreased risk of all-cause death [hazard ratio (HR) 0.81, 95 % confidence interval (CI) 0.70–0.95]. Haematocrit change was also associated with decreased cardiovascular mortality or heart failure hospitalization at ≤100 day's post-randomization (HR 0.73, 95% CI: 0.71–0.76). The authors concluded that haemoconcentration was associated with greater improvements in congestion and decreased mortality and heart failure re-hospitalization despite an increased risk of in-hospital worsening renal function in heart failure patients [38]. In the PROTECT trial authors also found haemoconcentration, defined as absolute in-hospital increases in haemoglobin, to correlate with favourable prognosis despite a decrease in renal function [39]. In the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial patients with haemoconcentration experienced greater net weight loss and substantially lower risk of mortality despite increased risk for worsening renal function [40]. On the other hand, Davila et al. demonstrated that in-hospital increases in haemoglobin associated with worsening renal function, but not mortality [41]. At this point one must mention that anaemia and iron deficiency may be important covariates in heart failure. As well known anaemia and iron deficiency is common in CKD. However, recent evidence suggests that these parameters are also important in heart failure. Indeed, patients with heart failure may be prone to the development of iron deficiency as a consequence of a depletion of iron stores or defective iron absorption and the reduced availability of iron recycled in the reticuloendothelial system [42, 43]. Indeed, in one prospective study it was shown that Treatment with ferric carboxymaltose for 24 weeks in patients who had chronic heart failure and iron deficiency with or without anaemia improved symptoms, functional capacity, and the quality of life. Importantly this benefit was seen in all patients with and without anaemia [44]. Thus apart from its role in showing extracellular fluid reduction, anaemia and iron deficiency may play a role in worse outcomes in heart failure patients with heart failure.

Is Renal Function Deterioration During Heart Failure Treatment Good or Bad?

Classically, it was accepted that deterioration in renal function was associated with increased mortality among patients with heart failure [45, 46]. A retrospective analysis of the ADHERE database suggests that serum creatinine >2.75 mg/dl is a significant risk factor for mortality in patients with heart failure [47]. However, recent findings challenged this concept and showed that deterioration in renal function had either no effect or beneficial impact [35, 48–52]. The cause of these contrasting findings is unknown but the effects of congestion may be

responsible. To address this issue the independent effect of deterioration in renal function and presence of congestion during discharge in acute heart failure patients were investigated by Metra et al. Congestion was defined as the persistence of one or more signs or symptoms of fluid overload at discharge. The following symptoms and signs were prospectively considered: third heart sound, pulmonary rales, jugular venous stasis, hepatomegaly, and peripheral oedema. The outcome measures were post discharge mortality and acute heart failure readmission. There was no difference with respect to outcomes in patients with deterioration in renal function and no congestion and without deterioration in renal function and no congestion. However, the outcomes were worse in patients with congestion alone (without deterioration in renal function) and with congestion and deterioration in renal function. In the last patient group the hazard ratio for mortality was 2.44 (CI: 1.24–4.18). The authors concluded that deterioration in renal function alone, when detected using serial serum creatinine measurements, is not an independent determinant of outcomes in patients with acute heart failure. It has an additive prognostic value only when it occurs in patients with persistent signs of congestion [53]. Taken together, these data suggest that change in congestion status is perhaps a key variable underlying the impact of deterioration in renal function in this population.

Second selection bias may be another explanation for contrasting findings. For example, sicker patients who are more congested and have a longer hospital stay tend to have more creatinine measurements done and hence have a greater likelihood of showing a creatinine increase. Thus an increase in serum creatinine would be simply a marker of more severe heart failure rather than of progressive kidney disease [53]. Third, increases in serum creatinine levels may just be caused by renal haemodynamic abnormalities and diuretic therapy [5]. Indeed, low cardiac output and increased CVP and renal vein pressure may cause a reduction in the glomerular filtration pressure, progressive kidney disease and resistance to furosemide administration [23, 24]. Fourth, CVP a common surrogate for venous congestion was recently found to track poorly with fluid removal [37, 54]. The highly compliant nature of the venous system enables large changes in blood volume to be associated with small changes in pressure. Thus, even an effective treatment of volume overload may not be sufficient to produce a meaningful reduction in CVP and, in turn, reduce the risk of renal impairment. Besides, in most of the experimental studies showing relationship with venous pressure and deterioration in kidney function, the venous pressure was abruptly raised to extremely high values that are usually not seen even in patients with severe heart failure (e.g. 25–50 mmHg) [55]. For example, in the isolated perfused rat kidney model, GFR was not significantly altered until the imposed venous pressure reached 25 mmHg [56]. However, it is also possible that the kidneys may be more sensitive to elevated CVP in the setting of heart failure, such that GFR may fall with moderate CVP elevations [57]. Thus all these issues may be responsible for these divergent results. Indeed, today we still don't know why some decompensated heart failure patients exhibit improvements in renal function with diuresis, whereas others display renal function deterioration, limiting attainment of euvolemia. Based on current data, one can speculate that deterioration in kidney function during heart failure is an adverse event given the fact that if the insult is progressive and long-lasting. However, transient deterioration in renal function may not pose worse prognosis.

Markers for Worsening Renal Function During Heart Failure

Although the detailed description of markers used to detect renal damage during heart failure is beyond the scope of this chapter some important points must be remembered.

BUN and Creatinine

Blood Urea Nitrogen (BUN) is one of the most used and traditional markers for detecting renal function. A pooled analysis of the Prospective Randomized Evaluation of Cardiac Ectopy with Dobutamine or Nesiritide Therapy (PRECEDENT) trial conducted in 541 New York Heart Association (NYHA) Class III-IV, heart failure patients with systolic dysfunction assessed the prognostic importance of four different measures of renal function namely BUN, serum creatinine, BUN/creatinine ratio and estimated creatinine clearance. After 1-year follow-up, BUN was the only significant predictor of mortality, with an adjusted relative risk (RR) of 2.3 in patients in the upper compared with the lower quartiles (95 % CI 1.3–4.1; p: 0.005). BUN/creatinine ratio yielded similar prognostic information as BUN (adjusted RR = 2.3; 95 % CI 1.4–3.8; p: 0.007) for patients in the upper compared with the lower quartiles [58]. Consistently, a post hoc analysis of the Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Chronic Heart Failure (ACTIV in congestive heart failure) trial showed that among 319 patients with reduced systolic function stratified into quartiles according to baseline BUN, those in the highest quartile (40 mg/dL) had the highest 60-day mortality compared with those in the lower quartile (14.3 vs. 0 % respectively, p: 0.001) and the highest rate of death or heart failure hospitalization (30.0 vs. 8.6 %, p: 0.001). After adjustment for covariates, BUN remained a significant predictor of both mortality and the composite endpoint of death or heart failure hospitalization at 60 days after hospital discharge. Serum creatinine and creatinine clearance did not predict mortality after covariate adjustment [59]. Other studies also show its relation with morbidity and mortality in

patients with heart failure [58, 59]. In the randomized Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF), BUN had a stronger relationship with outcomes as compared with GFR, calculated on the basis of serum creatinine levels [60]. Thus there is growing evidence that urea is a stronger predictor of outcome than creatinine in patients with heart failure. The exact cause of this association is not known but BUN has been accepted as a mediator of neuro-humoral activation during heart failure. Additionally, drawbacks of serum creatinine may play a role. These include the dependence of serum creatinine to other variables, namely, age, gender and muscle mass, the insensitivity of serum creatinine in detecting early renal injury (relatively large amount of renal damage can occur without producing a change in GFR calculated on serum creatinine levels which start to increase only at advanced stages of renal dysfunction) and inability of serum creatinine to measure renal injury. For example changes in renal function may occur as a consequence of changes in volume status in the absence of any renal damage.

Cystatin C

It has been suggested that cystatin C might be superior to creatinine in terms of predicting prognosis in patients with heart failure [61–63]. Wen et al. explored early markers of renal impairment in experimental post-myocardial infarction heart failure and found that it is the high blood cystatin C levels, rather than serum creatinine and BUN that predict increased post-MI heart failure incidence [64]. In acute heart failure, some studies have demonstrated that cystatin C can be a good prognostic marker. Lassus et al. measured cystatin C on admission and at 48 h in 292 patients hospitalized for acute heart failure. Acute kidney injury defined by an increase in cystatin C 0.3 mg/l within 48 h. The increase of cystatin C occurred in 16 % of patients. This increase was associated with longer length of hospitalization (P: 0.01) and with a significantly higher in-hospital mortality (odds ratio 4.0 95 % CI 1.3–11.7, P: 0.01). At 90 days, the increase in cystatin C was an independent predictor of mortality (adjusted odds ratio 2.8 95 % CI 1.2–6.7, P: 0.02) [65]. However, given the fact that studies regarding the cystatin in heart failure are scarce, more studies are needed to explore the role of cystatin C in patients with heart failure.

Neutrophil Gelatinase-Associated Lipocalin (NGAL)

In patients with acute heart failure, neutrophil gelatinase-associated lipocalin (NGAL) can predict deterioration of kidney function more accurately and in an earlier stage than serum creatinine. In fact, NGAL level rises about 24 h before serum creatinine values. In 91 patients admitted for acute heart failure, deterioration of kidney function was observed in 38 % within 5 days of follow-up. Patients who developed deterioration of kidney function had significantly higher median admission serum NGAL levels (194 ng/ml vs. 128 ng/ml, P = 0.001) with an increase in risk of developing deterioration of kidney function [66]. Besides, it was suggested that levels of urinary NGAL may be more sensitive as makers of tubular damage than serum levels [67, 68].

Kidney Injury Molecule 1 (KIM-1)

In chronic heart failure, Kidney injury molecule 1 (KIM-1) demonstrated a correlation with plasma N-terminal pro-brain natriuretic peptide levels and, independently of GFR values; it was associated with an increased risk of death or heart failure hospitalizations [68]. KIM-1 is highly sensitive to acute tubular injury but in the setting of acute heart failure its role is still unsettled.

Uric Acid

Current evidence suggests that uric acid may be either a marker of poor prognosis [69] or an active player in the pathogenesis of heart failure [70]. A study of 112 NYHA class III or IV patients found that serum uric acid level is a strong predictor of poorer outcomes, defined as mortality and need for transplant [71]. Janakowska et al. had similar findings regarding elevated uric acid levels and poorer outcomes in 119 NYHA class I–III patients, suggesting uric acid levels correlate with mortality and morbidity even in mild heart failure [72]. The Framingham Offspring cohort showed that incidence rates of heart failure were approximately sixfold higher among those in the highest quartile of uric acid compared with those at the lowest quartile [73]. The relationship between uric acid and heart failure was thought to be associated with inflammation, renal congestion and oxidative stress. The mechanism of renal congestion is a special concern. In 50 patients with reduced left ventricular systolic function, uric acid correlated significantly with pulmonary artery pressure, pulmonary capillary wedge pressure, and with clinical signs of volume overload (rales, oedema, and paroxysmal nocturnal dyspnoea). It also inversely correlated with left ventricular ejection fraction, suggesting that uric acid may be a non-invasive indicator of elevated filling pressures [74]. These findings were further supported by Kittelson et al. who found that not only were higher uric acid levels were associated with increased pulmonary artery and wedge pressure but with increased right atrial pressures as well [75]. Moreover, when patients with heart failure were monitored

longitudinally, uric acid correlated with clinical status of patients. Odds ratios of hyperuricemia were 1.67 (95 % CI, 1.21–2.32) for heart failure decompensation and 0.21 (95 % CI, 0.08–0.55) for compensation [76].

Natriuretic Peptides

It was stated that patients admitted with acute breathlessness due to heart failure and an elevated natriuretic peptide level (generally 600 pg/ml for B-type natriuretic peptide (BNP) or 6,000 pg/ml for N-terminal pro-BNP) have a high filling pressure secondary to volume overload [77]. High atrial natriuretic peptide (ANP) levels not only would be a marker of venous congestion, but there is also evidence that its beneficial natriuretic effects are attenuated in heart failure. High renal interstitial pressure due to venous congestion may impair preservation of GFR by loss of ANP's effects modulating transforming growth factor β [78]. A recent study has shown that BNP levels correlate with capillary wedge pressure, it can also serve as an indirect marker for deterioration of kidney function during the treatment of acute decompensated heart failure [79].

Vasopressin

Excess vasopressin levels have long been recognized in patients with heart failure, particularly those with severe clinical manifestations and have the potential to exert deleterious effects on various physiological processes in heart failure [80]. However, measurement of circulating vasopressin levels has been challenging because it is released in a pulsatile pattern, unstable and is rapidly cleared from plasma. Arginine vasopressin is derived from a larger precursor peptide (preprovasopressin) along with copeptin, which is released from the posterior pituitary in an equimolar ratio to arginine vasopressin and is more stable in the circulation and closely reflects arginine vasopressin levels. Copeptin levels have been found to closely mirror the production of arginine vasopressin and have been proposed as a prognostic marker in acute illness [81]. Thus studies are needed whether vasopression and/or copeptin levels are promising in heart failure.

Bioimpedance

Bioimpedance technique was introduced to study changes in the volume in a tissue in 1940s. Bioimpedance is based on the principle that fluid (oedema) is a good conductor of electrical current and is associated with a low impedance value. Decreased bioimpedance reflects total body water excess, with total body water derived from these values by making certain electrophysical assumptions [82]. Bioimpedance vector analysis has been used in heart failure patients [83, 84]. More studies are needed regarding the efficiency of bioimpedance in heart failure patients.

Treatment of Renal Congestion in Heart Failure

There are various treatment options in renal congestion in heart failure (Table 9.1). The main aim is the decongestion of excess fluid without compromising renal function. The forthcoming section deals with the main treatment strategies regarding decongestion in heart failure.

Loops Diuretics

Loop diuretics are commonly used in patients with heart failure. The detailed action of loop diuretic is beyond the scope of this chapter however some important issues must be remembered. First of all, in heart failure, the dose-response curve shifts downward and to the right and there is possibility that drug reaching the Henle's loop decreases which necessitates a higher dose to achieve the same effect. Thus reaching a therapeutic threshold is an important concept [101]. At this point on may argue that higher loop diuretic dosing in heart failure is associated with worse clinical outcome [102]. However, these studies are criticized because patients with more severe disease and underlying renal insufficiency require higher diuretic doses [48]. This issue is examined in a recent trial which 183 patients with advanced heart failure stratified by baseline diuretic dose (furosemide <80 or >80 mg daily). Patients receiving high-dose diuretics ($n=113$) had more markers of increased cardiovascular risk and were more likely to have had a recent history of clinical instability (33 % vs. 4 %). After adjusting for clinical stability, diuretic dose was no longer a significant predictor of increased risk [103]. Thus it is possible that a subgroup of patients with heart failure refractory to diuretics and thereby requiring higher doses of these drugs during heart failure decompensation are especially susceptible to the development of renal injury. In fact, these patients had significantly higher admission serum creatinine levels and included a higher percentage of patients requiring thiazide in addition to loop diuretics. Alternatively, patients with deterioration of kidney function required higher diuretic doses because of more advanced heart failure. Thus, the question of whether higher diuretic doses are responsible for deterioration of kidney function or are a marker of greater disease severity remains unanswered [104]. Secondly, in general loop diuretics are given as a single daily dose. However, a

Table 9.1 Treatment strategies of venous congestion in heart failure

Loop diuretics	Use of intravenous route is more effective
	Bolus dosing may be as affective as continuous infusion [48]
	Start the initial dose at 2–2.5 times the ordinary oral dose [48]
	Increase dose until the adequate symptom relief is achieved – in case of hypotension consider continuous infusion
	Multiple dosing more effective than single dosing
	Consider adding low-dose thiazide diuretics in case of resistance; monitor electrolytes carefully
Ultrafiltration	Peripheral veno-venous ultrafiltration
	Peritoneal dialysis
V2R antagonists	Increases free-water excretion and improvement in sodium level [85, 86]
	Experimental evidence suggest improved survival [87]
	Augment the diuretic and the natriuretic response to furosemide [88]
Adenosine receptor blockers	Dilatation of afferent arteriole and preservation of GFR
	Likely not causing worsened renal function [89]
	Favorable effect on dyspnea and short-term mortality [89]
	May be associated with higher rates of seizures and stroke [90]
Dopamine	Improve renal blood flow and diuresis at low doses [91, 92]
	In acute HF use with caution [93]
	No clear effect on mortality, rehospitalizations and prevention of renal damage [94]
	Compared with placebo, no effect of low-dose dopamine on decongestion, renal function, or clinical outcomes [95]
Natriuretic peptides	Reduce cardiac filling pressure, increase cardiac output, promote diuresis and reduce RAS and release of norepinephrine [96]
	Borderline effect on dyspnea [97]
	May have hypotensive effect
	Compared with placebo, no effect of nesiritide (recombinant BNP) on decongestion, renal function, or clinical outcomes [95]
Novel therapies	Spliced BNPs potential effects [98]
	Hypertonic saline with furosemide [99]
	Relaxin [100]

ACE-I angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blockers, *V2R* vasopressin type 2 receptor, *BNP* B-type natriuretic peptide

single furosemide bolus especially in heart failure, elicits a transient period of natriuresis followed by a longer period of increased renal tubular sodium avidity due to increase in systemic vascular resistance, plasma renin activity, and plasma levels of norepinephrine and arginine vasopressin [105, 106]. Thus there is an escape from the action of loop diuretics especially when given as a single dose. To overcome this effect, loop diuretic can be administered two or more times per day. Indeed, continuous loop diuretic infusion is an extrapolation of this concept in which the time interval between dosing is reduced to zero. In this scenario, there is no antinatriuretic rebound period and negative sodium balance is sustained [4]. However, it was shown that continuous dosing is not more effective than an intelligently prescribed bolus regimen as proven in the Diuretic Optimization Strategies Evaluation (DOSE) trial [48]. However, infusion may be preferred in patients with low systolic blood pressure. Thirdly, to overcome this escape the addition of a non-loop diuretic (i.e., thiazide or potassium-sparing diuretic) may be effective by decreasing the enhanced sodium absorption in the distal tubule above [107]. The excessive use of diuretics and sympathetic overactivity in heart failure promotes the activity of the RAS. Activation of the RAS leads to excessive salt and water retention and vasoconstriction of the venous beds, altering cardiac preload and afterload, which further worsens renal function. Thus addition of mineralocorticoid receptor antagonists, such as spironolactone and eplerenone, may attenuate the neurohumoral surge and prevent deterioration of kidney function. Previous small, non-randomized, open-label trials have shown that these drugs at high doses overcome diuretic resistance in heart failure without a significant effect on serum creatinine [108, 109]. However, in an acute setting in which aggressive diuresis is needed, these drugs may also cause deterioration of kidney function. The balance is tight and careful attention to renal parameters should be given in such patients, with adjustment of doses of both drugs. Sometimes, it is prudent to withhold ACE inhibitors and angiotensin receptor blockers particularly in patients at high risk of developing renal injury, such as patients with advanced age and aggressive diuresis. Lastly, loop diuretics may also have independent actions of tubules irrespective of systemic and renal haemodynamic effects.

In one interesting study in 30 patients with chronic systolic heart failure the effect of loop diuretic withdrawal and reinitiation on tubular dysfunction was evaluated. At baseline, subjects were withdrawn from their loop diuretics. After 72 h, their furosemide regimen was reinstated and patients were studied again 3 days later. Serum creatinine, atrial and B-type natriuretic peptide, KIM-1, urinary N-acetyl-beta-D-glucosaminidase (NAG), and serum as well as urinary NGAL were determined at various time points. Diuretic withdrawal resulted in increases in atrial and B-type natriuretic peptide (both $p<0.05$). Serum creatinine was unaffected. Both urinary KIM-1 ($p<0.001$) and NAG ($p<0.010$) concentrations rose significantly, after diuretic withdrawal, whereas serum and urinary NGAL were not significantly affected. After reinitiation of furosemide, both urinary KIM-1 and NAG concentrations returned to baseline (both $p<0.05$), but NGAL values were unaffected. The authors concluded that subclinical changes in volume status by diuretic withdrawal and reinstitution are associated with increases and decreases of markers of tubular dysfunction in stable heart failure and diuretic therapy may favourably affect renal and tubular function by decreasing congestion [110].

At this point one must also mention the importance of salt and fluid restriction in heart failure. Although salt and fluid restriction is the primary dietary therapy heart failure, this is mostly based on expert opinion and few controlled studies are available. Albert et al. demonstrated that fluid restriction (1,000 mL/day) in hyponatremic (serum sodium <137 mg/dl) patients improved quality of life at 60 days after discharge [111]. Hummel et al. showed that in heart failure patients with preserved ejection fraction sodium-restricted diet was associated with favourable changes in ventricular diastolic function, arterial elastance, and ventricular–arterial coupling [112].

Apart from direct effect on extracellular volume sodium restriction has been shown to improve endothelial function and arterial stiffness [113, 114]. Given the fact that studies are scarce, more randomised studies are needed to examine the effect of salt and fluid restriction in heart failure.

Diuretics vs. Ultrafiltration to Relief Renal Congestion

Diuretic therapy aimed at fluid withdrawal and relief of congestion which are the main currently available strategies for reducing venous congestion in decompensated heart failure. Ultrafiltration is another option for the same purpose. Although several guidelines state that ultrafiltration is reasonable for patients with refractory congestion not responding to medical therapy [115–117]; we do not know known which of the two is safer and more effective [118, 119]. Although the two treatments seem to work for decongestion some differences must be mentioned. Firstly, the amount of urine produced in response to IV diuretics is not predictable but fluid removal by ultrafiltration is completely controllable and adjustable. Secondly, a potential advantage of ultrafiltration over loop diuretics is that the ultrafiltrate is isotonic, whereas the urinary output with loop diuretics is hypotonic therefore ultrafiltration removes more sodium (and less potassium) than diuretics for an equivalent volume loss [120]. Thirdly, if fluid removal does not exceed the interstitial fluid mobilization rate of approximately 15 ml/min, then the intravascular volume can be preserved with ultrafiltration, potentially interrupting the vicious cycle of neurohormonal activation and renal impairment that can occur with loop diuretics [121]. Besides, adequacy of intravascular refill during ultrafiltration can be assessed by continuous monitoring of the haematocrit with sensors placed in the withdrawal line. When the haematocrit does not significantly change during ultrafiltration, regardless of the amount of fluid removed, this indicates a proportional shift of water from the extravascular to the intravascular space. An increase in haematocrit may indicate either that plasma re-fill rate is inadequate or that interstitial oedema has been eliminated. This hypothesis is supported by data demonstrating that patients receiving ultrafiltration have lower plasma renin, norepinephrine and aldosterone levels as long as 90 days after treatment compared with those receiving diuretics [122]. Fourthly, elimination of proinflammatory cytokines [26, 123] or sodium-retaining vasoconstrictive agents may occur during ultrafiltration which is potentially involved in improvement in urinary output or restoration of diuretic responsiveness during ultrafiltration [121, 124]. Lastly, ultrafiltration mediated neurohumoral regulation is more sustained. This is probably a reason why improvement in clinical signs and symptoms of volume overload and functional capacity were found to be persistent [122, 125] and rehospitalisations are lower in ultrafiltration compared in to diuretic therapy [126]. However, as stated earlier there are no strict recommendations regarding the preferential use of diuretics, ultrafiltration and or combination. In fact in the Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF) trial it was found that the use of a stepped pharmacologic-therapy algorithm was superior to a strategy of ultrafiltration for the preservation of renal function at 96 h, with a similar amount of weight loss with the two approaches Ultrafiltration was associated with a higher rate of adverse events [49].

Peritoneal Dialysis

In peritoneal dialysis, there is a continuous slow ultrafiltration leading to a reduction in fluid overload. Lowering afterload and lowering CVP could be important physiological

mechanisms by which peritoneal dialysis leads to clinical improvement in heart failure symptoms. Moreover, it provides some replacement of renal function, by removing metabolic waste products, so a possible decrease in renal function will be better tolerated. However, the role of peritoneal dialysis in heart failure and renal congestion is not examined satisfactorily. Additionally, there are no studies available comparing peritoneal dialysis, diuretic therapy and salt restriction head-to-head in congestive heart failure [127]. In some studies, there were improvements to echocardiographic or other cardiac parameters with ultrafiltration by peritoneal dialysis [128–130]. There are also reports that peritoneal dialysis can reduce the number of hospital admissions and improve quality of life in chronic heart failure patients, as supported by recent non-randomized and non-controlled prospective studies [131–133]. However, the number of studied patients is limited and these trials all lack a control group. Also most studied patients had advanced renal failure contributing to fluid overload, introducing a major confounding factor. Another potential concern is the elevation of intra abdominal pressure by peritoneal dialysis. Currently, neither the optimal dialysis schedule nor the optimal fluid status to be reached in heart failure patients is known. The available reports all describe different peritoneal dialysis intervals, types, fluids and dosages.

Vasopressin Type 2 Receptor Antagonists

Recently, vasopressin type 2 receptor (V2R) antagonists have shown promise for use in patients with heart failure by increasing free-water excretion and serum sodium level [93]. For example, the oral V2R antagonist tolvaptan caused an early and sustained reduction in body weight and improvement in serum sodium in the EVEREST trial although did not improve mortality or morbidity [85, 86]. In a recent experimental study, chronic tolvaptan administration in a rat hypertensive heart failure model was examined considering the functional and pathological effects on both the myocardium and kidney. The animals were chronically treated with low-dose or high-dose (HD) tolvaptan or vehicle from the left ventricular (LV) hypertrophic stage. Chronic tolvaptan treatment persistently increased urine volume but did not affect blood pressure. In the HD group, the animal survival significantly improved (log-rank test, $P<0.01$). At the heart failure stage, the progression of LV dysfunction was prevented and lung congestion was suppressed. Activation of atrial natriuretic peptide, endothelin-1, AVP, and V1aR mRNA levels were significantly suppressed in the LV myocardium. Meanwhile, renal histopathologic damage including tubular fibrosis and glomerulosclerosis was ameliorated and renal function was improved in the HD group at the heart failure stage. Concomitantly, not only activation of aquaporin-2 but also those of V2R, V1aR, renin, and endothelin-1 in the kidney were significantly suppressed (all $P<0.05$). V2R antagonists also caused redistribution of AQP2 from apical to intracellular domains [87]. Goldsmith et al. studied the effect of conivaptan on renal and hormonal effects compared with or in combination with loop diuretics in stable heart failure patients. There were no significant effects of conivaptan, furosemide, or the combination on any haemodynamic variable, neurohormonal level, renal blood flow, or glomerular filtration rate. Conivaptan and furosemide similarly increased urine volumes; the effect of the combination was significantly greater. Furosemide, but not conivaptan, increased urinary sodium excretion, and the combination was significantly greater than after furosemide alone. Without adversely affecting important haemodynamic variables, neurohormones, renal blood flow, or glomerular filtration rate, conivaptan significantly augmented both the diuretic and the natriuretic response to furosemide in patients with chronic heart failure [88].

Adenosine Receptor Blockers

Adenosine concentration is increased in patients with heart failure. In the kidney, adenosine is released by the juxtaglomerular cells in response to increase in sodium load in the distal tubule, sensed by the macula densa cells. Adenosine binds to adenosine 1 receptors located in the proximal tubule and afferent arterioles of the glomerulus. This leads to a reduction in intracellular cyclic adenosine mono-phosphate and an increase the activity of basolateral $Na^+/HCO3^-$ symporter in the proximal tubule and to constriction of the afferent glomerular arteriole. Thus, adenosine release following an increase of sodium load to the distal tubule, as during intensive diuretic treatment for acute heart failure, leads to sodium retention and reduces GFR. Thus adenosine release may be a major mechanism of renal dysfunction after high dose furosemide treatment [134]. In the PROTECT trial (A Placebo-controlled Randomized study of the selective A1 adenosine receptor antagonist rolofylline for patients hospitalized with acute heart failure and volume overload to assess treatment effect on congestion and renal function), 2,033 patients admitted for acute heart failure were enrolled and randomized 2:1 to the type 1A adenosine antagonist rolofylline or placebo. Worsening renal function, defined as an increase from baseline 0.3 mg/dl of serum creatinine at day 7 from enrolment persisting at day 14 was, for the first time, included as a component of the primary end-point and as an essential component, together with dialysis or haemofiltration, of a secondary end-point. However, PROTECT failed to show any beneficial effect of rolofylline on worsening renal function. Actually, the proportion of patients who developed deterioration of kidney function was numerically greater with

rolofylline compared with placebo, whereas rolofylline, likely through its mild diuretic effects, had a favourable effect on dyspnoea as well as short-term mortality [89]. Rolofylline was also associated with higher rates of seizures and stroke, compared with placebo, and this has further inhibited any development of the drug by the sponsoring company [90].

Dopamine

Dopamine, when administered at low doses, may selectively improve renal blood flow in both the large conductance and small resistance renal blood vessels through its action on dopaminergic receptors and this was attended by an improvement in diuresis [91, 92]. In the recent Dopamine in Acute Decompensated Heart Failure (DAD-HF) trial, 60 consecutive patients hospitalized for acute heart failure were randomized to high doses of furosemide or low doses of furosemide plus low doses of dopamine. Deterioration of kidney function and hypokalemia were more frequent in the high doses arm (P = 0.042 and P = 0.003, respectively), although the 60 days outcomes were similar in both groups. The study had some limitations, related to its small sample size, which do not allow drawing conclusions regarding the effects on outcomes, as well as with regards of the relatively high average systolic blood pressure on admission [135]. In the double-blind, placebo-controlled ROSE trial 360 hospitalized patients with acute heart failure and renal dysfunction (eGFR 15–60 mL/min/1.73 m^2), were randomized to placebo, low-dose dopamine or recombinant BNP (nesiritide; see below). Compared with placebo, low-dose dopamine or nesiritide had no effect on decongestion, renal function, or clinical outcomes [95]. No studies have shown favourable effects of dopamine infusion on major outcomes, defined as mortality, rehospitalisations and prevention of long-term renal damage [94]. Thus, there is no evidence to recommend dopamine administration for the protection of renal function in patients with fluid overload and need of diuretic treatment.

Natriuretic Peptides

Nesiritide, a recombinant form of endogenous human BNP has been shown to rapidly reduce cardiac filling pressure, increase cardiac output, promote diuresis and suppress RAS and release of norepinephrine [96]. In one study, nesiritide, has a borderline effect on dyspnoea without worsening renal function [97]. In order to assess the effects of nesiritide on symptoms and outcomes of the patients with acute heart failure, the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF), was designed [136]. This study included 7,141 patients with heart failure, randomized to placebo or nesiritide. The trial confirmed that nesiritide administration was associated with an improvement in dyspnoea, compared with placebo, although not meeting the prespecified criteria for statistical significance and no effects on outcomes were found. Thus, ASCEND- heart failure showed the safety of nesiritide administration although with only mild effects on symptoms and no effects on outcomes. Also in the ROSE trial mentioned above, nesiritide did not improve short-term endpoints compared to placebo [95]. Meta-analyses of previous randomized trials had raised concerns regarding untoward effects on renal function and mortality of nesiritide infusion [137]. Recently, developed alternatively spliced BNPs (ASBNP and ASBNP.1) lacked the hypotensive side effects of nesiritide but increased the glomerular filtration rate, suppressed plasma renin and angiotensin, while inducing natriuresis and diuresis [98].

Novel Therapies

Although it seems paradoxical, combining hypertonic saline with furosemide was thought to prevent the rebound sodium reabsorption and promote effective dieresis. Paterna et al. demonstrated that a combination of high-dose furosemide with bolus hypertonic saline infusion in patients with NYHA class IV heart failure improved diuresis, shortened hospital stay, decreased BNP levels, and reduced readmissions compared with IV diuretic therapy alone [99]. In another trial namely RELAX-AHF (Efficacy and Safety of Relaxin for the Treatment of Acute heart failure), will provide definitive information of the impact of relaxin on congestion, renal dysfunction, and outcomes in acute decompensated heart failure [138]. Relaxin acts via the nitric oxide pathways and endothelin B receptors to produce systemic and renal vasodilatation. In a preliminary phase II trial (pre RELAX), relaxin was associated with relief of dyspnoea and a tendency to greater weight loss with smaller doses of diuretics and nitrates [100]. The FAIR-HF study has recently shown that among 459 patients with stable chronic heart failure, those receiving intravenous ferric carboxymaltose were more likely to report an improvement in their quality of life after 24 weeks of follow-up than those receiving placebo. It is not known whether intravenous iron application may positively affect symptom burden in patients with iron deficiency presenting with renal failure and acute decompensated heart failure [44].

Conclusions

We still do not understand the complex interactions between the failing heart and the kidneys. Apart from the classical underflow hypothesis, renal congestion is becoming realised as a major contributing factor for worse outcomes in heart failure patients. The management of renal congestion in heart failure remains an

important but unresolved clinical challenge, owing to the lack of consistent data from randomized studies in this field, rendering it difficult to outline concise evidence based treatment guidelines. Pathophysiologic mechanisms on how renal congestion leads to worse outcomes are not completely understood. Additionally, renal congestion is not directly measurable at this moment although MRI and other imaging may allow detection of renal congestion in the future.

Renal congestion is part of a complex of process. The mechanisms may vary from patient to patient, and physicians should try to individualize the management of heart failure, with focus on preventing renal injury and decreasing renal congestion. Various treatment strategies alone or in combination can be used for this purpose. Novel therapeutic options such as BNP analogues, sympathetic denervation, and combination therapy with hypertonic saline with furosemide show some promise and may enter the clinic in the future.

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Effect of Vitamin D on Endothelial Function and Blood Pressure

10

Debasish Banerjee and David Goldsmith

Clinical Case Scenario

Pritpal is a 38 year old man originally from India. He works long hours in a small grocery shop, and rarely gets out. He is obese, dyslipidaemic, hypertensive and he has been told he has "pre-diabetes". Renal function was normal, but he had microalbuminuria. He was taking metformin, atorvastatin, and perindopril. Recently he has also noticed some erectile dysfunction. Starting the previous Winter, he had also begun to experience muscle aches and pains especially in his thighs, pelvis, and shoulders. His plasma CK level was normal, and stopping the statin for 6 weeks had no effect on his muscle symptoms. His General Practitioner sent off blood for a serum 25(OH) vitamin D concentration - this was unrecordably low at <10 nmol/L (indicating complete vitamin D deficiency).

He was prescribed a course of vitamin D (2000 IU daily for 6 months). After 6 months his serum 25(OH) vitamin D concentration was 56 nmol/L (ideal >75 nmol/L), his muscle pains had disappeared, and his erectile dysfunction, blood pressure and albuminuria had all improved without any other intervention.

Chronic kidney disease (CKD) is associated with an increased rate of cardiovascular events [1], *which is not fully explained by traditional risk factors and is increasingly associated with non-traditional risk factors* [2].

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Vitamin D deficiency is a non-traditional risk factor for cardiovascular events which becomes more relevant with declining renal function. At the same time, the deficiency of active vitamin D plays a major role in the mineral-bone disease of patients with CKD. The role of vitamin D deficiency in causing cardiovascular complications in the general population has attracted huge attention from researchers in recent years [3]. *However, patients with kidney failure deserve further attention due to the role of kidneys in activating vitamin D.*

Vitamin D and the Kidney

The story of Vitamin D and the kidney began in 1970 when a group of scientists from the Dunn Nutritional Laboratory in Cambridge, UK described the crucial role of the kidney in generating the active form of Vitamin D [4]. Elegant experiments in chickens and rats demonstrated that anephric animals were unable to complete the final polar hydroxylation and generate the dihydroxy form of Vitamin D. Further experiments established that the dihydroxy form was more potent than 25 hydroxy Vitamin D [5]. This led to the rapid realisation of the almost universal deficiency of 1,25 dihydroxy vitamin D and its effects on parathyroid glands and bone, in end stage renal disease patients in the newly established dialysis programs. Other experiments in the late 1970's established the role of supplementation with 1,25 dihydroxy Vitamin D in patients with end stage renal disease, to suppress parathyroid hormone and treat bone disease; this became normal practice by the 1980's [6]. Multiple studies, since then, including well conducted randomised trials have shown that active vitamin D and vitamin D agonists are very effective in suppressing parathyroid hormone [7].

However, the pleotropic effects of Vitamin D and the adverse effects on the cardiovascular system of vitamin D deficiency were not well appreciated and understood until the

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early 1990's [8]. Large retrospective epidemiological studies demonstrated the benefits of supplementation with active vitamin D on cardiovascular outcomes, suggesting a 37 % reduction in cardiovascular mortality in CKD patients [9].

Nutritional vitamin D deficiency, as defined by low levels of 25 hydroxy vitamin D, was common in both pre-dialysis and end stage kidney diseases patients. Supplementation with nutritional vitamin D was also associated with modest suppression of parathyroid hormone levels (by approximately 41 pg/ml) [10].

These findings led to a renewed interest in the role of vitamin supplementation in CKD, not only to treat bone disease but also potentially to address the abnormalities of vascular and cardiac structure and function seen in most CKD patients.

Endothelial Dysfunction and Atherosclerosis

The endothelium is the inner protective layer of all blood vessels, which responds to a variety of mechanical, immunological and chemical stimuli in order to maintain vessel reactivity, prevent vascular stasis and thrombosis and minimise downstream ischemia; when dysfunctional, causes vasoconstriction, inflammation, hypertension and atherosclerosis. Endothelial cell dysfunction and injury starts a chronic inflammatory and healing response which results in intimal hyperplasia and atherosclerosis as shown in Fig. 10.1.

The role of endothelial dysfunction in the progression of atherosclerosis and cardiovascular events has been shown in several clinical studies. Endothelial dysfunction predicted progression of carotid artery intima-media thickness in 213 middle-aged civil servants and 618 post-menopausal women, and predicted future cardiovascular events even after adjustment for traditional Framingham cardiovascular risk factors in 3,026 multi ethnic American males and 2,264 post-menopausal Italian women [11–14].

Endothelial Dysfunction in CKD

Endothelial function is highly abnormal in patients with kidney failure. Endothelial dysfunction starts in the very early stages of CKD, progresses with deteriorating kidney failure, is worst on dialysis, and partially improves with kidney transplantation [15]. Unlike in the general population, the evidence of endothelial dysfunction as a risk factor for cardiovascular disease is weak. In a small study with 304 CKD 1–5 patients flow mediated dilation predicted cardiovascular events [16].

Brachial artery flow mediated dilatation is a non-invasive, cheap, established method of determination of endothelial function; it is relatively easily measured by experienced operators [17]. It has been used in CKD patients to test the impact of a variety of interventions such as statins, ACE inhibitors, angiotensin receptor blockers, allopurinol, rosiglitazone, vitamin C, folic acid and sevelemar [18–23]. It is important to note that any changes in endothelial function can be very short lasting. For example, intravenous iron in haemodialysis patients causes endothelial dysfunction within 15–60 min after administration which normalises after 4 h [24].

Mechanism of Effect of Vitamin D on Endothelial Function

The effect of vitamin D on endothelial function has been extensively investigated in the laboratory with in-vivo and in-vitro [25]. Vitamin D modulates endothelial cell function via both genomic transcription and other non-genomic pathways. Endothelial cells are capable of enzymatically activating 25 hydroxy vitamin D to 1,25 dihydroxy vitamin D and hence can respond serum 25 hydroxy vitamin D in severe CKD, where renal activation is significantly impaired [26].

In the endothelial cell vitamin D increases nitric oxide (NO) availability by its possible non-genomic action on intracellular kinases P38, protein kinase B and extracellular signal related kinases (ERK) [27]. This action is mediated via the interaction of vitamin D with vitamin D receptor (VDR) and subsequent phosphorylation of the kinases. Vitamin D reduces reactive oxygen species (ROS) generation via non-genomic suppression of the p22 (phox) subunit of NADPH oxidase [28]. The non-inflammatory effects of vitamin D in endothelial cells are mediated by suppression by gene transcription, via inhibition of NF κβ, of cytokines IL6, IL8, RANTES and cell adhesion molecules ICAM-1, PECAM-1, VCAM-1 and E Selectin [29, 30]. See Fig. 10.2.

Impact of Vitamin D on Endothelial Function in the Non-CKD Population

Several studies have tested the impact of vitamin D and endothelial cell function in non CKD patients; as summarised Table 10.1 [31–43]. The dose, preparation and duration of therapy varied between the studies, as did the baseline vitamin D concentrations. Endothelial function improved with

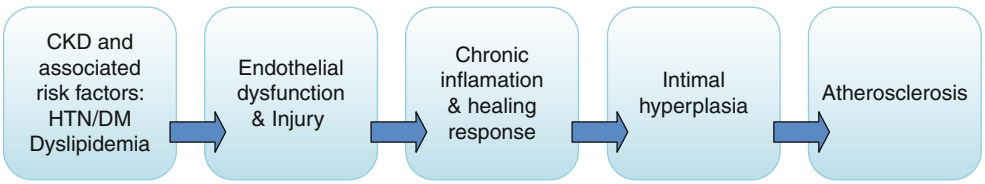

Fig. 10.1 Pathway of endothelial dysfunction and atherosclerosis

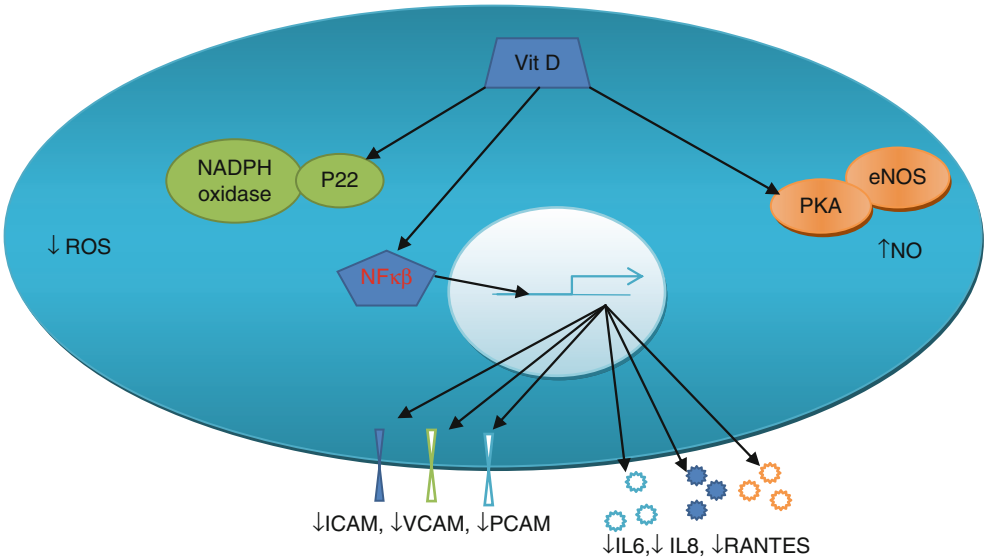

Fig. 10.2 Vitamin D effects on endothelial cell. Vitamin D in the endothelial cell increases nitric oxide (*NO*) via its non-genomic action on the eNOS system (in *orange*) and decreases production of reactive oxygen species (*ROS*) by its non-genomic action on p22 and NADPH oxidase system (*green*). It decreases the production of ICAM, VCAM and PCAM (*dark blue*, *green* and *light blue cylinders*) and IL6, IL8, RANTES (*light blue*, *dark blue* and *orange stars*) via genomic action and NFκβ

Table 10.1 Clinical trials of vitamin D supplementation on endothelial dysfunction in adult patients

Author/ref.	n	Duration (months)	Vitamin D use	Inclusion criterion change in vit. D	Patient type	Outcome
Stricker et al. [31][a]	62	1	100,000 once D3	<30 ng/ml 16 to 24 ng/ml	PVD	**No change**
Gepner et al. [32][a]	114	4	2500/day × 4 months D3	>10 <60 ng/ml 31 to 46 ng/ml	Post menopause	**No change**
Witham et al. [34]	75	6	100,000 × 3 D3	<100 nmol/L 44 to 71 nmol/L	Post MI	**No change**
Longenecker et al. [36]	45	3	4000/day × 3 months D3	<20 ng/ml 5 ng/ml rise	HIV patients	**No change**
Witham et al. [37][a]	61	4	100,000 or 200,000 D2	<100 nmol/l	Diabetes	**No change**
Sokol et al. [38][a]	90	3	50,000/week × 12 D2	<20 ng/ml 13 to 40 ng/ml	CAD	**No change**
Witham et al. [33][a]	50	2	100,000 D3	<75 nmol/L 27 to 43 nmol/L	South Asian women	**No change**
Yiu et al. [39][a]	50	3	5,000/day × 12 weeks D3	<30 ng/ml 21 to 55 ng/ml	Diabetes	**No change**
Tarcin et al. [40]	23	3	300,000[b] × 3 D3	<25 nmol/L 20 to 116 nmol/L	Healthy volunteers	**FMD improved**
Harris et al. [41][a]	45	4	60,000/month × 4 D3	34 ± 38 nmol/L 34 to 101 nmol/l	African Americans	**FMD improved**
Witham et al. [42][a]	58	4	100,000 D2	<75 nmol/L 38 to 54 nmol/L	Post stroke	**FMD improved**
Sugden et al. [43][a]	34	2	100,000 D2	<50 nmol/L 38 to 53 nmol/L	Diabetes	**FMD improved**
Dreyer et al. [44][a]	38	6	350,000 D2	<30 nmol/L ~90 nmol/L	CKD 3,4 (not diabetic)	**Micro-circulation improved**

Legend: *n* number of patients, *D2* ergocalciferol, *D3* cholecalciferol; *PVD* peripheral vascular disease, *CAD* coronary artery disease
[a]Randomised controlled trials
[b]Intramuscular dose

the administration of vitamin D3 300,000 IU once a month for 3 months in healthy volunteers and with 60,000 IU monthly for 4 months in African Americans [41]. A single dose of 100,000 IU Vitamin D2 was able to improve endothelial function over 2 months in two different studies in patients with diabetes and stroke [42, 43]. The changes in endothelial function 4 months after vitamin D therapy in the post stroke patients were not significant, indicating that the effects were short lasting without on-going supplementation.

Several other studies have failed to show any improvement of endothelial function with vitamin D supplementation [31–39]. Some studies used comparatively lower doses

of vitamin D, and others included patients who were not vitamin D deficient or insufficient. However the reason for failure of improvement of endothelial function were not always evident.

Clinical Studies of Vitamin D and Endothelial Function in CKD

Pre-intervention studies in kidney failure patients have examined the relationship between vitamin D deficiency and endothelial function. Vitamin D deficiency has been associated with endothelial dysfunction in both dialysis and pre-dialysis patients. In 52 prevalent dialysis patients flow mediated dilatation (FMD) was directly associated with serum 25 hydroxy vitamin D and 1,25 dihydroxy Vitamin D concentrations [45]. Similarly, in 50 CKD patients decreasing 25 hydroxy Vitamin D levels were associated with decreasing FMD [46].

Very few studies have tested the impact of supplementation of vitamin D on endothelial function in CKD patients. The use of the vitamin D agonist Paricalcitol in two different doses (1 and 2 μg/day) was able to reduce albuminuria and, at higher dose CRP in 24 CKD 2–3 patients; but failed to change FMD [47]. The changes in FMD with placebo, 1 and 2 μg/day was −0.1 % (95 % CI −2.9 to 2.7; p=0.95); 0.4 % (−2.6 to 3.4; p=0.79) and 0.3 % (−3.4 to 4.0; p=0.87) respectively. There was no change in clinic blood pressure and 24 h BP. The baseline PTH concentrations were not significantly elevated and did not change with therapy.

In another study with 26 vitamin D insufficient/deficient patients with CKD stages 3 and 4, two doses of 300,000 cholecalciferol for 16 weeks increased Vitamin D (43 ± 16 to 84 ± 29 nmol/L p<0.001) decreased PTH (10.8 ± 8.6 to 7.4 ± 4.4 pmol/L, p=0.001) and improved FMD (3.1 ± 3.3 to 6.1 ± 3.7 %, p<0.001) [48]. Cholecalciferol therapy improved endothelial cell blood biomarkers E selection, ICAM-1 and VCAM-1. There was no change in blood pressure. Although Vitamin D deficiency is associated with endothelial dysfunction in pre-dialysis and dialysis dependent CKD patients, any benefit of supplementation is not established and randomised controlled trials in CKD patients are required.

Dreyer's study [44]] involved 38 subjects (CKD stage 3,4 non diabetic) 20 of whom received ergocalciferol and 18 received placebo. After 6 months, there was a significant improvement in the ergocalciferol-treated group in endothelium dependent microcirculatory vasodilatation after iontophoresis of acetylcholine (p=0.03) and also there was a reduction seen in tissue advanced glycation end products (p=0.03). There were no changes in sublingual microcirculatory parameters. Pulse pressure (p=0.01), but not aortic pulse wave velocity, was reduced. There were no significant changes in bone mineral parameters (curious not to see a PTH reduction), brachial artery blood pressure, or left ventricular mass index suggesting that ergocalciferol improved endothelial function independently of these parameters (or that the effect is too small to detect in a small study group such as here). In parallel ex vivo experiments, expression of endothelial nitric oxide synthase and activity were increased in human endothelial cells in a dose dependent manner.

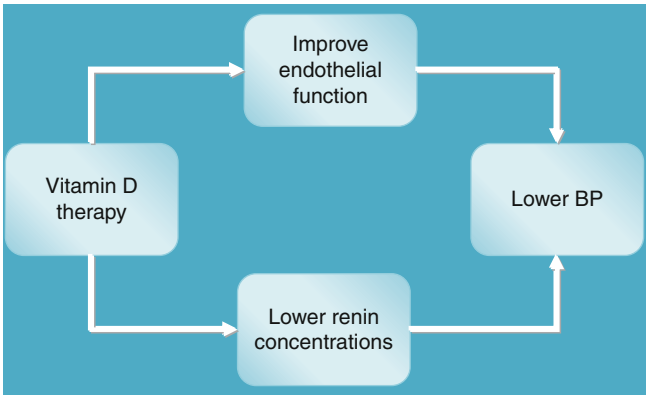

Fig. 10.3 Vitamin D effects on blood pressure. Vitamin D may lower BP via its action improvement of endothelial function and suppressing renin release

Hypertension in Chronic Kidney Disease

Hypertension, predominantly systolic, in CKD is almost universal and is the end result of multiple pathophysiologic mechanisms. The activation of the renin-angiotensin and sympathetic nervous systems, fluid retention, endothelial dysfunction, and central arterial stiffness all play major roles in elevating the blood pressure. Hypertension is the most common reversible cardiovascular risk factor for both cardiovascular events and progression of kidney failure in patients with CKD. It is often difficult to reach target blood pressure despite lifestyle modifications and multiple medications. Hence, new methods and new pharmacological agents for the treatment of hypertension in CKD could potentially benefit large numbers of patients suffering from the ill effects of poorly controlled blood pressure.

Mechanism of Effect of Vitamin D on Blood Pressure

Vitamin D can potentially improve endothelial function and lower renin activity and hence lower blood pressure in patients with chronic kidney disease (see Fig. 10.3). Vitamin D affects endothelial function by its genomic transcriptional and other non-genomic actions as discussed above. Vitamin D modulates the renin-angiotensin system by decreasing renin production in experimental animals and humans. This was shown in 15 patients of essential hypertension and hypovitaminosis D, in whom administration of 200,000 IU

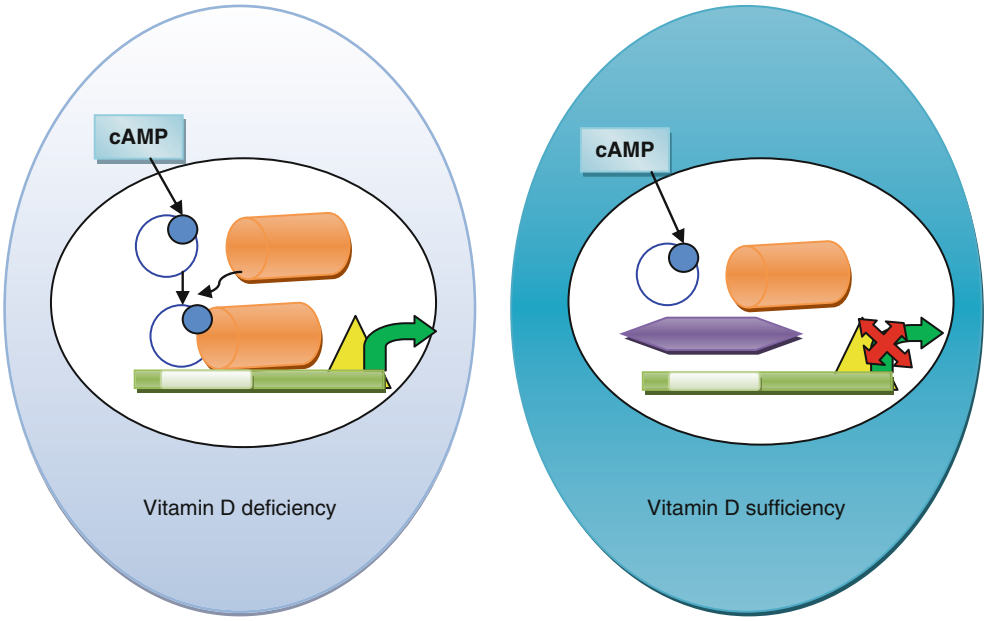

Fig. 10.4 Renin mRNA production in vitamin D deficient and vitamin D sufficient states. Cyclic AMP donates the phosphate (*blue dot*) to the CREB (*blue open circle*) and activates it. CRB binds with CBP/p300 (*orange cylinder*) which in vitamin D deficient state binds to the cAMP responsive element or CRE (*white box*) on the upstream promoter region of renin gene, activates the RNA polymerase (*yellow triangle*) and starts transcription of renin mRNA (*green arrow*). In presence of vitamin D, the vitamin D-VDR (*purple hexagon*) prevents binding of CRB with CRE

vitamin D in divided doses over 8 weeks was associated with a reduction of renin and aldosterone levels [49].

Animal experiments suggest 1,25 dihydroxy Vitamin D suppresses renin gene transcription by blocking cyclic AMP-dependant renin gene regulation (see Fig. 10.4) [50]. Cyclic AMP is an intracellular signal for renin production in the juxtaglomerular cells in the kidney. Cyclic AMP, once generated, phosphorylates the transcription factor CREB which with co-activation of CBP/p300 activates the cyclic AMP responsive element (CRE) and promotes renin gene transcription (see Fig. 10.4). The 1,25 dihydroxy vitamin D and vitamin D receptor (VDR) complex interacts with CREB, prevents its binding with CRE, and stops renin gene transcription.

Impact of Vitamin D on Blood Pressure in the Non-CKD Population

Studies in the general population on the effect of Vitamin D therapy on blood pressure have shown conflicting results [51]. Observational studies clearly demonstrate increasing blood pressure with low vitamin D concentrations, as shown in a meta-analysis of 18 studies [52]. Intervention studies have shown conflicting results. Recently, in 159 elderly patients with isolated systolic hypertension 400,000 IU of cholcalciferol did not show any significant effect on blood pressure [35]. Whereas, in 283 middle aged black patients administration of 90,000–360,000 IU of cholcalciferol was associated with improvement in systolic blood pressure [53]. Several meta-analyses from multiple interventional trials have similarly demonstrated equivocal results on the impact of vitamin D and blood pressure in the general population [54].

Clinical Studies on Impact of Vitamin D on Blood Pressure in CKD Patients

Several studies have examined the effect of vitamin D on blood pressure in CKD, but none had treatment of hypertension as the primary goal; in majority of the studies vitamin D was administered to examine the effect on proteinuria. In a recent study with 101 CKD patients, using 666 units/day cholecalciferol, there was no change in blood pressure [55]. Similarly, in a longer 1 year trial, high dose cholecalciferol 50,000 IU every week for 12 weeks followed by 50,000 IU every fortnight for 40 weeks in CKD stages 2 and 3 patients had no effect on blood pressure [56]. In another study of 98 haemodialysis patients, treatment with 40,000 IU cholecalciferol every week for 8 weeks in the deficient patients did not change blood pressure [57]. Paricalcitol used in a short, 4 week study with CKD was unable to alter BP [47]. Several other studies have used different preparations and doses of Vitamin D, mostly of short duration (4–16 weeks) but none have been able to improve blood pressure.

Conclusion

The role of vitamin D supplementation in improving patient outcome remains tantalising, but, incompletely explored, and not bolstered adequately by RCTs [58]. Vitamin D therapy for improving cardiovascular health has shown both positive and negative results; the same is true to some extent for skeletal health [59].

The mechanism of effect of Vitamin D needs to be better understood in light of evolving knowledge on the bioavailability of the hormone and binding with its receptor, which are known to be genetically determined. We are

beginning to understand the genetic variations of the vitamin D binding protein and vitamin D receptor [60, 61]. More research is needed to better understand the mechanism of action of vitamin D, and with utilisation of the knowledge from randomised controlled trials we will able to identify the right patient, right formulation and right dose of vitamin D, to improve patient health.

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Vitamin D and Its Effects on the Heart

11

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Clinical Case Scenario

A 67 year-old gentleman with hypertension, hyperlipidemia, heart failure with preserve ejection fraction (left ventricular ejection fraction 65%), symmetric left ventricular hypertrophy, chronic kidney disease Stage 3B presents in follow up of his multiple cardiovascular issues. He has a normal serum calcium level and his parathyroid hormone is within target range. Would this patient benefit of vitamin D treatment and if so, which form and dose of vitamin D?

Introduction

Although primarily involved in bone and mineral metabolism, both 25-hydroxy vitamin D (25[OH]D) and its active hormonal form (1,25-dihydroxy vitamin D [1,25$(OH)_2$D]) have been associated with cardiovascular effects [1]. The very high prevalence of vitamin D insufficiency or deficiency, commonly defined as <30 and <20 ng/mL [1], respectively, makes this association especially important to unravel. Since cardiovascular disease is the number one cause of mortality in the United States, the topic is particularly relevant to disease prevention strategies aimed at improving public health [2–5].

Although the vitamin D receptor (VDR) is known to be expressed in cardiomyocytes and fibroblasts [6, 7], the role of supplementation with vitamin D and/or its analogs on cardiac function has yet to be elucidated. Epidemiological data to date are inconclusive [8, 9] and randomized studies are scarce (Table 11.1 provides a summary of longitudinal studies evaluating 25(OH)D associations with cardiovascular outcomes). Furthermore, most studies aimed at establishing a link between vitamin D and cardiovascular outcomes have focused on total circulating levels of 25(OH)D, but important new information suggests that the fraction of 25(OH)D that is not bound to its specific high-affinity carrier protein may be a more appropriate indicator of vitamin D status [22]. In the current chapter we will focus on the biological pathways by which vitamin D may play a role on cardiac function as well as observational and randomized studies of vitamin D supplementation in cardiovascular disease.

Observational Studies

Observational studies can assess the exposure (25(OH)D) and outcome (i.e. cardiovascular diseases) at the same point in time (cross-sectional) or they can assess the exposure and then outcome occurring after the exposure is measured (longitudinal). The cross-sectional studies are faster, cheaper and allow us to evaluate the relationship between the variables of interest at a given time point. However, the cross-sectional studies do not provide any information regarding the timing of the events as the longitudinal studies do. All observational studies are subject to confounding, which can be best minimized by randomization to intervention or placebo. In this section we will evaluate the data supporting the effects of vitamin D in cardiovascular diseases by study type.

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Table 11.1 Summary of longitudinal studies evaluating 25(OH)D associations with cardiovascular outcomes

Study	Population	N	Male (%)	Age (years)	Baseline 25(OH)D (ng/mL)	Follow-up (years)	Exposure ([25(OH)D] in ng/mL)	Outcome	Association
Wang et al. [10]	Community-dwelling adults, no previous CVD	1,739	45	59	19.7	5.4	25(OH)D <15 vs. 25(OH)D ≥15	MI, angina, Stroke, TIA, HF	HR 1.62 (95 % CI 1.11–2.36)
Giovannucci et al. [11]	Men between 40 and 75, no current CVD	18,225	100	64	23.6	10	25(OH)D <15 vs. 25(OH)D >30	Nonfatal MI, fatal CHD	RR 2.42 (95 % CI 1.53–3.84)
Sun et al. [12]	Community-dwelling adults, free of CVD and cancer	118,864	38	n/a	n/a	21	Intake of 25(OH)D ≥600 IU/day vs. intake <100 IU/day	CHD and stroke	RR 0.84 (95 % CI 0.72, 0.97) for men; RR 1.02 (95 % CI 0.89, 1.17) for women
Brøndum-Jacobsen et al. [13]	Community dwelling adults without vitamin D fortified-diet.	10,170	44	57	17.6	29	25(OH)D <6 vs. 25(OH)D >24	Myocardial infarction	HR 1.64 (95 % CI 1.25–2.14)
Dobnig et al. [14]	Patients referred for coronary angiography	3,258	Stratified	62	Stratified	8	25(OH)D 13.3 vs. 25(OH)D 28.4	Cardiovascular death	HR 1.82 (95 % CI 1.29–2.58)
Wolf et al. [15]	Incident dialysis patients	825	53	63	21	90 days	25(OH)D <10 vs. 25(OH)D >30	Cardiovascular death	OR 1.9 (95 % CI 1.0–3.4)
van Ballegooijen et al. [16]	Community-dwelling older adults	256	Stratified	67	23	8	25(OH)D <14 vs. 25(OH)D >32	Change in LVMI	RC 9.9 (95 % CI 3.3, 16.6)
Fall et al. [17]	Elderly subjects, no previous heart disease	870	48	70	23.2	5	Baseline 25(OH)D	LVMI	B = –0.035 (95 % CI –0.915, 0.846)
Liu et al. [18]	Patients with heart failure	548	61	74	14.6	1.5	Decrease in [25(OH)D] by 4	HF hospitalization or death	HR 1.09 (95 % CI 1.00–1.16)
Pilz et al. [19]	Patients referred for coronary angiography	3,299	Stratified	Stratified	Stratified	8	25(OH)D <10 vs. 25(OH)D ≥30	HF or sudden cardiac death	HR 2.84 (95 % CI 1.20–6.74)
Forman et al. [20]	Community-dwelling adults without hypertension	1,809	Stratified	Stratified	Stratified	4	25(OH)D <15 vs. 25(OH)D ≥30	Incidence of hypertension	RR 3.18 (95 % CI 1.39 to 7.29)
Margolis et al. [21]	Postmenopausal women without hypertension	4,863	–	66	Stratified	7	Quartiles of 25(OH)D	Incidence of hypertension	Change in SBP or DBP by 25(OH)D quartile was not significantly different at any point in time

Note: *HR* hazard ration, *RR* relative risk, *OR* odds ration, *RC* regression coefficients, *CI* confidence interval, *IU* international units, *CV* cardiovascular, *CVD* cardio vascular disease, *CHD* coronary heart disease, *MI* myocardial infarction, *TIA* transient ischemic attack, *HF* heart failure, *LVMI* left ventricular mass index, *HF* heart failure, *SBP* systolic blood pressure, *DBP* diastolic blood pressure

Cross-Sectional Studies

A growing body of literature suggests that vitamin D insufficiency or deficiency may be associated with an increased risk of cardiovascular disease. However, the evidence thus far is inconclusive and subject to debate. Early studies reported a higher prevalence of hypertension in countries located in northern latitudes where populations are exposed to less sunlight than in countries nearer the equator [23, 24]. Similarly, large population studies such as the Third National Health and Nutrition Examination Survey (NHANES) identified cardiovascular risk factors (elevated blood pressure, plasma glucose and cholesterol) associated with lower 25(OH)D levels [25]. In contrast, an analysis of the Longitudinal Aging Study Amsterdam that included 1,205 participants patients older than 65 year-old did not find any association between 25(OH)D levels and blood pressure [26].

A second analysis of the NHANES database conducted by Melamed et al. included 13,331 free-living adults in the United States. These authors reported an increase in coronary artery disease (CAD) and stroke in patients with total 25(OH)D levels <20 ng/mL vs. those with 25(OH)D of >32 ng/mL [odds ratio (OR) 1.2 (95 % confidence interval (CI): 1.01–1.36)] [27]. Others have described an association between low 25(OH)D (<30 ng/mL) and heart failure (OR 1.7 [95 % 0.87–3.32]) in the same NHANES cohort [28]. In cases of extreme vitamin D deficiency (<15 ng/mL) in children (rickets), severe cardiomegaly and heart failure have been reported [29–33] Interestingly, patients with Vitamin D–resistant rickets as a result of congenital mutations in the VDR mostly die from cardiovascular diseases, but show no abnormalities in angiotensin converting enzyme activity, or in levels of angiotensin II and aldosterone [34].

Longitudinal Studies

Ischemic heart disease has been associated with extreme forms of vitamin D deficiency. For example in 1,739 participants of the Framingham Offspring Study, the risk of ischemic heart disease was associated with total 25(OH)D <15 ng/mL (hazard ratio [HR] of 1.62; 95 % CI 1.11–2.36, P = 0.01) compared to individuals with levels ≥15 ng/mL [10]. In a stratified analysis by diagnosis of hypertension at baseline, the association between 25(OH)D levels and ischemic heart disease was evident in patients with hypertension (HR 2.13, 95 % CI 1.30–3.48), but not in those without hypertension (HR 1.04, 95 % CI 0.55–1.96). Similar results were found in a study involving 18 225 men in the Health Professionals Follow-up Study [11] Furthermore, higher vitamin D intake from foods and supplements was associated with a decreased risk of cardiovascular disease including coronary artery disease and stroke in the Nurses Health Study and the Healthcare Professionals Follow- up Study [12]. Large global cohort studies have yielded similar findings. One such study of 10,170 women and men from the Danish general population showed that the risk for myocardial infarction was 64 % higher in participants with extreme 25(OH)D deficiency (<6 ng/mL) than participants with 25(OH)D >24 ng/mL [13]. Similarly, in the Ludwigshafen Risk and Cardiovascular Health (LURIC) study, both low 25(OH)D and $1,25(OH)_2D$ levels were associated with cardiovascular mortality [14]. Of note, patients with extreme forms of chronic kidney disease who cannot convert 25(OH)D into the active hormonal form $1,25(OH)_2D$ also have a high risk of cardiovascular mortality [15].

Studies evaluating the role of vitamin D in patients with left ventricular hypertrophy (LVH) show mixed results. An analysis of 256 participants from the Hoorn study, which is a population-based cohort in the Netherlands, demonstrated an association between low 25(OH)D and LVH only in individuals with history of cardiovascular disease and in those with low renal function (median estimated glomerular filtration rate ≤77.5 mL/min/1.73 m^2) [16]. The effect appeared to be attenuated when adjusted for parathyroid hormone (PTH) levels. The Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study suggested an association between low 25(OH)D levels and altered left ventricular (LV) geometry and function at baseline (left ventricular end-systolic diameter and left ventricular ejection fraction), but failed to show the same association after 5 years of follow up [17]. In contrast, an analysis of 711 participants from the Baltimore Longitudinal Study of Aging revealed a relationship between 25(OH)D levels and left ventricular mass index (by echocardiogram), but did not find an association with left ventricular ejection fraction or geometry [35]. Similarly, a study that utilized cardiac magnetic resonance in 992 Icelandic community dwelling individuals found an association between 25(OH)D and left ventricular mass [36]. Populations with extreme forms of 25(OH)D deficiency such as the chronic kidney disease have a higher prevalence of LVH than patients with similar risk factors with normal renal function [37]. Heart failure patients with low 25(OH)D levels have a poor prognosis and higher inflammatory markers than those with higher 25(OH)D levels [18]. Furthermore, 25(OH)D levels are negatively correlated with natriuretic peptides and New York Heart Association class [19]. However, the relationship between vitamin D and heart failure is still controversial [38].

Blood pressure and vitamin D have been inconsistently linked in longitudinal studies. A combined analysis of the Health Professionals' Follow-Up Study and the Nurses' Health Study with 1,811 patients encompassing up to 8 years of follow-up reported a 2.67 fold increase in the relative risk of hypertension when comparing individuals with 25(OH)D

Table 11.2 Summary of randomized trials evaluating 25(OH)D or 1,25(OH)2D analogs on cardiovascular outcomes

Study	N	Population	Intervention	Follow-up	Outcome	Result
Thadhani et al. [45]	227	CKD stage 3b-4	Paricalcitol 2 μg/day or Placebo	48 weeks	Change in LVMI	No effect in LVMI
Wang et al. [46]	60	CKD stage 3–4 with left ventricular hypertrophy	Paricalcitol 1 μg/day or Placebo	52 weeks	Change in LVMI	No effect in LVMI
Shedeed et al. [47]	80	Infants with chronic heart failure	Cholecalciferol 1,000 IU/day or Placebo	12 weeks	Left ventricular end-diastolic diameter	32.8 ± 4.6 mm before and 24.9 ± 3.1 mm after treatment
Larsen et al. [48]	130	Subjects with hypertension	Cholecalciferol 3,000 IU/day or Placebo	20 weeks	24 h blood pressure	BP significantly decreased in subjects with 25(OH)D <32 ng/ml
Hsia et al. [49]	36,282	Postmenopausal women	Cholecalciferol 400 IU/day or Placebo	7 years	Myocardial infarction, coronary death and stroke	No difference between groups
Trivedi et al. [50]	2,686	Men and women over 65 years	Cholecalciferol 100,000 IU/4 months or Placebo	5 years	Mortality by cardiovascular disease (fatal MI, stroke)	No difference between groups
Prince et al. [51]	302	Older women with low 25(OH)D (<24 ng/mL) and previous history of falling	Ergocalciferol 1,000 IU/day or Placebo	1 year	Ischemic heart disease (MI, angina)	No difference between groups

Note: *HD* hemodialysis, *IU* international units, *LV* left ventricle, *LVMI* left ventricular mass index, *LVEDD* left ventricular end diastolic diameter, *MI* myocardial infarction, *CKD* chronic kidney disease, *BP* blood pressure

<15 vs. >30 ng/mL [20] In contrast, the Women's Health Initiative study reported no association between 25(OH)D and hypertension [21]. In the Norwegian Tromso study (n = 2,385), no difference in the incidence of hypertension was found in participants with lower vs. higher quartiles of 25(OH)D after 14 years, except for a small increase (4 mmHg) in systolic blood pressure when the lowest (<16 ng/mL) vs. the highest 25(OH)D quartiles (>25 ng/mL) were compared [39].

It is important to note that none of these studies evaluated the role of vitamin D repletion in the aforementioned outcomes. Observational studies cannot rule out other characteristics of these populations that may explain the associated cardiovascular effects. Well-designed randomized trials are needed to confirm or rule out the suspected associations [40].

Clinical Trials

Nonrandomized Open-Label Trials

A few small open-label studies have been conducted. One included 27 infants with vitamin D deficient rickets and ten controls. Both groups were administered one dose of 600,000 IU cholecalciferol and calcium for 2 weeks and showed an improvement in ejection fraction [41] Another study administered 50,000 units of cholecalciferol weekly for 12 weeks to 30 chronic hemodialysis patients with 25(OH)D levels <30 ng/mL followed by 20,000 IU weekly for another 12 weeks [37]. Interestingly, a significant reduction in left ventricular hypertrophy (by echocardiogram) and inflammatory markers was detected at 6 months. Similarly, several small short-term studies in hemodialysis patients with hyperparathyroidism experienced reductions in left ventricular hypertrophy after treatment with $1,25(OH)_2D$ for 3 months [42, 43], or cholecalciferol for 1 year [44].

Randomized Trials

Randomized trials evaluating the effects of intervention with either 25(OH)D or active $1,25(OH)_2D$ analogs on cardiovascular outcomes as a primary objective are very scarce (Table 11.2). Supported by extensive animal experiments and observational human studies suggesting an effect of vitamin D on left ventricular hypertrophy [10, 52–54], PRIMO (Paricalcitol Capsule Benefits in Renal Failure–Induced Cardiac Morbidity) was one of the first large randomized trials designed to evaluate the cardiac effects of vitamin D repletion. In PRIMO, 227 patients with Stage 3b-4 chronic kidney disease were randomized to receive either the active vitamin D compound paricalcitol or placebo for 48 weeks to evaluate its effect on left ventricular mass index (LVMI) [45]. Despite the supporting data in both animal and human studies, PRIMO found no effect of paricalcitol

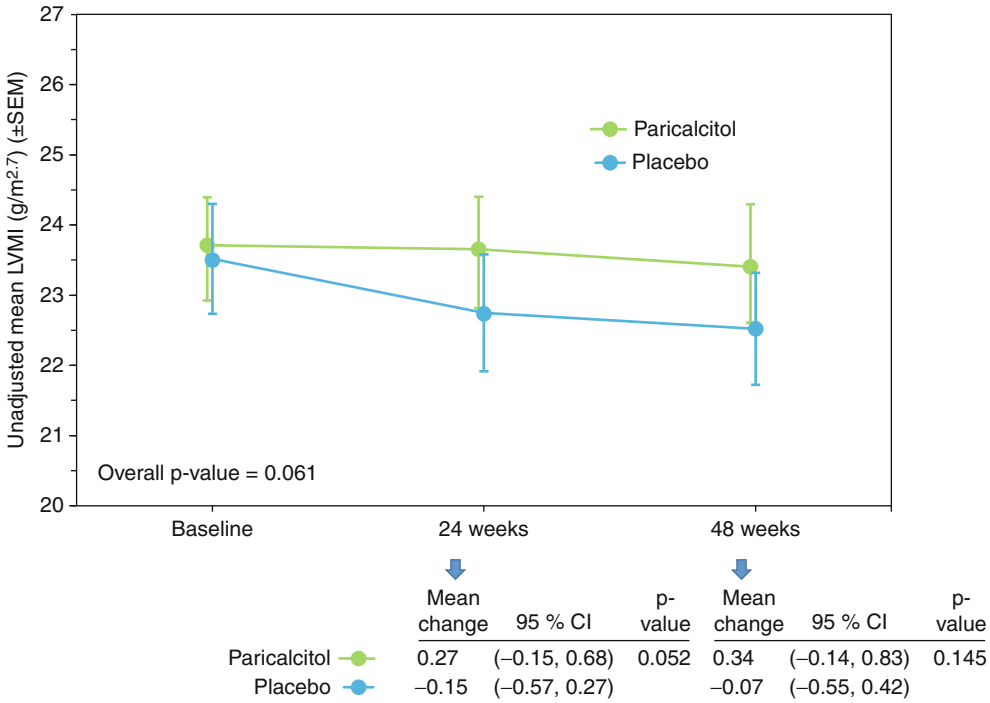

Fig. 11.1 Unadjusted mean left ventricular mass index (*LVMI*) at baseline, week 24, and week 48 by treatment group

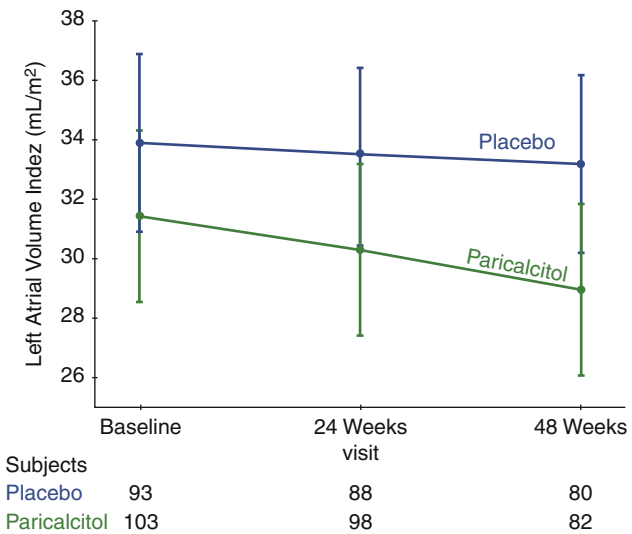

Fig. 11.2 Adjusted mean left atrial volume index (LAVi) at baseline, week 24, and week 48 by treatment group (Reprinted from Tamez et al. [55] with permission from Elsevier, Mosby, Inc; Copyright © 2012 Mosby, Inc. Terms and Conditions)

on LVMI (Fig. 11.1). All patients met left ventricular hypertrophy criteria by echocardiogram at baseline, but not by cardiac magnetic resonance, which may explain why this was a negative trial. A smaller study that included patients with severe LVH showed similar results [46]. A sub-analysis of PRIMO revealed significant reductions in left atrial volume index (Fig. 11.2), natriuretic peptides and cardiovascular hospitalizations (mostly due to heart failure) in the paricalcitol group [55]. Another very small study in children with severe heart failure and vitamin D deficiency randomized participants to either 12 weeks of cholecalciferol 1,000 IU or placebo and found a significant improvement in the heart failure score and left ventricular ejection fraction, among other parameters [47].

A handful of studies have evaluated the effect of cholecalciferol on blood pressure. A recent study in Denmark randomized 130 patients to 3,000 IU of cholecalciferol or placebo for 20 weeks. Although treatment with cholecalciferol was associated with a non-significant reduction in blood pressure compared to placebo, a post-hoc subset analysis restricted to vitamin D deficient patients (<32 ng/mL) revealed a small but statistically significant reduction in both systolic and diastolic blood pressure (4 and 3 mmHg respectively) [48]. Secondary analyses of other studies have yielded mixed results [56].

No studies have yet evaluated prevention of ischemic heart disease or cardiovascular mortality as the primary outcome. The Women's Health Initiative randomized 36,282 postmenopausal women to calcium and vitamin D 200 IU twice daily or to placebo and found no significant difference in the rate of myocardial infarction, angina or stroke (secondary outcomes) after 7 years of follow up [49]. Similarly, another study of 2,686 participants (men and women) who were randomized to 100 000 IU of cholecalciferol or placebo administered every 4 months over 5 years found a non-significant improvement in all-cause mortality

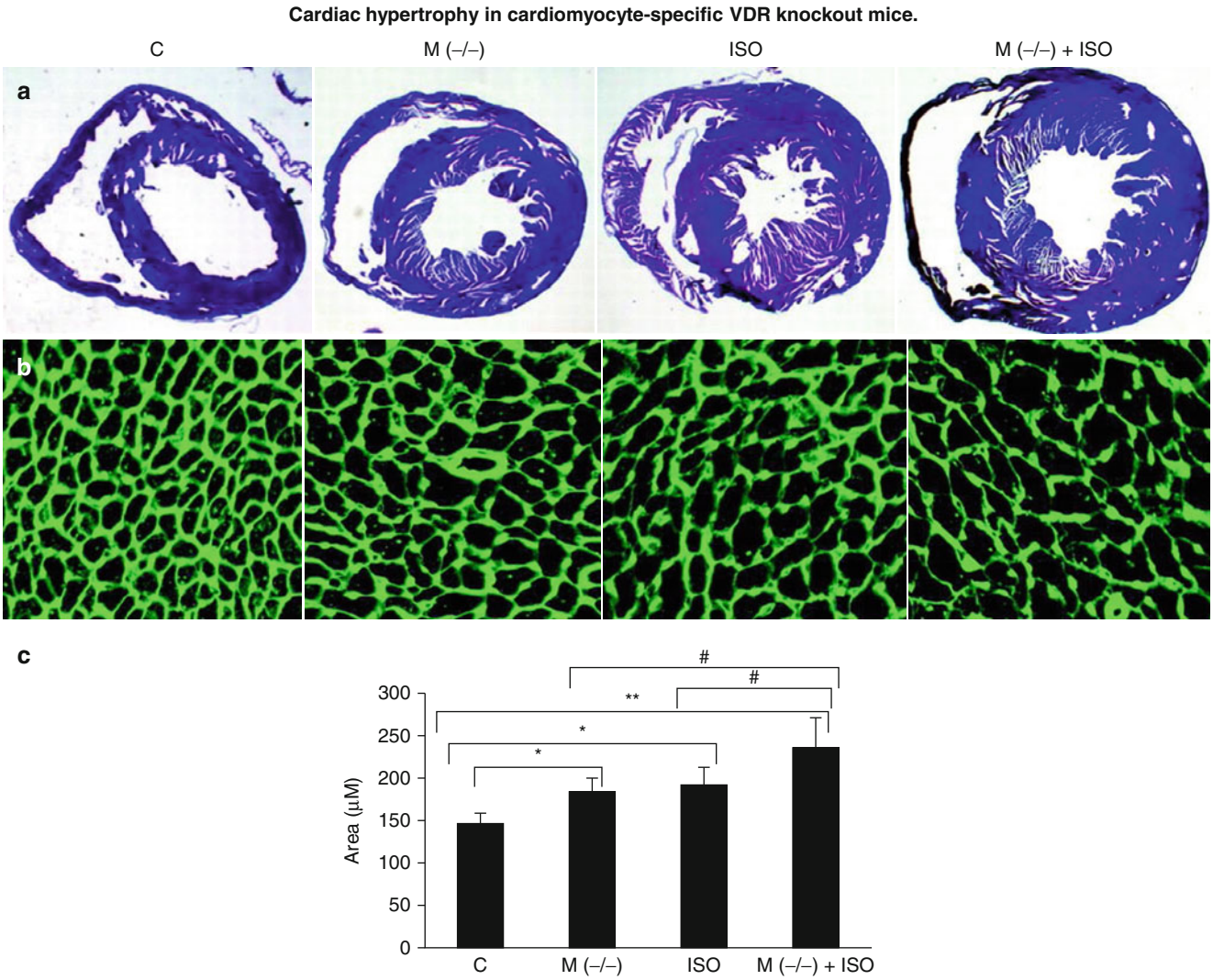

Fig. 11.3 Cardiac hypertrophy in cardiomyocyte-specific VDR knockout mice. (**a**) Left ventricular sections of hearts from mice with genotype indicated were stained by hematoxylin and eosin. Representative sections are shown. (**b**) Cardiac sections were stained with fluorescein isothiocyanate-conjugated wheat germ agglutinin, which delineates cell dimensions by staining glycoprotein enveloping individual myocytes. Representative photomicrographs are shown. (**c**) Individual myocyte size was assessed using Image J (National Institutes of Health). The mean myocyte area was evaluated by measurement of 400 cells per heart (4–5 hearts per genotype). Bar graphs displaying mean and standard deviation from 8 to 12 mice per group are shown. *P < 0.05, **P < 0.01 versus control, #P < 0.05 versus M(−/−)+ISO. *M(−/−)* indicates MLC-Cre/VDRloxp/−, *ISO* isoproterenol (Reproduced from Chen et al. [72] with permission from Lippincott Williams and Wilkins/Wolters Kluwer Health; Copyright © American Heart Association, Inc. All rights reserved)

(mostly cardiovascular) [50]. Consistent with these findings, one smaller randomized Australian study that included 302 women with low 25(OH)D levels (<25 ng/mL) evaluated 1,000 IU daily of ergocalciferol or placebo and showed a non-significant reduction in cardiovascular events (2.0 % in ergocalciferol vs. 1.3 % placebo) [51].

The ongoing VITamin D and OmegA-3 TriaL (VITAL) aims to evaluate the role of cholecalciferol supplementation on cardiovascular diseases (primary outcome) [57]. VITAL has randomized 16,000 participants to either 2,000 IU of cholecalciferol daily or placebo with a median follow up of 5 years. Results of this well-designed trial are expected by 2016.

Biology

Cardiac tissue expresses the VDR gene, suggesting that vitamin D may have a direct effect on the heart [6, 7]. Furthermore, VDR expression is increased in hypertrophied hearts [58]. Cardiac tissue also expresses the 1-alpha hydroxylase and 24-hydroxylase genes, so in theory has the

potential to convert 25(OH)D into active $1,25(OH)_2D$ locally as well as convert $1,25(OH)_2D$ into inactive 1,24,25-tetrahydroxy vitamin D [59].

Animal models that are vitamin D deficient develop cardiac hypertrophy, fibrosis and hypertension [60, 61]. Other animal models such as Dahl salt-sensitive rats, which develop hypertension and proteinuria, also become profoundly vitamin D deficient [52, 62]. These rats develop LVH, high left ventricular end diastolic pressures and elevated levels of natriuretic peptides that can be reversed with administration of $1,25(OH)_2D$ analogs (such as paricalcitol) [52, 63] or doxercalciferol (a pro-hormone vitamin D2 analog) [63] . Similarly, vitamin D analogs prevent progression of LVH and heart failure [64] in animal models. One possible mechanism whereby hypertrophic changes occur is through a decrease in protein synthesis in cardiomyocytes, such as actin [54]. Treatment with paricalcitol has also been associated with higher VDR expression, reduction in Proliferating cell nuclear antigen (PCNA) [65], and inhibition of Protein kinase C alpha (PKCα) in the heart [51] Several other animal models including spontaneously hypertensive rats [66, 67], uremic rats [65], and even in swine [68] have shown similar associations. Among this abundance of positive data, one study utilizing a murine aortic constriction model failed to show that administration of a vitamin D analog could reverse cardiac hypertrophy, but reduced extracellular matrix proteins and natriuretic peptides [69]. Similarly, calcitriol reduced fibrosis and collagen synthesis in the hearts of rat models after partial nephrectomy, with no differences in heart weights [70].

VDR knockout mice models develop severe forms of hypertension and LVH that improve with vitamin D repletion [53, 71] Chen et al. developed a cardiomyocyte-specific VDR deletion mice, which had elevated natriuretic peptide genes and severe left ventricular hypertrophy similar to chronic hypertensive cardiomyopathy (Fig. 11.3). A similar animal model is the 1-alpha hydroxylase knockout mouse, which cannot convert 25(OH)D into the active form of the vitamin, $1,25(OH)_2D$, and therefore is functionally vitamin D deficient. These mice also develop LVH and can be rescued by administration of $1,25(OH)_2D$ analogs.

The exact mechanism by which vitamin D and its active analog predispose animals to develop LVH is not fully understood. VDR knockout mice have higher renin levels, which led to higher angiotensin activity and aldosterone levels [53]. Administration of $1,25(OH)_2D$ directly suppresses renin transcription by blocking the activity of the cyclic AMP responsive element in the renin promoter [73]. In mice that received an infusion of angiotensin II and developed LVH, the LVH was partially reversed by administration of an $1,25(OH)_2D$ analog [74]. Accordingly, the protective role of $1,25(OH)_2D$ in the heart of VDR-null mice is independent from its effects on calcium or phosphorus, and can be reproduced by repressing the renin-angiotensin system with captopril or losartan [75, 76].

Other possible pathways by which vitamin D may affect the heart include the regulation of extracellular matrix integrity through expression of matrix metalloproteinases (MMPs) as well as tissue inhibitors of metalloproteinases (TIMPs) [77], which can contribute to both systolic and diastolic dysfunction [78]. VDR knockout mice underexpress TIMP-1 and TIMP-2 and up regulate MMP-2 and MMP-9, which correlate with increases in fibrotic lesions [79]. These findings are consistent with data from a human trial that showed an inverse correlation of 25(OH)D and MMP-9 at baseline, and a reduction in levels of serum MMP-9 and TIMP-1 after 25(OH)D supplementation [80].

Another potential mechanism whereby vitamin D might influence heart structure, function, and cardiovascular events is via its association with atherosclerosis. Mice with 25(OH)D deficiency fed a high fat diet had ~2 to 8-fold greater aortic atherosclerotic lesions and increased macrophage infiltration and fat accumulation in atherosclerotic plaques compared to 25(OH)D sufficient controls [81]. A possible mechanism for this observation was suggested in ApoE −/− mice models in which calcitriol administration led to a decrease in atherosclerosis by augmenting T-reg cells (Foxp-3+ T cells), decreasing the number of macrophages, and decreasing dendritic cell maturation in atherosclerotic lesions [82]. In human ex-vivo experiments, macrophages from diabetic subjects showed a decrease in foam cell formation and LDL uptake after being cultured in $1,25(OH)_2D$ enriched media compared to $1,25(OH)_2D$ depleted media or after deletion of VDR. The underlying mechanism is thought to be decreased phosphorylation of c-Jun N-terminal kinase (JNK), a key player in the activation of transcription factors related to inflammation [83], with a consequent change in macrophage phenotype [84].

Conclusions

Extensive animal data using a variety of models suggest prominent effects of vitamin D in the heart (direct and indirect). Observational studies have shown mixed results, but overall appear to indicate that severe vitamin D deficiency is associated with LVH, ischemic heart disease and heart failure. However, these results have yet to be corroborated in the few randomized trials available. Well-designed randomized trials evaluating hard outcomes such as myocardial infarction, cardiovascular mortality, etc. are needed before vitamin D therapy can be recommended for prevention or treatment of cardiovascular diseases. Some of these trials will be coming within 3–4 years [40, 57]. Furthermore, the role of bioavailable 25(OH)D levels (compared to total 25(OH)D) is yet to be determined in future studies.

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Part II

CKD Complicating Cardiovascular Presentations, Treatment and Outcome

12 Volume Overload in CKD: Pathophysiology, Assessment Techniques, Consequences and Treatment

Mihaela Dora Donciu, Luminita Voroneanu, and Adrian Covic

Introduction, Definitions and Epidemiology

'Fluid balance' is generally defined by the difference between the daily fluid input and the daily fluid output and it should not be associated with weight and insensible losses, but it could be correlated with dialysis fluid removal if an individual is on renal replacement therapy (RRT) [1].

'Fluid overload' (FO) is defined by a percentage of body weight – a cut-off value of 10 % has been associated with increased mortality [1]. Volume overload (VO) is a common scene for patients on RRT [2–4], but, also for those with pre-dialysis chronic kidney disease (CKD), even though only a limited number of studies have been conducted in these patients [5–8]. All studies performed until now in CKD patients described a significant proportion of overhydrated patients, even in the absence of clinically detectable signs of hypervolemia.

Chronic VO leads to hypertension, left ventricular hypertrophy (LVH), increased arterial stiffness, heart failure (HF), and even an increased morbidity and mortality, especially in dialysis patients [9–11]. Hence, as shown in several studies, VO is considered to be an important contributor to an adverse prognosis, an effect modifier and an independent predictor of all-cause and cardiovascular (CV) mortality in pre-dialysis CKD patients and end stage renal disease (ESRD) patients on RRT [8, 10, 12, 13]. Tsai et al. reported, in 472 non-dialysis patients with stage 4–5 CKD, a significant statistical association between the severity of VO and an increased risk of rapid decline in renal function and necessity of RRT initiation. VO was found to be a better predictor of renal dysfunction progression than the presence of diabetes (DM) in these patients [8, 14]. Also, in non-renal clinical settings, VO is the primary cause of hospital admission and readmission of patients with HF and it is associated with HF progression [15].

Pathophysiology

Sodium and Water Metabolism: The Importance of the Kidney

Tonicity is characterized by the movement of the osmoles on the interior and exterior of a cell causing, therefore, the movement of water. The body fluids tonicity is maintained within normal range (280 mOsm) throughout homeostatic mechanisms that supervise the intake and excretion of water and sodium (Na) [16, 17]. Important for these processes are:

- the function of thirst and the secretion of the antidiuretic hormone (ADH), by activation of hypothalamic osmoreceptors in response to changes in tonicity;
- the kidney – participating in the maintenance of normal water and Na balance, as it both preserves and removes water and Na (Na reabsorption, vasopressin release, the medullary gradient) [16, 17];

Although they play integrated physiological functions, it is important to differentiate the mechanisms that control water balance (tonicity, osmoregulation) from the mechanisms that control Na balance (extracellular volume). Anomalies of water balance determine modifications of serum Na concentration, leading to hypo/hypernatremia, whereas anomalies of sodium balance determine modifications of the extracellular volume (ECV), leading to volume depletion/volume overload.

Water balance is primarily controlled by thirst and the ability of the kidney to produce more concentrated urine when osmolality increases or more diluted urine when osmolality decreases [16, 18]. The most important inductor of thirst is hypertonicity, with a sensitivity of only 2–3 % increase in the plasma osmolality. In normal individuals,

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the osmotic threshold of thirst is approximately 290–295 mOsm/kg H_2O [16].

ADH secretion is stimulated primarily by hyperosmolality and by arterial volume decrease (HF, cirrhosis, vomiting) [16, 18]. The osmotic threshold for ADH release is 288–290 mOsm/kg but andosmo-receptors react to changes in plasma osmolality of as little as 1 % [18]. The cell membrane composition is impermeable to water, so, in order for water to pass across it, the cell membrane must express water channels [18]. In the kidney, ADH interacts with the V_2 receptor located in the basolateral membranes of the CD cells. The renal aquaporin channels are: AQP-1 (active in all water-permeable segments) and AQP-2, AQP-3, AQP-4 (regulated by ADH). AQP-2 is the responsible channel for the high water permeability of the luminal membrane, whereas AQP-3 and AQP-4 seem to have a larger involvement in the elimination of water from the cell [16, 18, 19]. Usually, AQP-2 is re-immersed back into the cell after the interruption of ADH secretion; however, if ADH levels are very high (like in chronic HF), this channel remains permanently in the plasma membrane leading to a continuous water reabsorption, leading to interstitial water excess and edema [19]. A Dutch team has found recently a way to inhibit AQP-2 abnormal settling, through a small molecule – 4-acetyldiphillin. Their results represent a new step for a better understanding of the molecular mechanisms of AQP-2 'trafficking' [19].

Extracellular blood volume (EBV) is generally conditioned by the interconnection of arterial tonus, cardiac stroke volume and the water and solute content of the ECV. The balance between Na intake and Na excretion is determined by: baroreceptors and vascular hormone-sensors modulated by atrial natriuretic peptides, the renin-angiotensin-aldosterone system (RAAS), Ca^{2+} signaling, adenosine, vasopressin and the neural adrenergic axis [18].

New Insights on the Pathophysiology of Volume Overload

Role of Interstitial Fluid Compartment in Fluid Homeostasis

Recently, an essential role of the interstitium in the underlying mechanisms involved in fluid homeostasis was recognized [20]. Interstitial fluid pressure is determined by a complex interplay between the fluid influx (blood capillary filtration), the fluid outflow (lymph flow), and the compartment's ability to expand (tissue compliance) [20]. The interstitial fluid pressures are negative in healthy subjects and positive in CKD patients, but with no association between body fluid volumes and blood pressure [21]. Moreover, it seems that the increase in the interstitial fluid pressure observed in CKD patients can be associated with compensatory changes in the local microcirculation and this could further lead to either reduced transcapillary filtration in the interstitium, or to an increased limph flow [20]. Acute interstitial VO is associated with relatively quick boosts of interstitial fluid pressures, while interstitial fluid excess in chronic edematous state cause only moderate escalation of interstitial fluid pressure [21], suggesting that compliance of the interstitial space is a third important additional determinant for interstitial fluid pressure homeostasis. These findings, are consonant with the Guyton's hypothesis that considered interstitial space as an additional determinant for l fluid pressure homeostasis [20, 22].

A relative fluid shift from the interstitial into the intravascular space is induced by a high sodium intake. In the Heer et al.'s study 50–550 mmol of Na were given to normal men in order to evaluate sodium balance [23, 24]. Plasma volume increased by about 330 ml when Na intake was 550 mmol/day, but without modifications of TBW or body weight even when Na intake was as high as 1,700 mmol. Titze et al. combined conventional H-magnetic resonance imaging (H-MRI) with Na-MRI for a better estimation of skin-Na, calf-Na and tissue water concomitantly [23, 25]. Human measurements found that skin-Na and muscle-Na were increased in patients with primary aldosteronism and that these values decreased significantly after surgical removal or spironolactone treatment. It was also noticed, in line with Heer et al.'s findings, that Na storage does not determine body weight modifications [23, 25]. Another important cohort study enrolled hypertensive patients and normotensive control subjects and showed that patients with refractory hypertension had increased tissue Na content, assessed by Na-MRI measurements, in comparison to control subjects [23, 26]. In order to provide a better support of his hypothesis that Na is stored in the tissue and that tissue-Na storages have important regulatory functions, Titze et al. performed a rather unusual, 2 phases experiment: they analyzed the long-term Na balance in 4 normal men (in Mars 105) and 6 normal man (in Mars 520), studied for 105 and 205 days respectively, in a simulated space flight to Mars. The men received fixed amounts of Na intake and underwent numerous investigations. The results showed a weekly (circaseptan) Na excretion that was positively associated to cortisol levels and negatively correlated to aldosterone levels. TBNa was found to have longer (≥monthly) infradian rhythms independently of ECW, body weight and BP, and a non-dependent status to Na intake [23, 27].

Cardiotonic Steroids (CTS): Involvement in CKD

CTS are also called 'digoxin-like' endogenous substances found in the serum and urine of uremic and overhydrated patients and, also, in other clinic conditions, such as CHF, hypertension, renal ischemia and preeclampsia [28–32]. They represent a relatively new discovered class of

endogenous cardiotonic steroid hormones that act as a specific ligand for the Na/K-ATPase transmembrane protein on the surface of cardiomyocytes by coupling reduced Na/K--ATPase's activity with a reduction in Na/Ca; this determines, therefore, an accumulation of intracellular Na and an increase in cytosolic Ca [33, 34].

The Na/K-ATPase plays a pivotal role in regulating the cellular transmembrane ion gradient of Na and K through ATP-dependent transport across the plasma membrane [35, 36]. The Na/K-ATPase is formed by two subunits, α and β; the first one is the catalytic subunit, with four isoforms, and presents with specific binding sites for Na. K, ATP and CTS [37, 38]. It has been demonstrated that, when CTS binds to the α_1 subunit of the Na/K-ATPase where it becomes able to activate multiple protein kinase cascades: the epidermal growth factor receptor (EGFR), phospholipase C (PLC), phosphoinsitide 3-kinase (PI3K), protein kinase C (PKC), mitogen-activated protein kinases (MAPKS) and reactive oxygen species (ROS) [34, 39–41]. CTS binding to Na/K--ATPase determines the endocytosis of this new-formed complex in a way consistent with classic receptor tyrosine kinases [42].

It has previously been reported that marinobufagenin (MBG), an endogenous bufadiendolide CTS, is elevated in both in clinical and experimental renal failure [31, 35, 36, 43, 44]. MBG presents a greater affinity for the α_1 subunit of the Na/K-ATPase and has a greater importance in the pathogenesis of renal failure [31, 43].

In 2006, Kennedy et al. performed a study on Sprague-Dawley rats, highlighting the central role of MBG in the pathogenesis of experimental uremic cardiomyopathy [31]. Since MBG levels were elevated in partial nephrectomy rats, they administered MBG to sham-operated rats in order to achieve similar concentrations. Also, for neutralizing MBG in the setting of renal failure, they actively immunized the rats against MBG, before partial nephrectomy. Their results are summarized as follows: partial nephrectomy was associated with all of the signatures of clinical uremic cardiomyopathy; partial nephrectomy rats developed systemic oxidative stress and impaired diastolic function as seen in CKD patients; the MBG infusion produced almost the same increase in plasma levels of MBG + a similar degree of oxidative stress and cardiac abnormalities, as seen in partial nephrectomy rats. Also, both partial nephrectomy rats and MBG infusion produced an important amount of cardiac fibrosis. Active immunization against MBG was associated with substantial attenuation of cardiac hypertrophy, fibrosis and oxidative stress, but, even though MBG infusion determined an increase in BP, the immunization did not improve this parameter [31]. These results were further supported by clinical findings. In 25 ESRD patients (20 on HD and 5 on PD) MBG levels, and not ouabain levels, were 3.5 fold higher in cf. the control group [43].

It appears, therefore, that CTS and especially MBG might become the new therapeutic targets in the management of uremic cardiomyopathy. Tian et al. demonstrated that administration of spironolactone attenuates cardiac fibrosis in partially nephrectomized rats and in MBG infusion models [36]. Also, considering the recent evidence showing that Friend leukemia integration-1 (Fli-1), which is a negative regulator of collagen synthesis, is also involved in the pro-fibrotic signaling of CTS, Haller et al. found that in experimental chronic renal failure, increased levels of MBG contribute to hypertension and cardiac fibrosis through suppression of this transcription factor and suggested that this could represent a new potential therapeutic target [44, 45].

Malnutrition-Inflammation and VO in CKD

Protein-energy malnutrition (PEM) develops when the diet cannot satisfy the body's need for protein and/or energy – a frequent status in dialysis patients [46]. PEM is accountable for a poor quality of life and increased all-cause mortality in ESRD patients [47, 48]. In renal patients, there is an important pro-inflammatory status [49–52]. Furthermore, it has been found by several investigators, that these two conditions coexist in ESRD patients [46]. Inflammation promotes atherosclerosisso,thetermof'malnutrition-inflammation-atherosclerosis' (MIA) syndrome or 'malnutrition-inflammation complex syndrome' (MICS) has been adopted. MIA syndrome is considered as one of the main cause of mortality in ESRD patients [46, 53, 54], extremely difficult to be modified – as shown by many studies that also failed to demonstrate an improvement in survival rates when dialysis dose or membrane permeability was increased [55, 56], or when drugs (statins, etc.) were used [57, 58].

The main cause of PEM and inflammation in dialysis patients are well detailed in several reviews [58]. New recent studies are associating to a greater degree malnutrition and inflammation with VO. In 95 prevalent PD patients, VO was significantly associated with malnutrition, inflammation and atherosclerosis markers [59]. Hung et al. found in 338 predialysis CKD patients that volume overload was positively correlated with IL-6 and TNFα and the only parameter that was strongly associated with all components of the MICS syndrome. At the same time, the presence of MICS had additive deleterious effects to VO [12]. It is, nevertheless, difficult to determine if MICS is a consequence of VO. TNFα levels are increased in CKD overhydrated patients [12], and in patients with CHF [60]. Also, an in vitro experiment had shown an overexpression of TNFα in the hearts of animal models with volume overload and myocardial TNFα plays an important role in the pathophysiology and progression of HF and cardiac dilatation [61, 62].

Lately, endotoxemia appears to become a new piece in the puzzle of systemic inflammation of renal patients with VO. Endotoxemia implies the translocation of intestinal

molecules frequently encountered in cases with fluid excess and an increased inflammatory status. A recent prospective study aimed to evaluate the association between renal function, fluid status, systemic inflammation and endotoxemia in 74 stage 1–5 CKD patients. Eighty four percent of these patients had VO and signs of endotoxemia were present in all patients but with endotoxin levels higher in overhydrated patients. In contrast, the investigators did not found a role of endotoxemia in systemic inflammation since endotoxin levels were not associated with inflammation markers [63]. Also, endotoxin levels were found to be higher in CKD patients with important cardiovascular comorbidities, and increasing with CKD stage [64].

Assessment of Fluid Status in CKD

One of the most important tasks for a nephrologist is the correct assessment of fluid status. ESRD patients, treated by a standard dialysis prescription, are affected by chronic volume overload and by intermittent interdialyitic weight gain (IDWG). Statistical analyses demonstrate an association between these two conditions and mortality [2, 3, 11, 65]. An inaccurate assessment of dry weight leads to hypertension/hypotension, cardiac and vascular dysfunction, omission of small changes in nutritional status, and intradialytic morbidity and mortality [66].

Clinical Assessment of Fluid Status in Chronic Kidney Disease

This was the first method used for the estimation of a patient's water status, but its use as a unique assessment tool has been plagued by its lack of sensibility and specificity. It comprises the evaluation of: BP, pedal edema, pulmonary congestion rales, turgid jugular veins, dyspnea, weight increase, history of previously excessive salt and water intake and the maximum ultrafiltration tolerated by the patient. There are several important shortcomings:

- a patient can present ECV excess without displaying signs/symptoms of VO [9]
- high BP levels are not a reliable tool for assessment of VO as there is aproportion of patients that are normotensive despite VO and other patients that are hypertensive but normovolemic [9, 67]
- pedal edema cannot account only for VO, being, also, present in cases of vascular stasis, use of dihydropiridine calcium channel blockers or venous insufficiency; in contrast, a large proportion of volume overloaded patients does not present edema [68]
- weight changes can occur, also due to nutritional diet modifications or poor nutritional status and cannot be judge only on ECV variations [68, 69]

Nevertheless, clinical evaluation remains an important fluid status assessment tool in the hands of well-trained, experienced nephrologists. Vasko et al. conducted a study on this issue and demonstrated, in 30 HD patients, that clinical judgment was the single most important factor in OH estimation, even though a systematic approach using clinical assessment + BIA + laboratory and imaging parameters provided a superior accuracy in fluid status evaluation [70].

Echocardiography and Inferior Vena Cava Measurements

Echocardiography is considered as the most important tool in the diagnosis of CHF in CHD patients, but it proves to be a difficult maneuver to perform in these conditions. It can reveal concentric LVH, eccentric LVH, isolated LV dilatation and systolic dysfunction [71]. In early CKD stages, LVH develops as a physiological response to pressure and VO, but its prevalence and severity increases with progressive loss of renal function leading to structural changes due to chronic overload and CKD-associated factors [72]. In dialysis patients, LV volumes fluctuates due to chronic VO, IDWG and the presence of associated cardiac impairment, so, echocardiography should be performed at an achieved DW, for reliable results [71].

Measurement of IVC is a simple, rapid and non-invasive method of fluid status assessment, based on the theory that, in VO, there is an increase of the intravascular volume and a secondary increase in the venous system. This could actually be considered a limitation of the technique in HD patients where, an increased rate of ultrafiltration could shrink the echocardiographic volumes even in patients that are, in fact, volume overloaded, leading, therefore, to a 'false state of normovolemia' [73]. On the other hand, Katzarski et al. found that IVC diameter is dependent on the vascular refilling, which seems to be more rapid in patients that undergo a more aggressive ultrafiltration [74]. There are, also, several possible cofounding factors that could undermine the diagnostic value of IVC measurement in these patients: the influence of diastolic dysfunction and the low venous compliance that determines an expansion of the IVC diameter even to a small change in volume [73, 75]. The first study, performed by Cheriex et al. in 18 HD patients, found that IVC diameter and its collapse index are associated with right atrial pressure, but failed to demonstrate an association between IVC collapse index and blood volume modifications [76]. A 2010 study, performed in 160 HD patients, could not correlate VO with an IVC augmentation, measured before the midweek HD session, and concluded that IVC has a positive predictive value of VO of only 18 %, with an important proportion of false negative cases (45 %) [9]. Another recent study showed that IVC diameter is modifiable with DW reduction

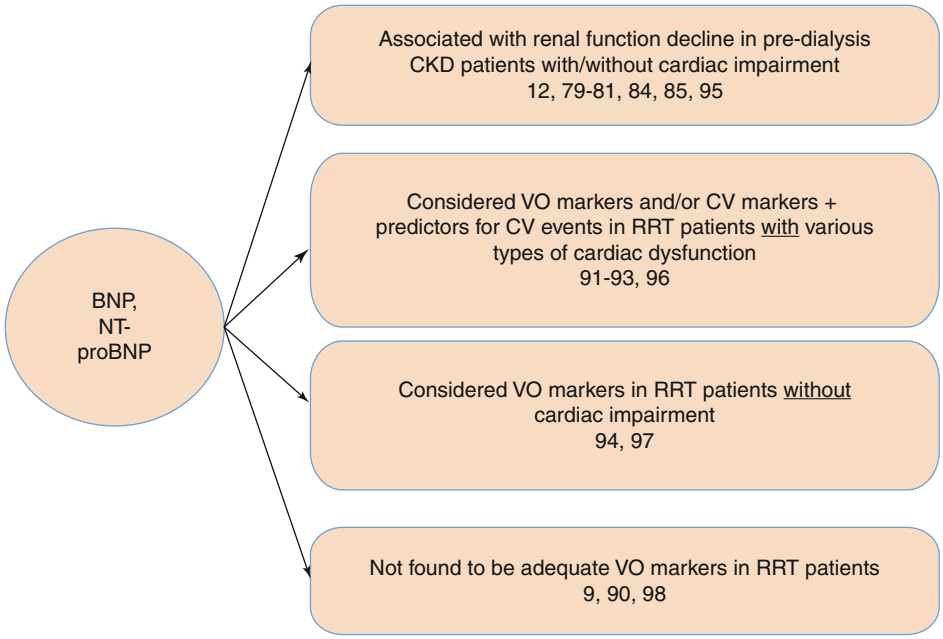

Fig. 12.1 Summary of the main findings regarding BNP and NT pro-BNP in CKD patients

reflecting its volume-dependent response; the same results were found in respect to left atrial diameter. However, an association between an improved inter-dialysis BP and a decrease of the IVC collapse index could not be marked [73].

Biomarkers of Volume Overload in CKD

In HF, several biomarkers, in particular B-type natriuretic peptide (BNP) and its N-terminal fragment (NT-proBNP) have proven their important role for the diagnosis, early risk stratification, detection of acute CHF and adjustment of therapeutic strategies [77]. An increase in BNP levels of 100 pg/ml was found to be predictive of a 35 % increase in the relative risk of death in HF patients [78]. These biomarkers are vasopeptide hormones secreted from the LV in response to myocardial wall injury. In CKD patients, BNP and NT proBNP were correlated with renal function decline [79–83], with cardiac impairment and with survival [82, 84–89]. A comprehensive scheme is provided for a better understanding of all of these aspects, containing, also, references for a more detailed analysis (Fig. 12.1) [9, 12, 79–81, 84, 85, 90–98].

Theoretically, overhydration increases parietal stress and secretion of BNP and NTproBNP; therefore, BNP and NTproBNP could be used as markers for volume status evaluation. However, the diagnostic value has been considered to be limited in CKD patients because renal dysfunction itself and associated cardiovascular diseases that may affect BNP levels. The use of BNP and NT-proBNP as adequate parameters for measurement of VO was compared with other validated methods, such as clinical assessment, BIA or IVC measurements [91–94, 99], with different conclusions. Jacobs et al. also demonstrated in 44 HD patients followed for 6 months that VO parameters measured by BIA had a strong correlation with *baseline* BNP and NT pro-BNP levels, independently of the patient's cardiac history [94]. In 2013, Antlanger et al. reported similar results in 212 HD patients in which NT pro-BNP levels were strongly associated with overhydration (fluid status evaluated by bioimpedance), independently of inflammation or high BP [93]. In contrast, Panigua et al. in a large cohort including 753 dialysis patients (both HD and PD) found no correlation between NTproBNP and volume status parameters. Additionally, several studies described a statistically significant relationship between overhydration and BNP or NTproBNP only in patients with left ventricular dysfunction. David et al. found that a cut-off value of ≥7,200 ng/L for serum NT-proBNP discriminates HD patients without LV dilatation (LVD) from those with LVD and that persistent post-HD VO is associated with increased levels of NT-proBNP levels in patients with LVD [91]. Similarly, Booth et al. reported in 62 HD patients with LVD, that NT pro-BNP levels were significantly associated with markers of fluid overload assessed both by clinical evaluation (peripheral edema) and BIA measurement (ECW/TBW) [96].

Importantly, *changes in NTproBNP* could be better associated with volume status. Davenport et al., report in 2012, after conducting 189 serial measurements in 92 PD that changes in NT-proBNP levels were strongly associated with TBW, ECW and ECW/TBW assessed by BIA. Patients who experienced the highest decrease in NT-proBNP levels also

presented with significant reductions of ECW, TBW and ECW/TBW and a decrease in systolic BP from 143.8 ± 24.6 to 136.5 ± 18.7 mmHg; patients with the greatest increase in NT pro-BNP suffered also an increase in systolic BP from 133.5 ± 22.7 to 142.7 ± 28.8 mmHg. Chazot et al. analyzed retrospectively the BNP levels at baseline and during the second quarter of HD treatment, in 46 patients that initiated HD in the last 6 months [100]. At HD initiation, the plasma BNP level was 1,041 ± 178 pg/ml and it was correlated with age, gender (males) and cardiac disease history, but not with mortality risk. The analysis performed at the second quarter of the HD treatment showed that the BNP levels decreased to 631 ± 707 pg/ml and this reduction was associated to SBP decrease. At this stage, higher BNP levels were independently associated with increased risk of mortality, suggesting that BNP could represent a beneficial parameter to follow patient dehydration after HD initiation and that initial fluid overload may act as a confounder factor for its predictive value [100]. In contrast, Breidthardt et al. found no correlation between hydration status and BNP in a 113 chronic stable hemodialysis cohort [101].

Bioimpedance Analysis (BIA) in CKD

This represents a non-invasive, volume measurement technique based on the electrical principle that the body is a circuit with a given resistance (opposition of high and low frequency current flow between intracellular and extracellular compartments) and a given reactance (the ability of cells to store energy) [1, 68].

The BIA method includes: monofrequency and multifrequency bioimpedance analyzed by segmental and whole-body spectroscopy. The details on BIA technologies, physics and methods can be found elsewhere [102–104]. The main difference between BIA methods includes the fact that whole-body single frequency BIA (SF-BIA) measures the resistance, the reactance, the impedance and the phase angle to calculate ECW and TBW, while whole-body multifrequency bioimpedance spectroscopy (MF-BIS) calculates extracellular and intracellular volumes, providing ratios (ECW to TBW, ECW to ICW) [105]. The SF-BIA is based on a regression model, while MF-BIS is based on the Cole-Cole equation that is dependent on measurements performed in healthy control subjects, allowing, at the same time, correction for cofounder parameters such as gender and age [103–105]. The segmental bioimpedance measurement is providing additional information and is considered more accurate since it allows the calculation of body composition parameters in each segment and the results are dependable on a MRI comparable model data [103, 105].

BIA measurements were validated in healthy and renal populations by different 'gold-standard methods for fluid status assessment: blood volume monitoring (BVM) and by isotope dilution methods [106, 107]. The direct isotope dilution methods include: deuterium oxide (D_2O) for the measurement of TBW, bromide dilution (Br) for the measurement of ECV and total body K (TBK) for the measurement of ICV; nevertheless, there are some data stating that these direct methods and their 'confirmation' relationship to BIA are not free from bias [107]. A recent study aimed to compare the precision and accuracy of SF-BIA and MF-BIS to direct estimation measurements (DEM) of TBW, ECV and ICV in 49 HD patients. The authors found that estimation of $TBW_{SF\text{-}BIA}$in comparison to $TBW_{MF\text{-}BIS}$ and TBW_{DEM} did not significantly differ; the same results were found for ECV_{DEM} and $ECV_{MF\text{-}BIS}$, but with a statistically significant difference between $ECV_{SF\text{-}BIA}$ and ECV_{DEM}, suggesting that evaluation of ECV with MF-BIS is more accurate than using SF-BIA. This study, also, compared the overall DEM results of VO parameters with the indirect estimation methods (IEM) and concluded that, in dialysis patients, there is no real 'gold standard' [105].

BIA is a useful tool for fluid management in pre-dialysis CKD patients. There are several studies that are suggesting the importance of BIA in these patients for a better estimation of overhydration and improvement in clinical management [6, 7, 12, 108].

In 84 patients with mild to severe CKD, $TBW_{SF\text{-}BIA}$ was significantly higher than in healthy control subjects and this method was proven to be an efficient clinical tool to assess impairment in body composition [6]. The same results were found by Hung et al. who showed, in 338 patients with stages 3–5 CKD, that 20 % of them presented with VO ≥7 % in the absence of clinically detectable edema and concluded that BCM could be the most beneficial technique for detection of overhydrated CKD patients with clinically hidden signs [12]. In another study, ECV measured by MF-BIS was associated, in CKD patients, to renal function decline and various CV parameters [7]. Verdalles et al. aimed, in 50 CKD patients with resistant hypertension, to evaluate fluid status (using the BCM® device) and assess whether this method could be useful in controlling BP and diuretic treatment. The ECV expansion was observed in 60 % of the included patients; after 6 months of follow-up, BIS-guided fluid management lead, after an intensified diuretic treatment, to a decrease of TBW and SBP, with a GFR that remained stable [108].

Independently of the different BIA techniques, different targets and various protocols used, BIA-guided fluid management appears to be clearly associated with improved surrogate and hard end-points.

In dialysis patients, BIA was associated with: better management of fluid status [109–112]; improved BP control [11, 109, 111, 113]; improved arterial stiffness and other CV parameters [109, 111] and better survival both in HD and PD patients [11, 110, 114].

Wizemann et al. found that OH (defined as ECV/TBW cut-off value of >15 % or a VO >2.5 L) is an independent factor of mortality (HR = 2.1) and this value has become standard reference for VO definition in dialysis patients [13]. Measurement of VO status by BIA and measurement of before-HD values of systolic BP allow a classification of these patients into five categories [115]: Group I: VO >2.5 L and SBP >140 mmHg; Group II: VO <1 L and SBP >150 mmHg; Group III: under hydrated patients with normal-low SBP (<140 mmHg); Group IV: VO >2.5 L and SBP <140 mmHg; Group V: VO between 1 L and 2.5 L + SBP between 100 and 150 mmHg; this group is associated, in general, with healthy subjects or dialysis patients with well-managed VO.

Data provided by an analysis of 1,500 HD patients in 22 European centers showed that >25 % of these patients present with VO >2.5 L [116]. Therefore, the necessity for an objective and effective technique for the measurement and management of fluid status has become imperative. Current data is supporting BIA as a promising tool for the adequate assessment of DW in RRT patients [9, 106, 117].

Moissl et al. conducted the first trial that combined active BIS-guided fluid management with time-averaged fluid overload (TAFO) targets, in 56 HD patients, aiming to assess the feasibility and clinical consequences of this integrated technique for fluid management [106]. TAFO represents the average cardiovascular fluid overload over 1 week, assuming a linear fluid accumulation during the inter-dialysis period. The results showed that active fluid management with bioimpedance lead to a decrease in TAFO and BP for the patients in the VO group. At the end of the study, 86 % of all patients were either on TAFO target or closer than at baseline [106].

There are only two hard end points-RCT that evaluated the usefulness of BIS in fluid status management [109, 111]. The first one, conducted by a Turkish team, randomized 156 HD patients, with BIA measurements and clinical assessment of DW, into two groups: in the intervention group, the treating physician received information about fluid status and used it to adjust HD-fluid removal, whereas in the control group, DW was adjusted only by usual clinical practice. In the intervention group TAFO was significantly decreased in comparison with the control group, LVMI regressed from 131 ± 36 to 116 ± 29 g/m, in comparison to the control group where it remained the same and, also, other cardiovascular parameters were improved [111]. The second trial, performed by a Romanian team, showed in 131 HD patients that received DW prescription based on fluid management guided by BCM or by clinical judgment that, after a follow-up period of 2.5 years, the bioimpedance group showed a higher decline in arterial stiffness, SBP and a better control of VO [109].

Finally, a new bioimpedance technique was proposed for accuracy continuous monitoring of ECV during HD sessions – calf BIS (cBIS). This method is based on the hypothesis that, due to gravity, the lower limb is more likely to present an ECV expansion than the arms or trunk and, therefore, the calf could represent the last fluid feeding capital for the intravascular compartment during ultrafiltration [118]. During ultrafiltration, the extracellular resistance of the calf (cR_E) increases until all fluid accumulation is completely removed and the bioimpedance parameters would not change (further increase), even if ultrafiltration still continues [119]. A very small study (N = 21 patients) compared the DW determined by cBIS and normal hydration weight predicted by whole-body BIS (NHW_{WBM}). From the 21 included patients, 12 patients did not reach DW_{cBIS}. Changes of whole-body ECV using whole-body BIS were more accurate in the DW_{cBIS} group than in the non-DW_{cBIS} group [120]. A new, also small study, that is actually an opening base for future research, showed that the use of cBIS for reaching DW in HD patients could, in fact, translate into a reduction of LV mass and BP in these patients, improving, therefore, cardiovascular outcomes [119].

The BOCOMO study is a multicenter, prospective RCT that will enroll 1,300 participants from 16 clinical facilities with the objective of evaluate the effects of BIA-guided fluid management compared to standard care for a minimum follow-up period of 36 months. The primary outcome will be a composite end point of death, acute myocardial infarction, stroke or incident peripheral arterial occlusive disease and the secondary outcomes will include LV wall thickness, BP, medication and hospitalization parameters [121].

Blood Volume Monitoring (BVM) and Volume Overload

This technique uses relative blood volume (RBV) monitoring devices incorporated in the dialysis machine that allow non-invasive, real-time assessment of intra-dialysis changes of hemoglobin/hematocrit concentrations (by optical absorbance) or of the concentration of total plasma protein (by ultrasound recorded blood waves velocities) [102, 122].

The BVM method has been proposed for predicting DW but was, initially, conceived for a better management of intra-dialysis hypotension [123–125]. However, there are several reports that contradict the usefulness of BVM for the management of fluid status and overall hemodynamic stability [126–128].

RBV monitoring offers information on RBV changes, but no data about the absolute blood volume and the interstitial hydration [119, 122]. Accordingly, this technique is not able to differentiate between the actual DW and excessive ultrafiltration rate (UFR) in relation to plasma refilling rate [119].

Lopot et al. found that flat intradialytic relative plasma volumes (RPV) slopes are correlated with VO in HD patients [129]. The DRIP study showed that HD patients with flat

RPV slopes at baseline are overhydrated and that these patients had a higher decrease in interdialytic SBP upon probing DW [102, 130, 131]. In contrast, Reddan et al. found in the CLIMB study that interdialytic BVM was associated with higher hospitalization and mortality than for conventional monitoring patients, with no advantage for BVM regarding dialysis-associated complications or need for physician's intervention [132]. Finally, Seibert et al. showed that combining BVM with cBIS may prove to be more useful in assessing the relationship between plasma refilling and tissue hydration during the HD session [119].

Hecking et al. are conducting a multicenter, prospective, triple-arm, parallel-group, crossover RCT to test the hypothesis that, in comparison to conventional HD (CHD), BVM-regulation of UF and dialysate conductivity (UCR) and/or regulation of UF and temperature (UTR) will decrease the complications that appear when UF volumes are systematically increased in volume overloaded HD patients [133]. The patients will be randomized 1:1:1 into UCR, UTR and CHD. The primary end-point will be a comparison between intra- and post-dialysis complications between groups, and, in addition, changes in relative weight reduction, residual renal function, quality of life and pre-dialysis laboratory parameters will be, also, assessed as secondary outcomes at the beginning and at the end of study [133].

Ultrasonography of Extravascular Lung Water (ELW) in CKD

ELW represents the water contained by the lung interstitium and it depends on the ventricular filling pressure of the LV [179]. Lung ultrasound (LUS) data of this compartment translates into ultrasound B-lines (BL-US), known also as lung comets. This method has been validated by CT scans, thermodilution with Swan-Ganz catheterization, natriuretic peptides levels and echocardiographic measurements [134–138]. LUS has been found to be a useful tool for risk stratification and fluid management of ICU patients, evaluation of lung water (LW) in HF patients, or acute respiratory failure patients and for the diagnosis of alveolar-interstitial syndrome [135, 139–141]. More than that, it seems that it is an excellent method for differential diagnostic between HF and COPD, with a sensitivity of 85.7–100 % and a specificity of 92–97.7 % [135, 142, 143].

Recently assessment of ELW by LUS has been proposed as an important and accurate mean of evaluation and fluid management guidance in HD patients [131, 142, 144, 145]. Mallamaci et al. found in 75 HD patients that 47 of them presented with LUS-evaluated severe lung congestion before HD and that this finding was observed in both symptomatic and asymptomatic HF patients [144]. In this study, LW excess was not associated with hydration status, but was strongly correlated with NYHA functional status, LV ejection fraction (LVEF), LA volume and pulmonary pressure; in a multiple regression model that included traditional and non-traditional risk factors, only LVEF maintained an independent association with LW excess. The authors concluded that this method is a reliable technique to detect pulmonary congestion at a pre-clinical stage in HD patients [144]. Consistent with these findings, Zoccali et al. wanted to test the prognostic value of LUS evaluation of ELW as a predictor for cardiac events and mortality in ESRD patients. The study, conducted in 392 HD patients, found that 45 % of them had moderate to severe lung congestion, 14 % severe lung congestion and that this latter group presented a 4.2-fold risk of death and a 3.2-fold risk of cardiac events in comparison to the first group. The results proved BL-US score as a strong, independent death and cardiac events predictor in HD patients [131].

Noble et al. assessed the dynamics of BL-US in 40 HD patients that underwent three LUS evaluations: the first one – before the start of HD session, the second one at the halfway into the HD session and the third one at the end of HD session [142]. This evaluation allowed the demonstration that B-lines change in real-time as fluid is being removed from the body. This fact could contribute to the importance of this method in assessing real-time changes of ECW during HD session and its usefulness as a fluid management guidance tool [142].

Siriopol et al. conducted recently an innovative, prospective observational study in 96 HD patients and compared, for the first time, three different strategies to predict mortality in this population [145]. The patients were analyzed, pre- and post-dialysis, by LUS, MF-BIS and echocardiographic parameters. The pre-dialysis ultrasound lung congestion score was strongly associated with all of the MF-BIS measurements, but, only the BL-US score had a significant discriminator power for survival. The BL-US score was found as the best predictor for the hydration status-mortality relationship, independently of MF-BIS-derived parameters [145].

All of these studies represent the ground-stones for the development of future interventional studies [146, 147].

Heart Rate Variability (HRV) and Volume Overload in CKD

Autonomic nervous system (ANS) dysfunction occurs in approximately half of all ESRD patients [148]. It has been demonstrated that these patients have a withdrawal in parasympathetic modulation of heart rate and an increase of the sympathetic input to the sinoatrial node [149]. Uremic toxins seem to be implicated in the genesis of cardiovascular dysautonomy, condition that is associated with dialysis hypotension, arrhythmias and sudden death [148].

The susceptibility of HD patients to cardiac dysfunction has been attributed to several factors: myocardial ischemia, LVH/LVD, serum electrolyte changes, VO and fluid removal during the dialysis session, OSA, the sympathovagal imbalance and dialysis-techniques related factors, all of which have an impact in cardiac reactivity – a pivotal parameter for the maintenance of hemodynamic stability during HD [10, 115, 148, 149].

HRV is a simple, non-invasive technique used to evaluate cardiac dysautonomy in healthy individuals as well as in pathological settings [150–153]. The HRV measurement provides data about the sympathetic and parasympathetic activity and reflects the ability of the sinoatrial node to modify the heart rate [10, 115]. In a simple manner, it measures the periodic variations in R-R interval from beat to beat [148].

The association between HRV and fluid overload is supported by several findings and hypothesis:

- cardiac hypertrophy is associated with HRV modifications and volume overloaded patients have a decreased HRV due to cardiac hypertrophy [115]
- ANS is affected by variations in central volumes [10]
- the sympathetic activation observed in renal patients is influenced both by a decrease in the LV filling and by fluid status [10, 154]
- mechanical stretch of the sinoatrial node in a pig heart model reduces the parasympathetic modulation of the heart rate [149, 155]

The most commonly used and validated techniques for evaluation of HRV include time domain and spectral domain analysis. The time domain analysis includes the measurement of multiple statistical calculated parameters of the R-R interval duration and its variation over time (minimum, maximum, average and SD) [115, 148]. The spectral domain analysis estimates the sympathetic-vagal influence of the HRV through frequency domain analysis. It uses high-frequencies (0.15–0.40 Hz) that correlate respiratory-driven vagal efferent input to the sinoatrial node and low-frequencies, that correlate with parasympathetic and sympathetic activity and baroreceptors-mediated BP control [149].

HRV changes were described in HD patients and were associated with hematocrit, body mass index, HD duration, LVH and ischemic heart disease [115]. HRV was found to be an independent predictor of mortality in 383 HD patients with 24-h ambulatory electrocardiographic records and time and frequency domains analysis [156].

A recent trial was the first one to analyze the association between VO and ANS dysfunction in 69 HD patients. VO was evaluated by whole-body BIS before the start of the midweek HD session. Also, at the same time, a 24-h HolterECG was started. Even though this is small, observational study, their results are the first to demonstrate a correlation between reduced HRV and higher values of VO in these patients [10]. A 2013 study aimed to compare the effectiveness of various measurement methods of fluid status for an adequate estimation of DW [157]. Thus, 30 HD patients underwent BIS, BL-US score, BNP and IVC diameter measurements, that were further analyzed by two nephrologists. All methods, except for evaluation of IVC collapse index after the end of the HD session, were able to assess overhydration before and after HD. In terms of evaluating fluid status, BL-US correlated better with BIS than IVC diameter and the authors concluded that BL-US could provide real-time evaluation of fluid status [157].

Volume Overload-Consequences in CKD Patients

VO and Cardiovascular Disease (CVD)

Renal patients present a higher risk for the development and progression of cardiovascular disease (CVD) due to an increased prevalence of traditional risk factors (older age, male gender, hypertension, dyslipidemia, DM, LVH), but also due to non-traditional factors (albuminuria, anemia, hyperparathyroidism, ECV overload, oxidative stress, inflammation, malnutrition) [71]. The severity and incidence of CAD is higher with the reduction of the glomerular filtration rate (GFR) and CV morbidity and mortality are increased with impaired renal function (especially when GFR <15 ml/min/1.73 m^2) [158]. Similarly, the risk of CHF is doubled in patients with a GFR <60 ml/min/1.73 m^2) [159]. Two studies [160, 161], one from Canada and the second one from Taiwan investigated on a large scale the CV risk associated with CKD fluid overload is an important risk factor for CVD in CKD patients. Recently, Hung et al. reported in 338 patients with stages 3–5 CKD, that volume overload was strongly associated with both traditional and novel risk factors for cardiovascular disease in a multivariate analysis (male sex, diabetes, pre-existing cardiovascular disease, systolic blood pressure, serum albumin, TNF-α, and proteinuria) [12].

VO, Sodium and Heart Failure in CKD

VO is the most important mechanism leading to decompensated HF [162]. When kidney function is impaired or in chronic HF associated with renal hypo-perfusion, the kidney ability to excrete sodium is exceeded, salt sensitivity increases, the sodium-effect of aldosterone is reduced and other conditions, such as renal resistance to natriuretic peptides and non-osmotic release of ADH, appear [1, 68, 163]. In the initial phases, the etiologic factors induced by HF are represented by arterial under-filling and venous congestion; these are further translated into compensatory mechanisms [1]. First, the decreased distension of arterial baroreceptors during arterial under-filling determines the activation of SNS, RAAS and non-osmotic release of vasopressin, leading to a

decreased water and Na excretion [1, 163]. The response is represented by vasodilatation with natriuretic peptide release, activation of the kinin-kalikrein system and expression of endothelial relaxation factor, for an increased water and Na excretion [1]. These compensatory adaptive mechanisms eventually become maladaptive, further contributing to VO [162, 163]. There is still a paucity of data assessing the importance of VO as a risk factor for poor clinical outcomes in patients with CKD and CVD, as renal patients are an underrepresented subgroup population in CHF randomized controlled trials (RCT).

Recently, a direct and strong association between plasma Na and LA volume (LAV) was described in asymptomatic patients with 3–5 stages CKD [164]. The plasma Na had an important impact on the variability of LAV, only second to LVM, LV volume and age. Plasma Na was found to be a predictor of approx. 16 % of the total variance in LAV, independently of LVM and LV volume. Also, the study showed a very high prevalence (41.8 %) of subclinical LA enlargement that was not associated with a worsening GFR [164, 165]. Mallamaci et al. performed a subsequent analysis on this study and found that a-2 mmol/L increase in plasma Na is responsible for a 1 ml/m^2] increase in LAV [165].

VO, Hypertension and Left Ventricular Hypertrophy

The relationship between VO and BP was evaluated in several studies [9, 110, 166]. In predialysis patients, Verdalles et al. used bioimpedance to assess fluid status and to guide diuretic therapy for treating hypertension in these patients. Thirty patients with extracellular volume (ECV) expansion and a diuretic were compared to 20 patients without ECV expansion who instead received another additional antihypertensive medication. At 6 months of follow-up, SBP decreased by 21 mmHg in patients with ECV expansion compared to 9 mmHg in patients with normal ECW ($P<0.01$). In addition, more patients achieved the target BP of less than 140/90 mmHg at 6 months in the group with ECV expansion (nine of 30 patients with ECV expansion cf. two of 20 without ECV expansion).

Based on bioimpedance and cuff BP measurements, Wabel et al. described four distinct categories of individuals in dialysis: (i) normotensive – normovolemics; (ii) hypertensive – normovolemics; (iii) hypertensive – hypervolemics; (iv) normotensive –hypervolemics [110]. It is clear that BP management by different classes of drugs could be tailored much easier and related to prevailing underlying pathophysiological mechanisms. Similarly, our group found in 160 HD patients, using multi-frequency body impedance spectroscopy (MF-BIS) measurements, a large group of hypertensive patients with VO patients, despite an apparently achieved dry weight (DW) on clinical evaluation. Therefore, body composition monitoring (BCM) could represent an accurate measurement tool for the adequate management of BP and risk stratification in HD patients, providing accurate information of more abnormal cardiac and vascular profiles [9]. Similarly, in CKD predialysis and in dialysis patients, the inadequate evaluation of OH and its association with LVH have been established for a long time [9, 13, 109]. Essig et al. investigated 104 patients with early CKD followed-up for 5 years, in order to evaluate body composition, cardiac alterations and their association with GFR. The study showed that ECV was an independent predictor of LVH [7]. Moreover, the correction of the FO could be associated with an improvement of hypertension and left ventricular hypertrophy. Hur et al. in a recent RCT perform bioimpedance spectroscopy in 156 patients; at half of them, fluid removal during dialysis was adjusted based on bioimpedance measurement. After 1 year of follow-up, a substantial regression of the left ventricular mass index (mean difference between groups −10.2 g/m [2]; $P<0.001$) and blood pressure was noted in the interventional group but not in the control group [111]. Also in PD patients, FO was associated with hypertension and LVH. Cader et al. aimed to assess the prevalence and LVH and its determinants in a cross-sectional observational study that enrolled 31 stable asymptomatic PD patients. OH was identified as a predictor of higher LV mass index (LVMI) and, on multivariate analysis, was the main predictor of LVH in these patients [167].

FO and Arterial Stiffness

Arterial stiffness is best described by the viscoelastic property of the arterial wall that represents the relationship between pressure response and changes in volume [168]. The principal factors that alter the arterial wall are classified as stable factors (e.g. atherosclerosis) and dynamic hemodynamic changes (e.g. BP) [168].

In ESRD patients, the aorta, the common carotid artery and large arteries are enlarged in comparison to age-, sex- and BP-matched control subjects [169]. GusbethTatomir – Covic et al. found an association between VO (a common status in ESRD patients) and arterial stiffness [170], results that were confirmed by similar findings [65, 171]. Furthermore, an improvement in arterial stiffness was associated with a better survival in dialysis patients [172]. In these patients, chronic VO produces the proper conditions for arterial remodeling as a response to an increased wall stress, determining a thickening of the arterial intima-media [173, 174]. The increase in the arterial intima-media thickness (IMT) will further lead to a decreased arterial distension, an increased pulse wave velocity (PWV) and an early return of wave reflection [173, 175]. LVH in ESRD patients develops as a combined consequence of both non-hemodynamic uremic factors and of hemodynamic overload, the latter being the effect of flow and pressure overload [173]. Flow overload determines the enlargement of LV and it is caused by anemia, arteriovenous

fistulas and chronic VO; pressure overload is associated with structural and functional modifications of large arteries including stiffening of the arterial tree. At the same time, the arterial tree is also suffering remodeling from the flow overload burden. It is evident that cardiac and arterial changes are the consequence of the same hemodynamic abnormalities [173].

Regarding the decrease/amelioration of arterial stiffness by improving VO with HD, the literature provides conflicting data. Ie et al. combined carotid pulse contour analysis with aortic outflow measurement and found that aortic compliance was improved by HD fluid removal in patients with already achieved DW and steady BP although PWV did not differ after the HD session, suggesting that arterial stiffness in HD patients could be explained by a reversal reduction of aortic compliance due to volume expansion [176]. Another study measured PWV in 19 HD patients before and 24 h after they had achieved post-HD DW. The results failed to associate an improvement in PWV after volume reduction; this correlation was highlighted only after adding angiotensin converting enzyme inhibitors (ACEI) treatment for 1 week in a subgroup of ten patients, suggesting that the contribution of angiotensin II to arterial stiffness [177]. A more recent study demonstrated, in the same clinical settings, that HD significantly reduced PWV from pre-HD to post-HD [178]. These later findings were in addition supported by a study conducted by the same group that evaluated the long-term association of VO with arterial stiffness. PWV was measured at baseline, at the end of the intervention period (2.5 years) and at the end of the study (3.5 years) and was analyzed in correlation with VO status assessed by clinical methods and BIA. The results showed significant difference in PWV between the groups in relationship to VO, with PWV decrease in the BIA-managed group and a significant increase in the clinical-managed group, underlying the advantage of an adequate fluid status management in arterial stiffness improvement [109].

The newest information is provided by a very recent study that investigated for the first time the effect of different HD techniques on arterial stiffness. The authors aimed for a comparative evaluation between hemodialysis and hemodiafiltration on PWV, wave reflections, and central hemodynamic parameters. The results showed a decrease in the augmentation index (AIx) by both methods. Also, the aortic and brachial PWV were not modified by any of the two HD methods [179].

FO and Obstructive Sleep Apnea (OSA)

The presence of OSA in ESRD patients was associated with hypertension, LVH and increased mortality [180–182]. OSA presents a higher prevalence in patients that have VO status, such as CHF and ESRD in comparison to the general population [183–185]. The hypothesized mechanism is that the fluid overload status, so common in these patients, could increase the amount of fluid displaced from the legs into the neck during nighttime, leading to a compression of the upper airways. Indeed, it has been demonstrated that OSA in ESRD is ameliorated with conversion from conventional to nocturnal HD or conversion from conventional ambulatory PD to nocturnal- cycler-assisted PD [186, 187].

The proposed mechanism is supported by data from several studies. In a cohort of 26 ESRD patients studied throughout polysomnography, with BIA and neck circumference measurements it was found that nocturnal rostral fluid shift is indeed associated with OSA [188]. Another cohort of 20 patients was evaluated with polysomnography, leg fluid volume measurement and magnetic resonance imaging (MRI) of the upper airway. It was found that VO, through increased internal jugular vein volumes and increased amount of mucosal water is a contributing factor in the pathogenesis of OSA in ESRD patients [189].

FO and CKD Progression

Tsai et al. published in 2014 the results of a prospective cohort study designed to assess the association of VO to CKD progression [14]. The study enrolled 472 CKD stages 4–5 patients that were followed-up for a median 17.3 months period; 39.6 % had a rapid GFR decline while 15 % reached ESRD and started dialysis. The study showed that VO was independently associated with an increased risk of rapid GFR decline and that the severity of VO was associated with an increased risk of RRT initiation [14]. The same group further investigated the enrolled 207/472 diabetic patients [8]. In this subsequent analysis, the authors reported that TBW, ECW and ECW/TBW were higher in diabetic patients with VO than in those who had only CKD + DM or only CKD + VO. In a multivariate analysis of progression to RRT initiation, a significant association between DM and VO was shown. Also, the decline in renal function was significantly more rapid in patients with VO than in patients without VO, independently of DM presence. The authors concluded that VO has a higher predictive value for an increased risk of CKD progression than DM in late CKD [8]. A modest, inverse relationship between OH and GFR was also observed by Hung et al. in 338 stages 3–5 CKD patients, but in a multivariate analysis, this correlation was no longer noted [12].

FO and Survival

FO, FO-determinants and FO-consequences are associated, in prospective observational studies [2, 3, 11, 65, 131, 145, 171, 190–192] and in RCTs [109], with an increased risk of mortality among renal patients. Poor volume control is mainly related to at least three factors (i) high interdialytic

weight gain (IDWG); (ii) high ultrafiltration rate (UFR) causing as a consequence hypotension and (iii) chronic volume overload.

The association between *higher IDWG and poor survival* in HD patients was found in 11.142 USRDS database patients in which, pre- and post-dialysis BP values (by wide pulse pressures implication) were independently associated with mortality [171]. An analysis of DOPPS data showed that HD-nondherence lead to higher IDWG and increased risk of hospitalization and mortality. Comorbidities and lower dialysis dose were also associated with higher mortality risk [65]. In a prospective observational cohort study on 34,107 HD patients, the association between higher IDWG and all-cause mortality was analyzed. The comparison groups were 4,900 HD patients with IDWG between 0.5 and 1.5 kg and 29,207 HD patients with IDWG >1.5 kg. Higher IDWG was found in younger patients, in a greater percentage of males, with DM, higher BMI, protein intake, serum albumin levels, serum creatinine and phosphorus. Lower IDEG was more likely in females and older age patients. DM was associated with 94 % higher risk of VO and dialysis vintage >5 years with 67 % higher risk of VO. For the IDWG-survival analysis, 8 a priori defined increments of VO were created: seven 0.5 kg increments between 0.5 and 4.0 kg and the group with IDWG >4 kg. The 1.5–2.0 kg group was used as reference. When controlled for demographics and case-mix covariates, an IDWG >3.0 kg was associated with increased risk of death. A-2 consecutive IDWG >4.0 kg was associated with 25 % risk of CV mortality and 28 % risk of death, but minimal fluid retention (0.5–1.0 kg) was correlated with 26 % higher chance of survival and 23 % lower CV mortality. Mortality risk of higher IDWG (>1.5 kg) was a constant finding even in subgroup analysis [2].

High UFR could induce haemodynamic instability, intradialytic hypotension (IDH) and increased mortality risk [193]. Hypotension during HD and aggressive UFR increase the risk for intradialytic recurrent myocardial stunning and could determine, over time, irreversible fibrotic changes and chronic heart failure, arrhythmias and sudden cardiac death [194]. In 70 prevalent HD patients without severe left ventricular dysfunction, Burton et al. performed serial echocardiography during and at 30 min following HD [195] and found in 64 % of the patients, a significant reduction in cardiac function—the only predictors were the ultrafiltration volume and IDH. Shoji et al. found a 2-year mortality rate approximately 8 % higher for patients with intradialytic BP <110/59 mmHg [196] and Tisler et al. observed that patients with frequent IDH have a 25 % reduction in life expectancy in comparison with hypotension-resistant patients [197]. Agarwal et al. found in 308 HD patients an independent (from conventional and non-conventional CV risk factors, UF volume and rate) prognostic relationship of RPV slopes and mortality. Compared to steeper RPV slope, a flatter RPV slope was associated with 1.72 higher hazard of mortality [3].

Chronic volume overload and survival – Paniagua et al. showed in a prospective multicenter cohort of 753 prevalent adult patients on CAPD, APD and HD followed up for 16 months that, on a multivariate analysis, NT-proBNP levels and ECW/TBW were predictors of both all-cause and cardiovascular mortality, independently of dialysis modality and the presence of other known clinical and biochemical risk factors [198]. In 2012, Chazot et al. compared 50 selected (normohydrated) HD patients from Tassin, France to 158 patients from Giessen, Germany. The Dutch patients were divided into two groups: non-overhydrated (123 patients) and overhydrated (35 patients). After 6.5 years of follow-up, multivariate adjusted all-cause mortality was significantly increased in the overhydrated group (HR = 3.41), suggesting that VO is an important predictor for all-cause mortality in HD patients [11]. Siriopol et al. showed in 96 HD patients evaluated by three different methods of fluid status assessment (LUS, BIA and echocardiography measurements) the significant prognostic power for survival of BL-US performed before the start of HD session. After an observation period of 405.5 days, HR for mortality was higher in the group with severe lung congestion (UL comets >30) compared with the other two groups (HR = 5.03, 95 % CI: 1.5–16.5). In order to assess the real impact of lung water on survival, the investigators controlled in a multivariate Cox model for demographic, echocardiographic and BIA factors. LVMI and pre-HD BL-US score were survival predictors that maintained a statistical significance after adjustment [145].

A 2014 single-center retrospective analysis of prospectively collected data of 529 PD patients found that OH index (OH and OH/ECW) was an independent predictor of mortality in a multivariate analysis. The 30 % of patients that were most severely overhydrated as defined by ECW/TBW had the highest increased adjusted risk of death = 2.05 (95 % CI: 1.31–3.22, $P < 0.005$) [192].

The impact of VO may be modulated by the impact/interaction with aldosterone. In a 2013 study, Hung et al. aimed to investigate if the association of aldosterone levels with mortality is modified by the presence of VO in 328 HD patients followed for 54 months. The investigators found the following: (a) baseline aldosterone was significantly lower in the presence of VO than in its absence; (b) during follow-up, higher aldosterone levels and VO were associated with decreased HR for mortality and cardiovascular events; (c) in contrast, in the absence of VO, higher levels of aldosterone were associated with increased risk for mortality and cardiovascular events. The authors concluded that the association between aldosterone levels and adverse outcomes in HD patients is modulated by the confounding effect of VO and that their results support the treatment of hyperaldosteronism in HD normovolemic patients [5].

Volume Overload Treatment: Sodium Plays the 'Leading Role'

Non-renal Patients

In non-renal population, the association between salt intake or sodium excretion OH, BP and different CV outcomes has been extensively studied, although with disparate results, depending on multiple factors, such as different characteristics of the included populations, different assessment protocols of salt intake, poor quality of measurement methods of urinary Na excretion and various intervention strategies.

INTERSALT, a multi-national epidemiological trial, conducted in 10,074 normotensive and hypertensive patients across 32 countries, reported that each 2.3 g increase in 24-h urinary Na excretion was associated with a 6/3 mmHg increase in BP [199]. Patients included in the PREVEND study had a 6 % higher risk of developing HTN for each 2.3 g increase in salt intake [200]. The DASH RCT used a controlled diet (low on fruits, vegetables and dairy and rich on fats) and randomized the participants into three categories, to a low, medium and high Na intake for 30 days. A decrease in Na intake from 3.2 to 2.4 g was associated with a SBP reduction of 2.1 mmHg [201]. The TOHP I and II studies found that a decrease of Na intake to 44 mmol/24 h and respectively to 33 mmol/24 h is associated with a 25 % reduction CV events, suggesting an advantage for a moderate salt reduction in the general population [202]. These results are consistent with the American Heart Association (AHA) recommendations [203]. In addition, reducing Na intake in patients experiencing resistant HTN, is associated with a decreased SBP and DBP suggesting that a high Na intake is an important determinant of resistance to antihypertensive treatment [204]. Also, the contributing effect of high Na intake on arterial stiffness and endothelial vascular function was reported in several studies [200, 205–208].

In contrast to these positive findings, a recent meta-analysis of seven clinical trials, aiming to evaluate the efficacy of Na intake reduction on BP and BP-driven hard end points, failed to found an association to a reduced CVD risk or mortality risk [209]. More importantly, there is data supporting the 'U-shaped' optimum salt intake and the 'J-shaped' association between 24-h urinary Na excretion and cardiovascular events.

O'Donnel et al. showed, in a posthoc analysis of the ONTARGET and TRANSCEND cohorts, that a higher 24-h urinary Na excretion is associated with a higher risk of cardiovascular events. The cardiovascular mortality risk was 9.7 % higher with an estimated Na intake of 7–8 g/24 h and 11.2 % for an estimated Na intake of >8 g/24 h. Nevertheless, a paradoxical inverse relationship was found in 12 % of participants at an estimated Na urinary excretion of <3,000 mg/24 h [210]. The FinnDiane study, reported as well a 'J-shaped' relationship between urinary Na excretion and cardiovascular events [211]. An inverse relationship between urinary Na excretion and CVD and all-cause mortality was noted in several other studies [212, 213].

Pre-dialysis CKD Patients

In pre-dialysis CKD patients, excess Na intake – as a risk factor determines VO increased BP and proteinuria. Therefore, controlling salt intake could account for a simple, modifiable measure for reduction of VO, BP and proteinuria, the principal conditions leading to CKD progression [214, 215]. In CKD patients, a Na intake >4.6 g/day, compared to patients with a Na intake of <2.3 g/day was associated with renal function decline and increased proteinuria [216]. A double-blind placebo RCT determined the effects of modest salt reduction intake on 24-h urinary albumin excretion rate and on PWV in 69 patients with mild-untreated HTN, followed-up for 6 weeks. The results showed that a 55 mmol (3.2 g salt) reduction in Na cf. to placebo determined a significant decrease in BP, urinary albumin, albumin/creatinine ratio and PWV [217].

In a RCT that enrolled 52 non-diabetic, hypertensive CKD patients the effect of Na dietary restriction was compared to angiotensin receptor blockade at maximum dose or RAAS dual blockade. The authors concluded that dietary Na restriction, as recommended by guidelines, is more effective for BP and proteinuria control than the RAAS dual blockade [218].

Reports show that 80–89 % of CKD patients ingest >100 mmol Na/day, a higher amount than what the guidelines are recommending [219–222]. Thus, the most important therapeutic strategy is reducing salt intake, but this is a challenging task due to patient's poor adherence to diet restriction and the difficulty in achieving an unsalted diet, as the common western processed food contains high amounts of Na [215, 219–221].

A very recent RCT aimed to assess the effects of high versus low Na intake on ambulatory BP, 24-h protein and albumin urinary excretion, fluid status, renin and aldosterone levels and arterial stiffness in 20 stage 3–4 CKD hypertensive patients [223]. This trial represents, in fact, the first phase of the LowSALT CKD study, which is a 6 week randomized-crossover trial evaluating the impact of low Na intake (60 mmol/day) versus moderate Na intake (180 mmol/day) on cardiovascular risk factors and renal function decline in mild-moderate CKD. The phase II of this trial will assess the longer-term effectiveness of Na restriction and will continue the investigations initiated in phase I, with addition of patient-centered outcomes (dietary adherence, quality of life and taste assessment) [224]. The study phase I showed statistically significant and clinically important reductions

in: BP (mean reduction of SBP/DBP of 10/4 mmHg), extracellular fluid volume, albuminuria, and proteinuria when a low Na intake was applied. These changes were more pronounced than those observed in patients without CKD, suggesting that patients with CKD are particularly salt sensitive [223].

Beside Na intake, water intake has been previously evaluated, in small, underpowered studies, for its relationship to cardiovascular outcomes and impact on kidney function [225–228]. Palmer et al. investigated in a longitudinal cohort study the association between fluid intake, kidney function and long-term mortality [229]. The study included 3,858 participants identified from 1992 to 1994 and from 1999 to 2000 by a door-to-door census of all residents in two urban postcode areas. The subjects completed a self-administered food frequency questionnaire that assessed the total fluid intake from food and other beverages beside water; further, participants were divided into quartiles corresponding to water consumption, as follows: <2 L/day. 2.0–2.4, 2.5–3.0 and >3 L/day; each subject participated in a detailed medical examination at baseline and during follow-up. The statistical analysis for all-cause and cardiovascular mortality did not found a significant correlation between these outcomes and fluid intake, on a median follow-up period of 13.1 years. A total of 1,127 death were recorded with 580 cardiovascular deaths, but the controlled analysis for clinical and demographic parameters did not found an association between daily fluid intake and all-cause mortality per 250 ml/increase [229]. Also, kidney function was evaluated by repeated measurements of serum creatinine over a 10-year follow-up period in 1,479 participants and from these, 1,207 were included for the final analysis; there was no statistically significant association between daily fluid consumption and changes in GFR [229]. These results do not support the international guidelines recommendations of a beneficial impact for the kidney when eight glasses of water/day are consumed [230].

Renal Replacement Therapy Patients

Volume control and sodium restriction is associated with improved BP values and increased survival rates in dialysis patients. Ozkahya et al. in 218 HD patients with a salt restriction diet: mean salt intake 4–5 g/day) and no antihypertensive treatment and a mean follow-up period of 47 ± 34 months [190] showed an improvement in BP values and mortality rates. Our group performed recently a RCT in 131 HD patients, randomly assigned into two groups (BIA-analyzed group and clinical-evaluated group). After a 2.5-year period of follow-up, all-cause mortality was significantly lower in the BIA group compared to clinical-evaluated group. After adjustments for age, gender, CVD, DM, dialysis vintage, BMI, SBP, albumin level and relative fluid overload, the HR for mortality in the BIA group was 0.100 (95 % CI: 0.013–0.805, P = 0.04) compared to the clinical-evaluated group [109]. In 2012 Covic et al. analyzed the existing data supporting the hypothesis that uremic toxins are the principal determinants of morbidity and mortality in ESRD patients versus salt and VO. The final conclusion, based on recent studies, was that volume and salt-intake management are accountable for a better BP control, reduction of cardiovascular events and mortality in these patients [193].

For HD patients, Na balance and ECV control, through an established appropriate DW and normotensive status, represent the most important factor for reducing negative outcomes. Na balance in HD patients is dependent of Na intake and removal by the dialysis procedure. A positive relationship between serum Na (SNa) and elevated BP was described in several experimental and clinical settings [231–233]. A lower Na intake leads to a reduction in BP and LVH and higher Na levels are associated with both elevated BP and IDWG [190, 234, 235].

A number of proposed strategies were created over time for a better control of fluid status and BP: (1) Na profilling (modelling); (2) Na individualization; (3) UF profiling; (4) different HD techniques. These methods are further analyzed in terms of achievability, efficacy and safety.

Na Profiling ± UF Profilling

The dialysate Na (DNa) prescription is a modifiable, but underused parameter for achieving Na balance in HD patients. In HD, Na removal is achieved by convection or diffusion; under the current practice, approx. 80 % of Na is removed by convection and 20 % by diffusion [236, 237]. Hypothetically, a regular removal of 1 L of plasma water by UF, when a theoretically isotonic Na concentration of 140 mmol/L is considered in the ultrafiltrate, could remove 140 mmol of Na (8 g NaCl consumption for each interdialytic day) [236]. Diffusive Na losses take place across the dialyzer membrane in line with the diffusion gradient between plasma and dialysate, whereas the convective Na losses represents the quantity of Na removed by UF and it depends on the prescribed UFR [237]. Currently, the regular dialysate prescription is based on an isotonic Na level of 135–145 mmol/L [236]. Experiments for a better fluid control in HD patients, by altering Na prescription to a higher value of DNa concentration (>141 mmol/L) or to a lower value of DNa concentration (<137 mmol/L) have been conducted in various forms and protocols. Higher DNa prescription determines a rapid UF and the removal of fluid excess from the interdialyitic period, but, as highlighted by Davenport et al., this is not as adequate method to achieve Na balance, as is leading to hypernatremia, increased thirst and higher IDWG, higher pre- and post-dialysis SBP and an intensified antihypertensive medication [237, 238]. On the other hand, using

a low DNa concentration will lead to a rapid decrease in plasma osmolality and a hemodynamic instability and intradialytic hypotension [239, 240]. Various studies advocate for the benefits of using a lower DNa prescription, whereas others emphasize the 'dark sides' of the complications that arise with this method.

Na profiling is a HD method developed to avoid hypotension-related discomfort during HD (IHD) by modulating DNa prescription according to pre-established profiles; it was designed to preserve the advantages of a high DNa prescription without its intradialyitic complications [241]. It usually represents the prescription of a high DNa at the beginning of the HD session in order to determinate a hyponatremic status that will facilitate the water shift from the ICV to ECV compartment; during the HD session, DNa will be progressively decreased to avoid VO [242]. Time-averaged mean of DNa is associated with intradialytic diffusion Na overload and is generally higher with Na profiling than with a fixed DNa concentration [241, 243].

UF profiling is another way to prevent IHD and it represents the intermittent interruption or progressive reduction of UFR in order to promote plasma refilling. Therefore, during the high DNa period, a high UFR could provide an increase in plasma tonicity and a higher plasma refilling; during the low DNa period, a low UFR could avoid hypovolemia [241].

Song et al. conducted a prospective study to determine the optimal Na balance by Na profiling for prevention of IHD and to investigate if such an optimal Na profiling could result in HD sessions without Na gain-related complications. In 11 HD patients, 8 treatment modalities were evaluated: conventional HD (CHD) – control group, Na balance-positive step-down profiling HD (PS), Na balance-neutral step-down profiling HD (NS), Na balance-neutral alternating Na profiling HD (NA), UF only and PS + UF, NS + UF, NA + UF. Only PS, PS + UF, NS + UF and NA + UF had a significant positive impact; these were further analyzed in a phase II, randomized controlled, 6 weeks, crossover study [241]. The results were: (a) diffusive Na gain was significantly higher with both PS and PS + UF; (b) PS and PS + UF increased IDWG; (c) PS and PS + UF increased pre-dialysis weight and the amount of UF; (d) %UF achieved targetingDW was higher with NS + UF and NA + UF; (e) post-dialysis weight as closest to DW was achieved with NS + UF and NA + UF; (f) incidence of excessive weight gain and IHD increased significantly with PS. The investigators concluded that NS + UF and NA + UF are associated with less Na and weight gain, better UF performance, fewer IHD, a hemodynamic benefit and post-dialysis weight closest to DW [241]. DOPPS, an international database of dialysis patients was analyzed in an observational study by Hecking et al. respective to SNa and DNa [244]. The study found: (a) a higher DNa is associated with lower risk of hospitalization, even though it was, also, associated with higher IDWG; (b) DNa was not associated with mortality, but neither with lower SBP values [244]. The important disadvantages of inadequate Na profiling and the unconfirmed 'benefits' of this method are detailed elsewhere [245, 246].

Na Individualization

Na individualization was designed as an improved alternative for the adverse effects of Na profiling. It has been hypothesized that humans have an individual Na 'set-point', therefore, whenever there is a Na excess, higher than the fluid intake, SNa will increase above the set-point leading to a further fluid intake [69, 247], especially in HD patients where pre-dialysis SNa tends to remain stable over time [248]. Accordingly, if a patient has a positive Na balance during HD (dialysis against a higher DNa prescription) that individual's thirst will be stimulated and he/she will drink the amount of water necessary to drive the osmolality back to its set-point [237]. As a general concern, lower DNa is considered a potential determinant of SNa [249, 250]. Data, associating a low DNa with mortality, was previously reported, so lowering DNa for an alignment of the DNa with pre-dialysis SNa has to be pursued with caution [249, 251–253]. Also, Na individualization was associated with better surrogate and hard end points, supporting the lowering/tailoring of DNa in line with the SNaset-point, rather than using a fixed DNa concentration or DNa modelling [103, 249].

Na individualization method is well described by Arramreddy et al.'s case series of 13 patients that were switched from CHD to DNa individualization prescription. The strategy began with a phase A-stepwise weekly reduction of the standard DNa (140 Meq/L) by 2–3 mEq/L until reaching a Na gradient of −2 mEq/L. The tapering phase lasted 4 weeks. The Na gradient was defined as difference between prescribed DNa and average SNa and average SNa was calculated as mean SNa over the preceding 3 months. During the intervention period, the DNa was not further readjusted in line to monthly SNa levels. Further, on the same day that patients reached a −2 mEq/L Na gradient, they entered a 4 week-phase B-period during which all patients were dialyzed with a Na gradient of -2 mEq/L. Baseline pre-HD SNa was 135.3 ± 3.7 mEq/L; in phase A, post-HD SNa increased by 1.5 ± 3.7 mEq/L compared to pre-HD SNa. HD with an individually reduced DNa, achieving a gradient of −2 mEq/L, in phase B did not modify pre-HD SNa. Compared to standard DNa, individualized DNa reduced IDWG without significant increase in the frequency of intradialytic hypotension or cramps [254].

Hecking et al. performed two separate investigations on DOPPS trial results [244, 255]. In the first one, the investigators found an association between SNa and DNa and that this correlation influenced the mortality: DNa >140 mEq/L was associated with a trend towards higher mortality in patients with SNa ≥140 mEq/L; higher DNa was associated with

lower mortality in patients with SNa <137 mEq/L [249, 255]. In the second study, the analysis revealed: (a) a large variability of DNa prescription between centers: 55 % used fixed DNa and 44 % used DNa individualization; (b) in non-individualized DNa facilities, higher DNa was associated with higher SBP, but with a lower mortality; (c) in individualized DNa facilities, higher DNa was associated with lower SBP, but with higher mortality [247, 249]. Nevertheless, it should be noted that patients with higher non-individualized DNa were younger, lees likely to have DM and had lower serum albumin. Also, as in the non-individualized centers, DNa was not prescribed in line with patient' characteristics, there is possibility for confounding by indication [249]. The authors concluded that there is rather limited support for lowering DNa to control HTN, especially in the view of this method's association with hospitalization risk and mortality [244]. A higher DNa could be beneficial in some patients but detrimental in others [249]. De Paula et al.'s study, on 37 HD patients that received 3 weeks of HD with DNa at 138 mEq/L and 3 weeks of HD with DNa individualized according to patient's average pre-dialysis SNa, found that DNa individualization lead to lower SBP in patients with uncontrolled HTN, but with no impact on BP in those with controlled BP (<150/85 mmHg) [256].

Sayarlioglu et al. showed that DNa individualization is associated with better outcomes in 18 HD patients that underwent HD with DNa of 135 mEq/L when pre-HD SNa was <137 mEq/L and HD with DNa of 137 mEq/l when pre-HD SNa was >137 mEq/L. After a follow-up period of 8 weeks, lowered DNa was associated with lower pre- and post-HD SBP, lower pre-HD DBP, lower IDWG and improved cardiovascular parameters (reduction in LV systolic diameter, tricuspid regurgitation, IVC diameter and pulmonary arterial pressure) [257]. Actually, this is the first of the only two studies that analyzed the relationship between a lower DNa and cardiovascular parameters. The second study was performed by Kutlugun et al., in 30 HD patients, and showed that endothelial dysfunction, measured by flow-mediated dilatation (FMD), was significantly higher after using low DNa prescription (137 mEq/L) than after assigned standard DNa (143 mEq/L). Lower DNa resulted in a better BP and IDWG control, but no improvement in the LVM [258].

The SOLID trial is a multi-center, prospective, randomized, single-blind, controlled parallel 3 years clinical trial designed to investigate the impact of a low DNa on cardiovascular risk in HD patients. The study protocol was initiated after a previous investigation performed by the same group that showed a decrease by 4–5 mmHg in SBP and 2–3 mmHg in DBP with a 3 mmol decrease in DNa [259]. The present study intends to enroll 118 home HD patients from 6 sites for a follow-up period of 12 months; during this time the intervention and control groups will undergo HD with DNa of 135 and 140 mmol respectively. The primary outcome will be LVMI changes with other approximately 11 more secondary outcomes [240].

Non-conventional Dialysis Techniques

The virtues of more frequent dialysis on improved BP control, and even on survival are supported by results of small, observational cohort studies, as well as larger, RCTs. Prolonged dialysis schedules represent a more physiologic solute and fluid removal (a gradual UF) that can be translated into an improvement of dialysis adequacy. All of these HD methods can be performed in different locations: in-center, home-assisted, home and include: Short Daily HD (SDHD) – less than 3 h/session, 6 times/week; Long Daily HD (LDHD) – >5 h/session, 6 times/week; Nocturnal HD (NHD) – 6 to 8 h/session, 3–5 or 6 times/week.

In 1983, Charra and the Tassin group were the first to report the benefits of 3 times/week, 8 h/session, diurnal and nocturnal HD, along with reduction of salt intake on volume and BP control and survival [260–262]. Consistent with their results, similar findings were further provided by different studies using the same strategy. Beginning with 1998, studies performed in patients receiving SDHD or NHD reported improved BP, LVH, phosphorus and hemoglobin levels, decreased risk of hospitalization and even a better survival [250, 263–273].

Nocturnal Hemodialysis

Nocturnal home HD (NHHD) is associated with better outcomes, as shown in several observational, prospective studies and in RCTs: increased hemoglobin levels, reduced cardiovascular hospitalization and improved OSA [274–279].

In 2009, Johansen et al. used United States Renal Data System (USRDS) database to investigate, in a cohort study, the hospitalization and mortality rates in patients from various centers that used NHD for at least 60 days, comparing these outcomes with characteristic-matched patients on CHD. NHD was associated with significant reduction in mortality risk and risk for major morbid events [275].

Ok et al. performed in 2011 a prospective controlled study in 247 CHD patients and 247 ICNHD. Overall mortality rates were 1.77 % in ICNHD and 6.23 in CHD group/100 patient-years, after a mean 11.3 ± 4.7 months of follow-up. ICNHD was associated with 72 % risk reduction for mortality, decreased LV and LVMI end-diastolic diameters, improved cognitive function, lower serum phosphate and lower usage of phosphate binders [274].

The randomized controlled studies performed by Culleton et al. in 2007 and Rocco et al. in 2011 found conflicting results. Thus, Culleton et al. performed a 2-group, parallel RCT to compare the effects of frequent NHD (6 times/week) versus CHD on LVM and health related quality of life, for a 6 months follow-up period. Frequent NHD: significantly

improved mean LVM, was associated with improvements only in selected kidney-specific domains of quality of life and a better control of SBP and mineral metabolism [250]. However, the Frequent Hemodialysis Network Nocturnal Trial (Nocturnal FHN), which randomized 45 patients in the frequent NHD arm and 42 in CHD arm, failed to demonstrate a clear superiority of this method. NHD determined a 1.82-fold higher mean weekly stdKt/V_{urea}, a 1.74-gold higher average number of treatments/week, no significantly effect on LVM or mortality and a positive impact on HTN and hyperphosphatemia [276].

Nevertheless, there are also downsides reported respective to the NHD method: detrimental factors such as fear of self-cannulation, lack of confidence in conducting an adequate dialysis session, fear of possible complications and burden on family members were found in 56 patients that completed a survey [280].

Frequent Daily Hemodialysis

Kjellstrand et al. conducted in 2008 a survival statistical analysis of 415 patients treated by SDHD in 5 centers for a period of 23 years. 150/415 patients were treated in-center and 265/415 by home or self-care HD. The results showed a 5-year cumulative survival of 68 ± 4.1 % and a 10-year survival of 42 ± 9 %. Frequency of HD (5, 6 or 7 times/week) was not associated with mortality. The survival of patients on SDHD was 2–3 times better than that of matched CHD patients [263]. Johansen et al., in the same cohort study using USRDS database patients, showed for SDHD patients only a non-significant reduction in the risk of death compared to CHD [275]. In line with Johansen et al.'s report, Suri et al., found, in a multinational cohort study, that in-center daily HD did not improve the mortality rates. The study comprised in 318 patients from the International Quotidian Dialysis Registry that received >5 times/week daily HD and that were matched to 575 CHD-treated patients [281].

The effects of SDHD versus CHD, on LVH and inflammatory status, were investigated by Ayus et al. in a non-randomized, controlled trial. The study enrolled 26 SDHD (3 h/session, 6 times/week) patients and 51 matched CHD, for a 12 months follow-up period. After adjustments for cofounding factors, SDHD was associated with 30 % decrease in LVMI, improved fluid, phosphorus and inflammatory parameters control in comparison to CHD [282]. However, discordant results were found by the Daily FHN Trial: frequent daily HD (6 times/week) resulted into a significantly improved weekly stdKt/V_{urea}, improved control of HTN, hyperphosphatemia and significant benefits regarding LVM and mortality, even though the patients were more prone to vascular access-complications [283].

The FREEDOM study is a cohort matched pair study that will include approximately 500 HD patients from 70 centers trying to evaluate the benefits of home daily HD (DHD) – 6 times/week. The control group will consist of a matched CHD cohort derived from the US Renal Data System database using a 10:1 ratio, totaling 5,000 patients. The primary outcome is an analysis that compares hospitalization days/patient-year between the DHD and CHD groups. Other outcomes will include: non-treatment-related medical expenditures in both groups and, in addition, in the DHD cohort, changes in quality-of-life measures (baseline, 4 and 12 months, and every 6 months thereafter), urea kinetics, parameters related to anemia, bone and mineral metabolism, and nutrition, vascular access interventions, and medication will be examined. The follow-up period is at least 1 year [284]. An interim report of this study, in 128 patients, showed that DHD is associated with long-term improvement in depressive symptoms and post-dialysis recovery time [285] and another one, performed in 154 patients, demonstrates that DHD improves physical wellbeing, assessed by Health Related Quality of Life measurements [286].

Residual Renal Function

A major concern with all of these techniques remains whether they are helpful for preservation of residual renal function (RRF). RRF is increasingly becoming an important parameter for nephrologists and one of the major goals in the management of RRT patients. Jansen et al. showed in 279 incident HD patients and 243 PD patients that predictors for RRF decline are elevated DBP and higher proteinuria, dialysis hypotension and dehydration [287]. It has been also demonstrated that PD patients present, in general, a slower decline of RRF than patients on HD, maybe due to a more 'natural' fluid removal and fewer hypotension episodes [287–290]. It was found, in PD patients, that for every 1 ml/min increase in RRF there is a 50 % decrease in the risk of death; also, an analysis of the CANUSA study showed that a 250 ml increase in daily diuresis in associated with a 36 % reduction in mortality, suggesting, by expressing the RRF as urinary output, that a fluid control is more important than solute clearance [291–294]. Preserving RRF is associated with better fluid control and a more liberal fluid intake, maintained endocrine function, secretion of organic acids and a better dialysis adequacy [287]. RRF loss was associated with mortality, LVH, arterial stiffness and other ESRD complications [291, 293, 295–299].

An optimal management for preservation of RRF has not been yet determined since renal function decline appears both in dehydration and overhydration. Thus, some nephrologists are in favor of maintaining patients 'wet', whereas others prefer the patients 'dry'. Hypovolemia and hypotension are known factors to induce loss of RRF, especially in PD patients [295, 296, 300], but so are overhydration-associated HTN and LVH [287]. Gunal et al. showed that controlling fluid status, by salt restriction and increased UFR, led to 2.8 kg weight loss and a 28 % reduction in urine

output [301]. McCafferty et al. failed to demonstrate in PD patients that a better preservation of RRF is achieved with overhydration status [293].

As mentioned before, PD patients seem to preserve RRF for a longer time than HD patients, implying therefore that loss of RRF could be also determined by HD technique-related factors. Daugirdas et al. conducted recently an analysis of FHN studies to investigate if frequent HD could result in a more rapid decline of RRF, compared to CHD. They found that in both of FHN trials, baseline RRF was inversely associated with dialysis vintage. Frequent HD participants from these trials, with a percentage of RRF at baseline, suffered a significant progressive loss of RRF at the end of follow-up period: at 12 months, in the Nocturnal FHN, 67 % of patients had zero urine output in comparison to 36 % in CHD group and in Daily FHN, the method of treatment did not had a significant impact. The authors concluded that frequent NHD appearsto promote, by undetermined mechanisms, a more rapid loss of RRF [302].

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Reversing Arterial Stiffening and Calcification: A Pipe Dream?

13

Marc G. Vervloet

Clinical Case Scenario

After being admitted for congestive heart failure (CHF), a 58 year old male patient, with a BMI of 24 kg/m², was seen in the outpatient clinic. His dyspnea had completely resolved, and the slight peripheral edema he had prior to hospital admittance, was no longer present. Analysis had excluded a recent myocardial infarction, and the exacerbation of CHF was ascribed to diastolic dysfunction (seen on echocardiography), slight mitral valve regurgitation in combination with hypertension and high salt intake the weeks prior to admittance. In the past he appeared to be intolerant to angiotensin converting enzyme inhibitors, and was using nifedipine and metoprolol for years. During his hospital stay he has had hyperglycemia, but that had normalised prior to discharge, without any medication. His total cholesterol level was 260 mg/dl (6.7 mmol/l) and LDL cholesterol was 93 mg/dl (2.4 mmol/l). Over the preceding 8 years his kidney function had deteriorated to an estimated glomerular filtration rate of 28 ml/min/m², with a maximum 24 h urine protein excretion of 0.5 g. Currently he is using a salt restricted diet again. His blood pressure during the outpatient visit was 160/70 mmHg. During his hospital admission he was included in an observational study, and in that setting a carotid-femoral pulse wave velocity revealed a value of 15 m/s. The question arises if his cardiovascular risk profile can be further improved.

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Background

In recent years it has been increasingly recognised that the overall major threat for patients suffering chronic kidney disease (CKD), either defined by albuminuria or by a decline in estimated glomerular filtration rate (eGFR), is not to become dependent on any form of renal replacement therapy, but to experience a cardiovascular complication, like stroke, myocardial infarction, heart failure, or even to die from cardiovascular causes [1]. Since these increased risks in CKD are not completely explained by the aggregated traditional risk factors, like diabetes, hypertension, obesity, gender, smoking, and hypercholesterolemia, it became clear that kidney disease itself somehow jeopardizes cardiovascular structures. For many of these components both epidemiological and mechanistic studies point to its importance in the development of cardiovascular complications. However, in CKD, for none of these a definite proof of a clinical benefit exists, if this component is targeted.

It is clear that the identification of possible factors that are associated with cardiovascular disease in CKD is only one step in deciphering the pathobiology that culminates in the clinical events as mentioned above. These events are mediated by functional and structural changes that precede clinical complications. These include endothelial dysfunction and damage, like atherosclerosis, increased arterial stiffness, and left ventricular hypertrophy (LVH) [2, 3]. Although these changes of the cardiovascular system may be induced independently from each other, once established a vicious circle may be operating, with diseased heart function limiting tissue perfusion, and the other way around, vascular damage, especially arterial stiffness, propagating the development of LVH while jeopardizing coronary blood flow, as will be outlined below. All these individual components of this vicious cycle may be amplified by CKD (Fig. 13.1). In this chapter the focus is one of these contributing factors: the role of a stiffened arterial system in CKD.

Arterial stiffness is defined as a reduction in arterial distensibility. Several indices of a stiffened arterial system

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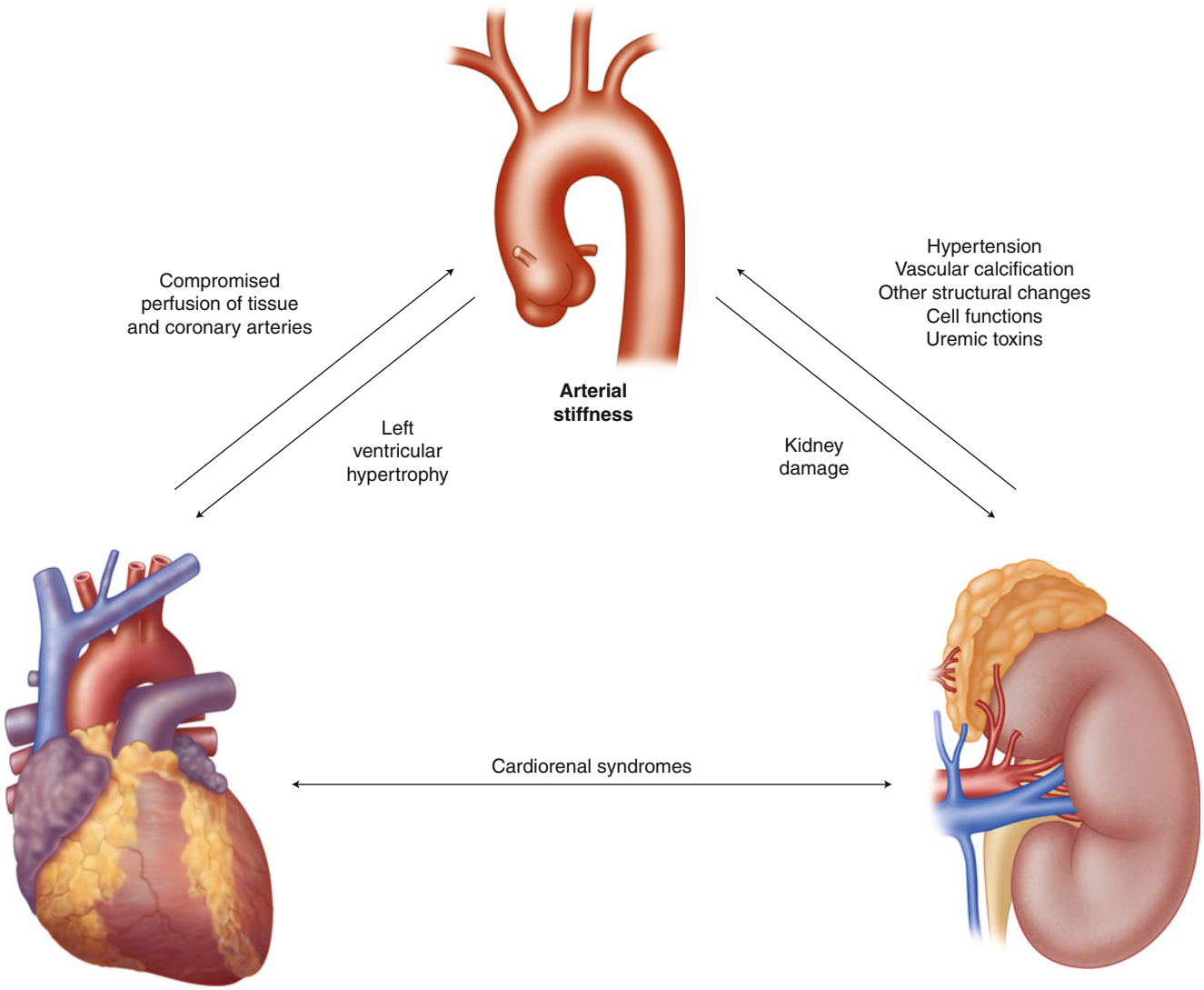

Fig. 13.1 Diagram representing the intermediate role of arterial stiffness in chronic cardiorenal syndromes. See text for explaining separate depicted, and additional amplifying components of the triangle

have all been associated with dismal cardiovascular outcome [4]. In CKD, aortic stiffness is an important additional risk factor for mortality [5]. Moreover, a wide pulse pressure (the difference between systolic and diastolic blood pressure) itself may induce glomerular damage [6, 7]. Clinically, arterial stiffness can be measured using sophisticated software programs that analyse arterial pressure curve on a single site like the brachial or radial artery, using pulse wave velocity (PWV), measuring time interval between arrival of systolic peak pressure at two sites with different distance from the left ventrical, or by estimating arterial stiffness by the difference between the systolic and diastolic blood pressure (pulse pressure) [8]. A stiffened central artery like the aorta has crucially different physical properties compared to a physiologically compliant artery. This translates into a completely different hemodynamic profile in the cardiovascular system during the cardiac cycle. The energy or power generated by the left ventricle during systole can be regarded as the sum of the blood volume replacement, i.e. the stroke volume, and pressure increment, the systolic blood pressure. When the compliance of the compartment where this energy is replaced to (the aorta) declines, more of this energy will comprise of pressure workload instead of volume, due to lack of capacity to dilate [9, 10]. In physiological situations a part of energy transfer from the left ventricle is "stored" as elastic expansion of central arterial structures. In stiffened central arteries this is not possible. Initially this will lead to an increase is systolic pressure and a decline in peripheral blood supply. The latter in turn will lead to a higher demand from the left ventricle to meet global blood flow requirements, and induce hypertrophy. A second physical feature of a stiffened artery is an increased velocity of the pressure wave generated during systole at the opening of the aortic valve. It is important to differentiate this pressure wave from the actual

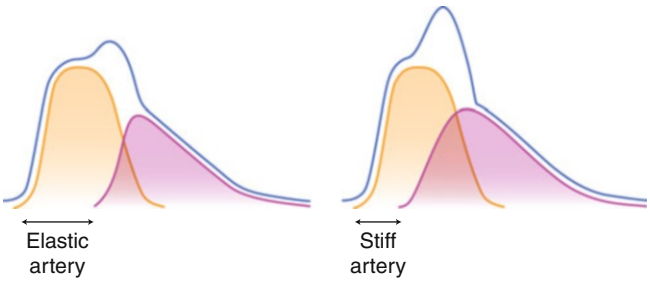

Fig. 13.2 Pressure curves measured in time form left to right in the proximal aorta during one cardiac cycle. *Left panel*: normal compliant central arterial system shows two components of the pressure curve. In *Orange* the hypothetical curve, assuming the absence of a reflected pressure curve. This curve is the sole consequence of antegrade pressure transduction form the left ventricle during systole. In *Purple* the pressure curve from the pressure reflection by more distal resistant arterial system that has traversed back retrogradely to the proximal aorta. The *Blue line* represents the actual pressure which is the sum of the two separate pressure curves. *Right panel*: Although the shape of the two pressure curve do not differ substantially the purple reflected curve returns more early in the cardiac cycle due to higher speed of pressure transduction along a stiffened arterial system. As a consequence the actual peak pressure (the *bule line*) is much higher: pressure augmentation. The additional height of the peak pressure, on top of the peak of the *orange curve* is referred to as the augmentation index

propagation of blood volume through the aorta, the latter being much slower. Since the pressure wave is reflected from the smaller peripheral arterial system, it traverses back in the opposite direction from the blood flow. With stiffened arteries, this reflected pressure wave reaches the aortic root more early, and eventually, as arterial stiffening progresses, close to the peak pressure of the cardiac cycle, as such augmenting peak pressure in the central arteries (Fig. 13.2). This induces an increase in cardiac afterload, and is an additional trigger for the development of LVH.

The elastic recoil of the distended proximal aorta after systole is an important driver of coronary perfusion during diastole, the time period in which myocardial perfusion is most optimal due to the relaxation of the myocardial wall [11, 12]. The loss of recoil capacity of stiffened arteries, in the presence of LVH, may induce a severe mismatch between metabolic needs of the hypertrophied myocardium and blood supply to that tissue, although to some extent this is attenuated by coronary autoregulation.

Arterial Stiffness

As outlined, stiffening of central arteries can be an important intermediate phenomenon linking cardiovascular risk factors in CKD to the increased prevalence of related clinical complications [13]. Therefore, at least hypothetically, arterial stiffness could be an attractive target for specific inventions to prevent these complications. This raises the fundamental question of reversibility of this phenomenon in CKD. It is important to underline that in CKD vascular pathology can differ from non-CKD subject by the presence of extensive calcification of the tunica media, a complication most likely to have detrimental consequences for arterial distensibility. Aiming to reverse arterial stiffness can conceptually be subdivided into attempts to either improve the quantity of vessel calcification, and to target functional and structural vascular changes that CKD patients have in common with non-CKD subjects with arterial stiffness. Clinically there are no methods to weigh the relative contribution of these two components, but examining the different pathophysiological processes, as will be outlined in the subsequent section, may form the basis of complementary therapeutic approaches, if available.

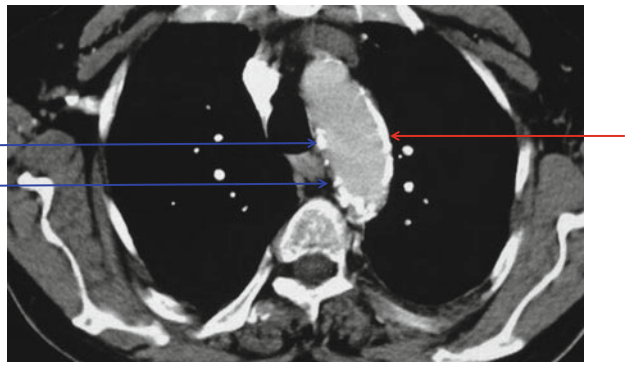

Fig. 13.3 CT scan of the thorax at the level of the arcus aortae, showing a large plate-like calcified area (*red arrow*) and some areas with more patchy distribution of calcified regions (*blue arrows*) (Courtesy of professor David Goldsmith)

Vascular Calcification

It is clear that the patient in the introduction has a stiffened arterial system, based on the high pulse pressure and the increased PWV of 15 m/s. Normal values of PWV have been firmly established and should be indexed to age and actual blood pressure [14]. Facing the fact this patient has CKD and possibly insulin resistance raises the possibility that the high PWV may be partly attributed to vascular calcification [15]. In CKD a typical form of calcification exists, called Monckeberg's sclerosis, which is located in the medial layer, the site responsible for the elastic and contractile properties of the arterial wall. Clinically, this type of calcification can be suggested using several radiological techniques, including sophisticated computed tomography or plain X-ray techniques such as lateral abdominal views (Fig. 13.3). These techniques do not differentiate between calcified atheromatous plaques of the intima, or medial calcification. However, it can be expected that any calcification, regardless of its histological location, interferes with arterial distensibility, but the impact on stiffness is probably higher for the medial calcification, because it is more continuous in localisation and

not patchy like calcified plaques. If present, the questions arise if progression of this calcification can be halted or even reversed, and ultimately if this modification of calcification benefits the patient.

When considering rational intervening in the process of vascular calcification, in-depth knowledge of its pathogenesis is required. The central player appears to be the vascular smooth muscle cell (VSMC) that undergoes a phenotypic switch when exposed to a uremic milieu, with key roles for abnormal levels of calcium and phosphate [16]. A complex interplay between deranged minerals, abnormal VSMC's, deranged gene expression profiles, unbalanced local calcification inhibitors and promotors, and deregulated endocrine networks all are involved in the development of calcification. Several of these components are modifiable, but clinically meaningful regression of established vascular calcification has not been shown [17]. Nonetheless, there are clues that some strategies might at least slow the progression of calcification. Active vitamin D appears protective against VSMC-mediated calcification [18] but caution is warranted since local actions of active vitamin D from plaque-infiltrating macrophages might worsen arterial stiffness [19], and its beneficial role is debated [20, 21]. Use of phosphate-binder therapy is generally applied in more advanced CKD, when phosphate concentrations exceed normal values. The rationale for its use is the central role of phosphate in the pathogenesis of calcification, and the fact that phosphate itself is a structural component of hydroxyapatite, the structure that calcified laesions are made of. Overall, phosphate binder therapy does not appear to influence vascular calcification [22, 23] or at best slow its progression in dialysis patients with the possible exception of calcium-containing binder that may even accelerate it [24]. Besides phosphate, a central role for calcium in cardiovascular calcification is evident. Indeed, calcium channel blocker therapy, besides being an antihypertensive drug, appears to attenuate coronary artery calcification [25]. Therefore, additional manipulations targeting calcium could theoretically interfere with the calcifying propensity in CKD. In dialysis patients, the use of the calcimimetic cinacalcet tended to slow the progression of calcification in the thoracic aorta, but this was not significant, and the compound cannot be used in more early stage CKD [26]. More importantly, it is clear that to slow progression is not to regress it and only regression could improve this component in arterial stiffness.

Recent insights point to the role of matrix gla protein (MGP), and its relation with vitamin K, which is required for activating the mineralisation-inhibiting properties of MGP. Especially in the setting of vitamin K deficiency or inhibition of its activity by the use of coumarin-therapy, this could be an important tool for intervention by either stopping coumarin or supplementing vitamin K [27, 28]. Although Fetuin A may be as important as MGP as calcification inhibitor, its role is not completely elucidated as levels do not parallel calcification burden in CKD, possibly because of initial upregulation as a defence mechanism against calcification [29]. The role of novel treatments, originally developed for the treatment of bone disease like bisphosphonates and RANK-L inhibitors (denosumab) is currently far from elucidated with possible some beneficial effects in older subjects using bisphosphonates, but no effect of denosumab [30, 31]. In conclusion, currently available pharmacological intervention are not proven effective in reversing calcification, beneficially influence vascular stiffness or lead to improved clinical outcome. However, novel insights into molecular mechanism of medial calcification do hold promise for future targeted interventions (Fig. 13.4).

Arterial Stiffness Not Related to Vascular Calcification

Despite having an increased risk for vascular calcification the patient in the introduction has several features that are associated with arterial stiffness, not attributable to calcification. Higher age, hypertension, diabetes (besides being a risk factor for vascular calcification), and high salt intake could all contribute to arterial stiffness, and could potentially be

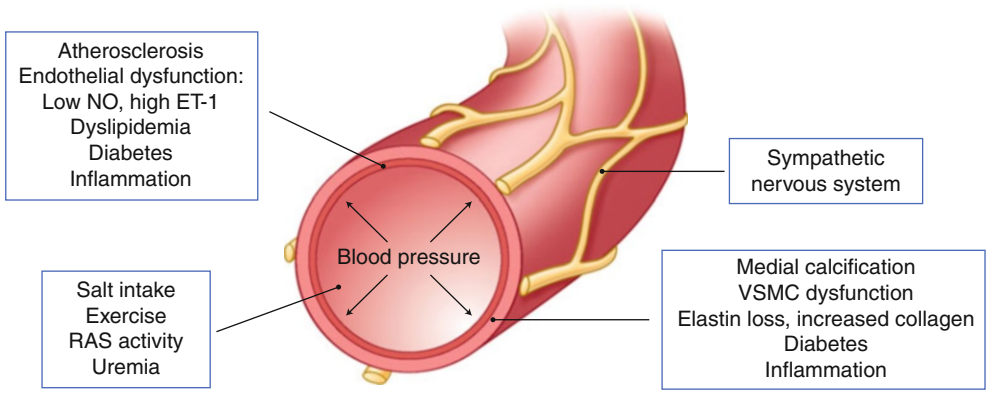

Fig. 13.4 Diagram representing well-established factors that contribute to arterial stiffness, grouped into four categories: primarily affecting the medial layer (*right lower panel*), intimal layer (*left upper panel*), distant or humoral and endocrine factors (*left lower panel*) and the sympathetic nervous system (*right upper panel*)

modified, except for age. To what extent CKD per se contributes to this causes of arterial stiffness is unknown, since many factors that are related to low arterial distensibility in the non-CKD population frequently aggregate in CKD patients. Data for instance of change in PWV in acute renal failure or following nephrectomy are lacking. However, since these non-calcifying modulators of arterial stiffness are highly prevalent in CKD, they are an integral component of treatment for these patients.

Since arterial stiffness frequently occurs in the absence of vascular calcification, it is clear other causes are operating too. Indeed, physical, structural and functional components can contribute to this vascular rigidity, and each could be modifiable [32]. From Fig. 13.2 it is clear that a direct relation between PWV and blood pressure exist. Since there is a limit to the maximum elastic expansion of central arterial structures, it is obvious that at higher central blood pressure these vessels are distended more, and as such are more close to the maximum distensibility and more rigid.

In understanding the relation between blood pressure and arterial stiffness it is crucial to realise that the blood pressure measured at the brachial artery may differ substantially form that in the aorta, and that the effects of antihypertensive agents may have different blood pressure effects centrally versus more peripheral like the brachial artery [33]. Especially inhibitors of the renin-angiotensin system (RAS) have a more pronounced central blood pressure lowering effect [34], possibly explaining the finding that despite similar peripheral blood pressure lowering effect, these compounds reduce PWV more than other blood pressure lowering drugs [35]. At the same peripheral blood pressure, those with a reduced central blood pressure had fewer cardiovascular events and declining renal function, as shown in a subset of the ASCOT study, that were treated by combination therapy using amlodipine and perindopril [36]. As inhibitors of the RAS, calcium channel blockers have consistently been shown to improve indices of arterial stiffness [37]. The reasons for the diverging effect on central blood pressure of several classes of antihypertensive drugs could either be a direct effect on the vessel wall itself or a replacement of the virtual reflection point of the reversed pressure pulse, and as such lowering the central pressure augmentation by the reflected wave. The latter may be of less importance since LVH correlates better with PWV than with augmentation index, once blood pressure is controlled [38]. In addition to the physical effects of blood pressure on arterial stiffness, chronic exposure to hypertension changes the structure of the vessel wall. Especially the loss and integrity of elastin and increased content of collagen may contribute to increased stiffness. Long-term treatment of hypertension may improve these structural changes to some extent [39]. Especially for the mineralocorticoid receptor antagonists like spironolacton and eplerenone it is suggested that their beneficial effects on arterial stiffness are better explained by an improvement in arterial structure than by their blood pressure lowering effects [40]. In addition to hypertension several other factors have been implicated to induce these non-calcification structural changes in the arterial wall. Among these are salt-intake (beyond its effect on blood pressure) [41], and possibly low intake of fish-oil [42], low levels of physical exercise and obesity.

The recognition that arterial tone is not only dependent on blood pressure and structural components in the matrix, like elastin, collagen and the presence of atheromatous plaques and medial calcification, pointed to functional properties that to a large extent depend on the interplay between endothelial cells and VSMC. Although the latter may play a more important role more distally in the arterial tree, compared to the more elastic most central artery, the aorta, the role of vascular cellular function on arterial stiffness is likely important [43]. Vascular tone is partly dictated by several endothelial derived substance like the vasodilator nitric oxide (NO) and the vasoconstrictor endothelin-1. Endothelin-A receptor inhibitors may improve arterial stiffness in CKD-patients when accompanied by a decline in ADMA (asymmetric dimethylarginine) and improve their risk profile, and hold promise for the future [44]. Statins, beside its well-known effects as cholesterol-lowering drugs, also improve arterial stiffness, an effect that too may be mediated by its effect on endothelial cells [45]. This potential beneficial effect of statins has also been clearly shown in CKD-patients, and even in patients on dialysis a minimal decline in PWV (of very doubtful clinical benefit) has been shown [46, 47]. In part due to the technical progress made in renal nerve ablation the role of the sympathetic nervous system (SNS) on arterial stiffness in physiology, which is an increase in PWV with increased sympathetic activity, has gained interest. [48, 49] Recently it was shown that renal denervation for hypertension in both non-CKD and CKD patients indeed showed marked improvement in arterial stiffness (measured by decline in augmentation index), which was independent from blood pressure lowering effects [50, 51]. As overactivity of the SNS in CKD is almost universal, targeting its activity may have unexpected beneficial effects on vascular stiffness, beyond possible hypertension improvements. Technically less challenging, though sometimes more difficult to achieve is the cessation of smoking. Arguably none of all described factors that deteriorate arterial stiffness have been so consistently described as smoking. Importantly, parameters of arterial stiffness all improve with time after smoking cessation [52].

As for its role in vascular calcification, the beneficial effects of vitamin D on vascular stiffness is debated. In a large observational study it was shown that in the general population low levels of cholecalciferol (the nutritional non-active form) were associated with more arterial stiffness [53]. Results of a placebo-controlled intervention study supplementing cholecalciferol was less convincing: though central

blood pressure decreased no change was noticed in PWV [53], while in older subject with isolated systolic hypertension or postmenopausal women no effect at all was noticed [54, 55].

In many aspects diabetes has comparable effects on the cardiovascular system as CKD, including vascular stiffness. Both conditions frequently coincide and clinically it is impossible to ascribe measurements of vascular stiffness, like high augmentation index or increased PWV to either condition if both are present. All (theoretical) possibilities to intervene in these cardiovascular characteristics that apply to CKD do so in diabetes as well. One important recent notion is that glycaemic control itself also improves arterial stiffness [56]. Besides all of the abovementioned factors that possibly all have influence on vascular health, a range of other components are involved in the pathogenesis of both malfunctioning endothelial cells and VSMC, like oxidant stress, inflammation, advanced glycation end products (AGEs) and specific uremic toxins like p-cresyl sulphate and indoxyl sulphate. For many of these its specific contribution to arterial stiffness is unclear, and unfortunately for most of these currently no specific therapy is available. For these reasons these are beyond the scope of this chapter.

Conclusions

Based on current knowledge as summarised in this chapter, it is clear that arterial stiffness most likely is an additional risk factor for cardiovascular complications, apart from, for instance, blood pressure itself. Therefore, the patient in the introduction does still not have an optimal risk profile. As described, several interventions might improve his arterial stiffness, like salt restriction, to stop smoking if he did, and to initiate an inhibitor of the RAS (not an ACE-inhibitor, for which he was intolerant). If the institution of an statin at this level of cholesterol is indicated is unclear, but as stated, its effect on vascular stiffness might provide a protective effect, different from its influence on lipid profile. Possibly the institution of a mineralocorticoid receptor inhibitor provides additional benefit. A moderate intense aerobic exercise program, healthy food that is low in salt (below 100 mmol sodium per day ≈5.5 g table salt) includes sufficient fish oil and is low in inorganic phosphate to prevent or slow vascular calcification could be advised. However, it is important to realise that currently it is unknown whether the improvement of vascular stiffness, if achieved by either pharmacological or life style interventions, is paralleled by a decline in cardiovascular risk, as suggested by observational studies. Only once that is firmly established, the more routine clinical measurement of arterial stiffness by either PWV or pulse-wave analysis from a single site, can be justified. On the other hand, if indeed improvements in arterial stiffness reduces the incidence of novel cardiovascular complications, a novel avenue of secondary and possibly even primary prevention is opened, with potentially large scale beneficial health care consequences. Clinical studies deciphering the independent effects of improved vascular stiffness may change the perception of this vascular function from a toy of scientist to a widely embraced modifiable target, and may lead to a dramatic change in the organisation of cardiovascular clinics. Novel intervention like renal nerve ablation, while debated as antihypertensive intervention, may hold promise for its assumed effect on vascular stiffness mediated by the SNS. Importantly, with the ever increasing prevalence of diabetes and CKD, it is likely that the contribution of arterial calcification to arterial stiffness will increase over the coming decades. As outlined, just that aspect of arterial stiffness is most difficult to treat. The recognition of that could be a call for intensified research on how to prevent its development and reverse established calcified deposits in the vessel wall.

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Pulmonary Hypertension in CKD: A New Problem Child

14

Davide Bolignano

Introduction

The pulmonary circulation is an exquisite and unique low-resistance, low-impedance, high-capacitance and high-flow circuit. Under normal conditions, the average resistance of pulmonary circulation is about 1 mmHg/min/L in young adults, increasing to 2.5 mmHg/min/L over four to six decades of life [1]. Pressure levels in the pulmonary arteries are roughly one-fifth to one-sixth of those usually found in the systemic circulation. This is partly related to the fact that, physiologically, medial thickening of major pulmonary arteries is notably lower than that of systemic arteries. As a result, the normal pulmonary circulation consists of highly compliant pulmonary arteries and a vast capillary network with large recruitment capability which is able to accommodate large increases in blood flow without significant increases in pulmonary pressure (e.g., in case of increased request during exercise or when left-to-right congenital intra-cardiac shunts are present). When this delicate pressures balance is altered, e.g. by the presence of left heart abnormalities or systemic vascular diseases, pulmonary hypertension may arise.

Diagnosis of Pulmonary Hypertension

According to the most recent definition, Pulmonary Hypertension (PH) is a pathological condition characterized by the presence of a mean pulmonary artery pressure ≥25 mmHg at rest, as measured at right heart catheterization [2]. Although this invasive procedure currently represent the gold-standard for the diagnosis of PH, non-invasive estimates of pulmonary artery pressure can also be performed by echo-Doppler examination (Fig. 14.1). In this case, the evaluation of pulmonary artery systolic pressure (PASP) is reflected by the tricuspid regurgitation jet, a phenomenon that can be observed in certain physiological and pathological conditions. If a pulmonary stenosis is not present, right ventricular systolic pressure (RVSP) PASP is estimated by the calculation of RVSP by the modified Bernoulli equation as the product of the square of maximum tricuspid regurgitation jet velocity (Vmax) multiplied by 4 ($4 \times Vmax^2$) plus the right atrial pressure (RAP). It is possible to estimate RAP from the vena cava diameter and the degree of its collapse under inspiration [3]. When inferior vena cava is not or cannot be evaluated during echocardiography (echo-CG), a fixed estimate of 10 mmHg is usually added if signs of central venous congestion (e.g. jugular venous distention) are not detectable. The presence of PH by Eco-Doppler is considered very probable with PASP values >50 mmHg and/or Vmax values >3.4 m/s. PASP values between 35 and 49 and Vmax values between 2.8 and 3.4 m/s can be considered suggestive, although not diagnostic, of PH. Although superior to clinical history and physical examination [4, 5], Doppler estimation of pulmonary artery pressure may become problematic when the tricuspid regurgitation jet is difficult to be assessed [6]. Furthermore, even if technically possible, the estimates of pulmonary artery pressure by Doppler echocardiography may be frequently inaccurate [6]. Other echo-CG parameters, such as right and left atrial volumes, systolic and diastolic function of the left ventricle (LV), right ventricular size, valve anatomy and functioning and the presence/absence of pericardial effusion, give useful complementary information for the diagnosis and the prognostic evaluation of PH [7].

Classification of Pulmonary Hypertension

The World Health Organization (WHO) has condensed all forms of PH into five main groups [8] (Table 14.1). Group I in the WHO classification includes all forms of pulmonary arterial hypertension (PAH), (Idiopathic (IPAH),

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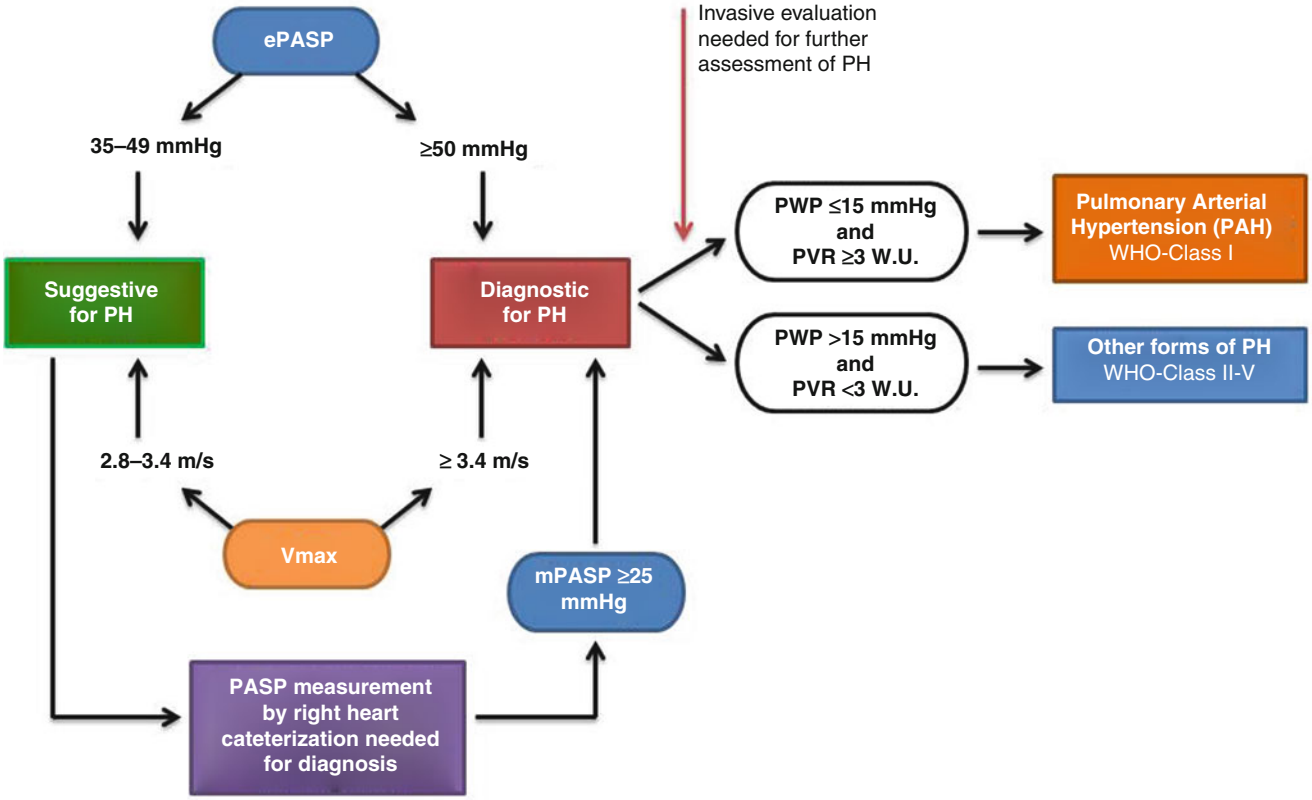

Fig. 14.1 Diagnostic algorithm of PH

Table 14.1 WHO classification of pulmonary hypertension (PH)

Group	Definition	Conditions
I	Pulmonary arterial hypertension (PAH) Idiopathic (IPAH) Familial (FPAH) Associated (APAH)	Congenital heart disease, connective tissue diseases, drugs and toxins, HIV infection, portal hypertension, pulmonary veno-occlusive disease
II	PH associated to left heart disorders	Left heart systolic dysfunction, left heart diastolic dysfunction, left-sided valve disease (mitral and/or aortic)
III	PH associated to lung diseases and/or hypoxia	Chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD), sleep apnea
IV	PH associated to chronic thromboembolism	Obstruction of pulmonary arterial vessels (proximal or distal) by thromboemboli, tumors, or foreign bodies
V	PH of unclear or multifactorial etiology	Renal, hematologic, systemic and metabolic disorders

Familial (FPAH) and Associated (APAH)). These forms of PH were formerly recognized as pre-capillary PH because the increase in PAP is mainly attributable to a sustained increase in the arteriolar tone. For diagnosing PAH, in addition to the above-cited criteria, pulmonary wedge pressure (PWP- that is the pressure measured by wedging a pulmonary catheter with an inflated balloon into a small pulmonary arterial branch) should be ≤15 mmHg and the pulmonary vascular resistance (PVR) ≥3 Woods Units [2].

Group II includes the vast majority of cases of PH, namely those associated with the presence left heart disorders. In these patients PWP is >15 mmHg. As the arteriolar tone is usually normal or just slightly increased, PH forms in this group were formerly defined as post-capillary. Group III and IV comprises any form of PH consequent to lung diseases and/or hypoxia and chronic thromboembolism, respectively. All forms of PH with unclear or multifactorial etiologies are eventually labeled as Group V PH.

Epidemiology of PH

Prevalence of PH in the General Population

In last years, evidence has been accumulated showing that mild to moderate forms of PH are much more common than usually supposed [7]. PH often remain undetected because of the long, preclinical asymptomatic phase and mostly suspected only when the clinical signs and symptoms of right ventricular dysfunction (dyspnea, fatigue, non-productive cough, angina pectoris, syncope, peripheral edema and, rarely, hemoptysis) appear [2]. In the Olmsted county study [9], a general population study conducted in a random sample of the same county, the prevalence of PH defined by a Doppler-derived PASP >35 mmHg in individuals older than 45 years was about 5 %. Most cases of PH detected in this population study were secondary to concomitant heart disorders, particularly those associated with LV function impairment. The presence of PASP was predicted by diastolic dysfunction (as measured by the E/e′ ratio (early trans-mitral flow velocity [E] to early mitral annular tissue velocity [e′]) and by the presence of systemic hypertension and high pulse pressure.

Pre-capillary PH (PAH, WHO Group I) is much more rare with an estimated prevalence of about 15 cases per million and an annual incidence of about 2–3 per million [7]. Adult females are almost three times as likely to present with PAH than adult males. In children, the presentation of PAH is more evenly split along gender lines. As mentioned, WHO group 1 includes a miscellany of forms spanning from PH associated with connective tissue diseases, drugs and various toxic agents sporadic and idiopathic forms. Conversely, the highest prevalence of PH (30 %) is associated with congenital heart disease [10] and sleep breathing disturbances (15–20 %) [11] while a lower prevalence has been reported in systemic sclerosis (7–12 %) [12, 13] and in portal hypertension (2–6 %) [14, 15].

Prevalence of PH in Chronic Kidney Disease

In chronic kidney disease (CKD) patients, it is now widely accepted that PH is a problematic condition not only confined to connective tissue and systemic diseases and that the impairment in kidney function may elicit *per se* the development and/or worsening of this condition. Epidemiological data on PH in CKD patients are scarce and sparse and mainly based on retrospective data. This hampers the possibility to provide precise estimations on the overall prevalence of PH in the CKD population. Furthermore, in only one study [16] PASP has been measured by right atrial catheterization, the gold-standard method indicated by current guidelines, while in the remainder PASP was estimated by Echo-Doppler with poor or no uniformity in the methodology implemented. Different PASP cut-offs (ranging from 25 to ≥45 mmHg) were considered as indicative of the presence of PH [17–36] and in one study a Vmax ≥2.5 m/s was assumed as the major diagnostic criterion [37]. Such a variability in the diagnostic criteria adopted by these studies explains the reported wide range of PH prevalence in CKD patients and limits the possibility to perform crude comparisons between studies.

No data on the prevalence of PH in early CKD stages [1–3] are currently available. Among pre-dialysis patients with CKD stage 5 (CKD-5 ND), the prevalence of PH is about two to eight times higher than in the general population, ranging from 9 to 39 % [17, 19–22]. PH prevalence is higher in the dialysis population (CKD-5D) than in CKD-5 ND patients. In the only study measuring PAP by invasive methods [16], PH was present in 81 % of HD and 71 % of CKD stage 4–5 patients. In this selected population, the prevalence of (pre-capillary) pulmonary artery hypertension (WHO Group I) was 6 % in CKD stage 4–5 patients and 13 % in HD patients and the prevalence of WHO Group-II PH was 71 and 65 % respectively. With regard to dialysis modality, the prevalence of PH is lower in patients on peritoneal dialysis (from 0 to 42 %) than in hemodialysis patients (from 18.8 to 68.8 %) [23, 28–31, 33–36]. The presence of artero-venous fistula (AVF) in HD patients has been hypothesized as one of the possible explanations underlying this difference (see below). In studies directly comparing HD and PD patients of the same center, PH was notably less prevalent in PD patients [21, 23, 28, 31]. Restricted evidence on PH in CKD has been accrued in western countries [19, 30–34, 37] while the majority of investigations were performed in the Middle East [17, 18, 20–29, 35]. In five studies performed in the US [19, 32–34, 37] the prevalence of PH ranged from 25 to 47 %. This prevalence resulted more homogenous (32–42 %) in the four studies that referred to the same diagnostic PASP cut-off (≥35 mmHg) [19, 32–34].

Risk Factors for PH in CKD Patients

As for PH in the general population, the vast majority of factors responsible for PH in CKD patients still remains poorly defined. Because most cases of PH in CKD patients are post-capillary in nature (WHO group II) [16], these forms are likely to depend mostly on the presence of associated LV disorders, which are quite prevalent in CKD and, particularly in HD patients. Even though the impairment of left heart plays a key role in the genesis of PH, yet most CKD patients often present with further conditions able to induce and/or exacerbate PH with mechanism(s) acting at the pre-capillary level (Fig. 14.2).

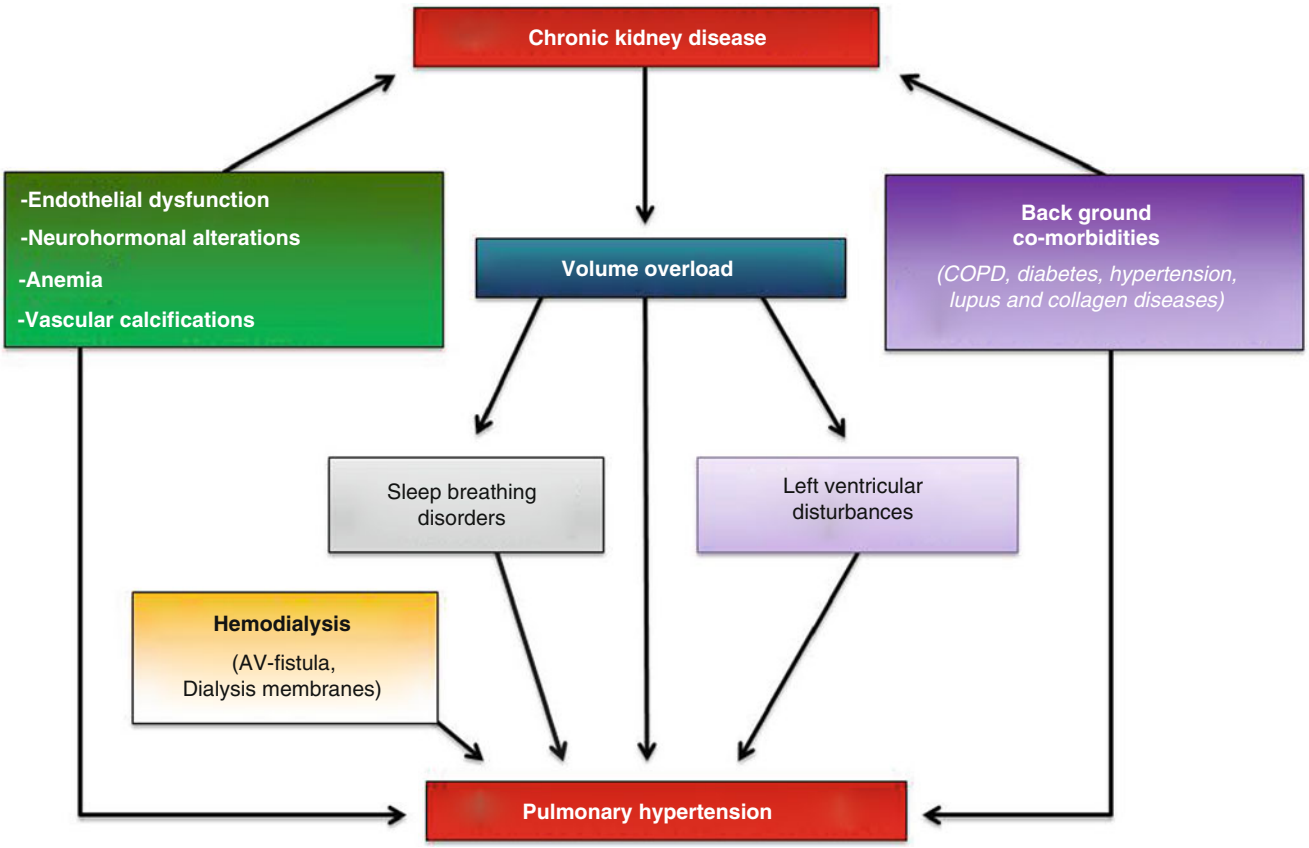

Fig. 14.2 Complex interplay mechanism among CKD and other risk factors in determining PH

Artero-venous Fistula

The presence of artero-venous fistulas (AVF) may in part explain the higher prevalence of PH among HD patients undergoing chronic replacement therapy than in PD or in CKD patients not on dialysis [18, 28, 31]. Evidences in HD patients indicate a rise in pulmonary pressures in strict parallelism with AVF creation [38]. Furthermore, PH tends to worsen overtime in the HD population [22, 31] and AVF-flow and AVF-duration are independently correlated with the severity of PH [20]. Temporary AVF compression by a sphygmomanometer [18, 21, 24] or surgical AVF closure [39] are both able to induce a rapid decrease in the mean cardiac output followed by a stable decline in pulmonary pressures. Many hypotheses have been proposed to explain the role of AVF in the pathogenesis and worsening of PH. AVF, be them traumatic or intentionally created, is known to exert profound hemodynamic effects such as decreased systemic vascular resistances, enhanced venous return and increased cardiac output to maintain proper blood flow to all organs and tissues. These adaptations might increase pulmonary blood flow and prepare the ground for pulmonary hypertension. Because pressure is the product of flow and resistance, at any level of pulmonary vascular resistance, increased pulmonary flow necessarily leads to increased pressure. Although important, the presence of AVF alone fails to explain the highest prevalence of PH observed in the dialysis population. The demonstration that kidney transplantation may revert to normal pulmonary artery pressure in patients who still have a functioning AVF [18] suggests that other factors than AVF might play an equally significant role.

Endothelial Dysfunction

Endothelial dysfunction – that is a systemic pathological state characterized by an imbalance between vasodilating and vasoconstricting substances produced by (or acting on) the endothelium- is a major determinant of PH [40] and is highly pervasive in CKD patients, especially in dialysis patients [41]. The hypothesis that endothelial dysfunction might play a central role in the genesis of PH in HD patients is supported by cross-sectional findings showing that plasma levels of nitric oxide (NO, a powerful vasodilator) are reduced in HD patients with PH as compared to those without PH and by the observation that in patients without PH,

HD treatment increases NO levels to a greater extent than in those with abnormal pulmonary resistances [24]. Asymmetric dimethyl-arginine (ADMA), an endogenous inhibitor of NO synthase which is copiously synthesized at lung level [42], has been strongly involved in experimental [43] and in primary forms [44] of PH. Since ADMA attains very high concentrations in subjects with renal function impairment [45], this uremic toxin might be considered as an additional factor potentially involved in PH in this population.

Sleep Breathing Disorders

Episodes of nocturnal hypoxia are frequent in both predialysis [46] and dialysis CKD patients [47]. Chronic nocturnal hypoxia is the key pathophysiological effect of a wide spectrum of sleep breathing disorders, including sleep apnea. Nocturnal hypoxemia by sleep apnea, in turn, is a strong trigger of PH in experimental models [48] and a close link between oxygen saturation and pulmonary artery pressure has been established in experimental studies in healthy humans and in patients with chronic lung diseases [49]. In CKD patients, volume overload is the major trigger of sleep apnea. Experimental studies suggest that hypoxemia increases pulmonary pressure by enhancing sympathetic activation [50]. Interestingly, ADMA is increased in patients with sleep breathing disorders [51]. Furthermore, circulating levels of ADMA in CKD patients go along with sympathetic nerve activity measured in the peroneal nerve [52] and with norepinephrine levels in dialysis patients [53]. Given the strong vasoconstriction potential of ADMA in the lung vasculature and the observation that sympathetic system activity and ADMA share a common pathogenic pathway leading to left ventricular hypertrophy and to cardiovascular events in CKD patients [54], it might be possible that this pathway is also somewhat implicated in the genesis of PH in the CKD population.

Exposure to Dialysis Membranes

During HD sessions, blood membrane contact and reversible neutrophil sequestration in the lung causes neutrophils activation [55]. This may contribute to cause and/or worsen microvascular lung disease in HD patients. Neutrophil activation is much marked with cellulosic membranes and it is much attenuated, although not abolished, with modified cellulosic and synthetic membranes. In a crossover trial in a series of 74 patients the use of high flux polysulphone filters was associated with a more pronounced fall in post dialysis pulmonary pressure than the use of cellulose acetate filters [35].

Systemic Diseases Associated with CKD and Other Risk Factors

In CKD patients the control of microvascular tone in the lung might also be affected by several pre-existing connective tissue diseases and superimposed liver, infectious and hematologic diseases. Even though all these conditions may contribute to PH in CKD patients however, collectively, these factors fail to explain the high prevalence of PH associated with CKD because most patients display PH even in the absence of these diseases [56]. Severe anemia is an established cardiovascular risk factor in CKD and its impact on the cardiovascular system includes direct effects to the pulmonary circulation. Low hemoglobin levels could contribute to PH by aggravating hypoxia triggered by concomitant conditions [57]. As a part of a systemic deregulation in mineral metabolism, arterial rigidity is increased in CKD and calcium deposits can be demonstrated in the pulmonary artery in kidney disease, thus implicating arterial stiffness in PH in this population [58]. Indeed, in the Olmsted study PASP was directly related to pulse and systolic pressure as well as to age, suggesting that stiffening of the pulmonary artery may play a role in PH at community level [9]. Experimental studies in the dog show that PTH may per se increase pulmonary resistances [59]. Nevertheless, two different studies in CKD patients [24, 25] failed to demonstrate an association between PTH levels and the severity of pulmonary calcifications and PTH levels were not different between patients with or without PH [24].

PH Is a Risk Factor for Worse Outcomes in CKD

PH is a risk factor for cardiovascular morbidity and mortality in the general population and a large US survey, recording data on all forms of PH over a 22 year-period (1980–2002), documented a stable death rate in patients with PH, ranging from 5.2 to 5.4 per 100,000 [60]. Findings in a cohort of 500 patients with PH WHO-Group 1 [61] indicate that the presence of an impaired renal function conveys a higher risk for PH. Furthermore, in the same cohort pathological serum creatinine levels were associated with higher right atrial pressure, lower cardiac index and an increased risk of death. Data about clinical outcomes in CKD-5 patients with PH are scarce. In one study on pre-dialysis CKD patients, the presence of PH (defined as having a Doppler-estimated PASP ≥45 mmHg) was associated with a higher risk (HR 3.6) of death [17]. In dialysis patients undergoing kidney transplantation the improvement in left ventricular geometry and function is usually associated with a parallel improvement in PH [18, 30]. Information on the impact of PH on cardiovascular outcomes in chronic hemodialysis patients is available

in five studies [17, 21, 24, 36, 37]. In two reports [17, 21] the same cohort has been studied with a different patients accrual and different diagnostic criteria of PH. In the first analysis performed on 58 patients [21], the presence of a Doppler-estimated PASP ≥35 mmHg was associated with a higher mortality rate (30.8 %) as compared to PASP values ≤35 mmHg (3.5 %). In the second analysis conducted on 127 HD patients PH (ePASP ≥45 mmHg) was an independent risk factor for death (HR 2.4) [17]. In 90 chronic HD patients with AVF [37], mortality was four-fold higher in patients with PH, defined by the presence of TRV ≥2.5 m/s (26 %/year), in comparison to those without (6 %). Furthermore PH was related with impaired left systolic ventricular function and elevated pulmonary capillary wedge pressure. Similarly, in another recent study [34] PH had a 38 % prevalence among 228 chronic hemodialysis patients and carried a high death risk (HR 2.17; 95 % CI 1.31–3.61, $P<0.01$) after adjustment for other risk factors. In a Chinese cohort of 278 HD patients [36] the prevalence of PH was reported to be even higher (64.7 %) and PH was an independent predictor of all-cause mortality [HR 1.85; 95 % CI 1.03–3.34] CV mortality [HR 2.36; 95 % CI 1.05–5.31] and CV events [HR 2.27; 95 % CI 1.44–3.58] after multiple adjustment. Interestingly, the presence of PH in 215 HD patients waitlisted for kidney transplant predicted the risk of death after kidney transplantation [19]; this suggests that this procedure may not reverse the excess risk associated with established PH. Whether PH in CKD represents a consequence of concomitant LV disorders with scarce direct impact upon clinical outcomes or whether it represents a truly independent risk factor for death and adverse cardiovascular outcomes still remains an unanswered question. Large prospective studies adopting well standardized criteria including right heart catheterization are eagerly awaited to establish the risk conveyed by the presence of PH in CKD stage-5 ND and in dialysis patients. In particular, epidemiological studies specifically focusing on the CKD population on conservative treatment (therefore, without AVF) are needed to assess the possible influence of PH on clinical outcomes independently of other concomitant cardiovascular or pulmonary diseases. No less important, well designed intervention studies in both pre-dialysis and dialysis cohorts are required to definitively assess if PH in CKD represents a modifiable risk factor.

Treatment of PH in CKD Patients

Current management and future therapeutic approaches for treating PH in the general population have extensively been reviewed elsewhere [62]. In the general population, treatment of PH varies according to the nature/etiology of this pathological condition (arterial, venous, hypoxic, thromboembolic, miscellaneous…). In PH secondary to congestive heart failure, treatments aiming at optimizing left ventricular function and alleviating fluid overload (e.g. diuretics, beta blockers, ACE inhibitors..) may ameliorate pulmonary circulation. The use of vasoactive agents including prostanoids, phosphodiesterase inhibitors or endothelin antagonists is usually limited to patients with established pulmonary arterial hypertension (PAH, WHO class I). Since LV disorders are highly prevalent in the CKD population the majority of CKD patients with PH in can be classified as WHO class II. No solid evidence on the treatment of PH in patients with CKD is available so far. Therefore, the recommendations for the treatment of PH WHO II category in the general population [63] can reasonably be extended also to CKD patients. The amelioration of underlying LV dysfunction appears of foremost importance in CKD stage-5 ND and in dialysis patients. As alluded to before, sleep apnea, which is highly prevalent among CKD stage-5 ND and dialysis patients, may elicit PH. Sleep apnea is currently ascribed in large part to rostral edema (edema in the hypopharynx). Rostral edema aggravates with supine position and with hypopharynx relaxation during nocturnal sleep [64]. Reduction or correction of volume excess by hemodialysis treatment intensification [65] or by peritoneal dialysis [66] produces a dramatic improvement in sleep apnea. Although there is still no proof that in dialysis patients this translates into a meaningful reduction in PASP, sleep breathing disorders should be systematically suspected and investigated in CKD patients with high PASP. Furthermore, on the basis of several observations in patients with other forms of sleep apnea, a beneficial effect on PH seems likely in dialysis patients. A randomized trial testing the vasodilator agent epoprostenol in 471 patients with PH and severe LV dysfunction was terminated ahead of time due to an increase in mortality in the treatment arm [67]. Therefore, vasodilator therapy, currently suggested for patients with established pre-capillary PH (WHO-I) should be avoided in CKD patients with PH secondary to LV disorders because potentially harmful while in CKD patients with WHO Group I PAH, these therapies should be considered on the basis of the individual risk benefit profile. In dialysis patients with persisting PH after correction of volume overload and adequate treatment of LV dysfunction, direct PH measurement by right heart catheterization and pulmonary wedge pressure evaluation might reveal whether the clinical assessment is accurate and can be helpful in discriminating whether further treatment for volume overload and/or LV dysfunction is needed. In few cases a direct treatment targeting PAH might even be indicated. Finally, interventions aimed at reducing artero-venous flow may be considered whenever clinically indicated in patients with PH and high AVF flow.

Conclusions

PH is highly prevalent in CKD patients, particularly in stage 5 patients on chronic replacement therapy by hemodialysis (Tables 14.2 and 14.3). Apart from the presence of other co-morbidities or systemic diseases, several CKD-specific risk factors including the presence of artero-venous fistula, fluid overload, sleep breathing disorders and the exposure to dialysis membranes can be implicated at various level in the genesis of CKD. PH in CKD is a potentially reversible process because, along with associated LV disorders, it may regress after kidney transplantation. However, in dialysis patients with established PH the excess risk for death may persist after kidney transplantation. PH was associated with a higher risk of death in small cohort studies conducted on stage 5 CKD pre-dialysis and dialysis patients. Large prospective studies adopting well standardized criteria of PAP measurement, such as right heart catheterization, are needed to clarify the risk of PH in CKD stage-5 ND and in dialysis patients.

Table 14.2 Summary of main studies available on PH in pre-dialysis CKD

Pulmonary hypertension in pre-dialysis					
Study, year	Country	Patients	PH diagnostic criteria	PH prevalence (%)	Findings
Pabst et al. [16], 2012	Germany	31	mPASP ≥25 mmHg	71	Evidence of pre-capillary PH in 6 % of patients and post-capillary in 71 %
Yigla et al. [17], 2009	Israel	127	ePASP ≥45 mmHg	13.4	PH before HD initiation was associated with a higher risk of death (HR 3.6)
Issa et al. [19], 2008	US	215	ePASP ≥35 mmHg	25	PASP ≥50 mmHg was independently associated with reduced post-transplant survival (HR:3.75)
Abdelwhab and Elshinnawy [20], 2008	Egypt	31	ePASP ≥35 mmHg	32.3	Mean PASP was significantly higher in HD patients than in CKD patients
Yigla et al. [21], 2003	Israel	12	ePASP ≥35 mmHg	8.3	After HD initiation, PH developed in 2/3 of CKD patients with an initially normal PASP
Havlucu et al. [22], 2007	Turkey	23	ePASP ≥35 mmHg	39.1	44 % of CKD patients with PH had an AVF

AVF arterio-venous fistula, *CKD* chronic kidney disease (pre-dialysis), *CI* confidence interval, *ePASP* estimated pulmonary artery pressure (echocardiography), *mPASP* measured pulmonary artery pressure (right heart catheterization), *HD* hemodialysis, *HR* hazard ratio, *PH* pulmonary hypertension

Table 14.3 Summary of main studies available on PH in dialysis CKD patients

Pulmonary hypertension in dialysis					
Study, year	Country	Patients	PH criteria	PH prevalence	Findings
Pabst et al. [16], 2012	Germany	31 HD	mPASP ≥25 mmHg	81 %	PH was post-capillary in 77 % and pre-capillary in 13 % of HD patients. There was a significant decrease of mPAP and PWP after dialysis
Yigla et al. [17], 2009	Israel	127 HD	ePASP ≥45 mmHg	29.1 %	PH after HD initiation was associated with a higher risk of death (HR 2.4)
Nakhoul et al. [18], 2005	Israel	42 HD	ePASP ≥25 mmHg (at rest) ePASP ≥30 mmHg (at exercise)	48 %	Higher cardiac output and lower circulating levels of NO metabolites in patients with PH compared to those without
Issa et al. [19], 2008	US	215 CKD/ HD/PD	ePASP ≥35 mmHg	32 %	No differences in mean PH between HD and PD patients. PASP ≥50 mmHg was independently associated with reduced post-transplant survival (HR:3.75)
Abdelwhab and Elshinnawy [20], 2008	Egypt	45 HD	ePASP ≥35 mmHg	44.4 %	PASP correlated to AVF blood flow, proBNP and LVDD
Yigla et al. [21], 2003	Israel	58 HD 5 PD	ePASP ≥35 mmHg	39.7 % HD 0 % PD	Higher mortality rate (30.8 % vs 3.5 %) in HD patients with PH compared to those without
Havlucu et al. [22], 2007	Turkey	25 HD	ePASP ≥35 mmHg	56 %	PASP was correlated directly to AVF flow and AVF duration and inversely to residual urine volume

(continued)

Table 14.3 (continued)

Pulmonary hypertension in dialysis					
Study, year	Country	Patients	PH criteria	PH prevalence	Findings
Bozbass et al. [23], 2009	Turkey	432 HD 68 PD	ePASP ≥30 mmHg	18.8 % HD 5.9 % PD	No differences in the prevalence of chronic obstructive pulmonary artery disease, asthma, smoking, hypertension and diabetes mellitus between patients with or without PH
Yigla et al. [24], 2004	Israel	49 HD	ePASP ≥35 mmHg	57.1 %	No correlations between severity of pulmonary calcifications and PH
Amin et al. [25], 2003	Egypt	51 HD	ePASP ≥35 mmHg	29 %	No correlations between PH and PTH levels or pulmonary calcifications
Tarrass et al. [26], 2006	Morocco	86 HD	ePASP ≥35 mmHg	26.7 %	No correlations between PH and PTH levels
Mahdavi-Mazdeh et al. [27], 2008	Iran	62 HD	ePASP ≥35 mmHg	51.6 %	Hemoglobin and albumin levels significantly lower in patients with PH
Etemadi et al. [28], 2012	Iran	278 HD 145 PD	ePASP ≥35 mmHg	41.1 % HD 18.7 % PD	Serum iron and hemoglobin significantly lower in patients with PH
Unal et al. [29], 2009	Turkey	135 PD	ePASP ≥35 mmHg	12.6 %	PASP independently associated with ECW and LVMI
Casas-Aparicio et al. [30], 2010	Mexico	35 HD	ePASP ≥40 mmHg	48.6 %	After kidney transplantation, LVF and ePASP significantly improved and PH prevalence decreases to 15.3 %
Fabbian et al. [31], 2011	Italy	29 HD 27 PD	ePASP ≥35 mmHg	58.6 % HD 18.5 % PD	PH independently associated with dialysis vintage and diastolic pressure
Zlotnick et al. [32], 2010	US	55 HD	ePASP ≥35 mmHg	38 %	PH in dialysis patients was associated with an increased risk of early graft dysfunction
Kumbar et al. [33], 2007	US	36 PD	ePASP ≥35 mmHg	42 %	PASP correlated to serum phosphorus, CaxP and PTH
Agarwal [34], 2012	US	288 HD	ePASP ≥35 mmHg	38 %	In multivariate analyses, PH was an independent predictor for all-cause mortality [HR 2.17; 95 % CI 1.31–3.61, P<0.01]
Kiykim et al. [35], 2010	Turkey	74 HD	ePASP ≥30 mmHg	68.8 %	Decrease in pulmonary artery pressure following HD procedure performed using high-flux polysulfone membrane
Li et al. [36], 2014	China	278 HD	ePASP ≥30 mmHg	64.7 %	In a multivariate Cox analysis, PH was an independent predictor of all-cause mortality [HR 1.85; 95 % CI 1.03–3.34] CV mortality [HR 2.36; 95 % CI 1.05–5.31] and CV events [HR 2.27; 95 % CI 1.44–3.58]
Ramasubbu et al. [37], 2010	US	90 HD	Vmax ≥2.5 m/s	47 %	After 12 months, patients with PH had increased mortality (26 %) compared to those without (6 %)

AVF arterio-venous fistula, *BNP* brain natriuretic peptide, *CaxP* calcium phosphate product, *CKD* chronic kidney disease (pre-dialysis), *CI* confidence interval, *CV* cardio-vascular, *ECW* extra-cellular water, *ePASP* estimated pulmonary artery pressure (echo-cardiography), *mPASP* measured pulmonary artery pressure (right heart catheterization), *HD* hemodialysis, *HR* hazard ratio, *LVDD* left ventricular diastolic dysfunction, *LVF* left ventricular function, *LVMI* left ventricular mass index, *NO* nitric oxide, *PAH* pulmonary arterial hypertension, *PH* pulmonary hypertension, *PWP* pulmonary wedge pressure, *PD* peritoneal dialysis, *Vmax* maximum tricuspidal jet regurgitation velocity

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How to Use Inhibitors of the Renin-Angiotensin-Aldosterone System in Patients with CKD and Heart Failure

15

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Introduction

Heart failure (HF) is the leading cardiovascular (CV) complication in patients with chronic kidney disease (CKD) and its prevalence increases with declining kidney function [1]. In the Atherosclerosis Risk in Communities (ARIC) Study [2], a large, population-based study of U.S. adults, the incidence of HF was three-fold higher in individuals with an estimated glomerular filtration rate (GFR) <60 mL/min/1.73 m^2, compared with the reference group with an estimated GFR ≥90 mL/min/1.73 m^2. According to the 2009 U.S. Renal Data System (USRDS) Annual Report Data [3], the prevalence of HF in the elderly U.S. population (>65 years-old) was 7.4 % in non-CKD individuals, whereas in patients with CKD stages 4 and 5 this percentage raised to 42 %. In dialysis patients, the prevalence of HF ranges from 30 to 40 % [4–7]. In a study by Harnett et al. [7], almost one-third of end-stage renal disease (ESRD) patients had HF at initiation of dialysis and more than half of these manifested recurrence of HF later on, whereas among patients without previous HF, 25 % subsequently developed HF during dialysis. However, the Dialysis Outcomes and Practice Patterns Study (DOPPS) showed considerable geographic variability in the prevalence of HF in hemodialysis populations – namely, 46 % in the U.S., but only 25 % in Europe and as low as 6 % in Japan [8]; to some extent, such differences may be explained by the fact that the U.S. patients were older and had more diabetes, coronary artery disease and other vascular diseases than their European and Japanese counterparts.

The presence of HF at the start of dialysis is a strong and independent predictor of short-term [9] and long-term mortality, in both hemodialysis [7] and peritoneal dialysis patients [10]. The median survival of dialysis patients with baseline HF has been estimated to be 36 months, in contrast with 62 months for those without baseline HF [7]. Over 80 % of ESRD patients recently diagnosed with HF are expected to die within only 3 years from the time of this diagnosis [11].

Finally, it must be noted that the relationship between CKD and HF is reciprocal, i.e. renal impairment is very common among patients with HF, as well. In recent cohort studies and randomized controlled trials, CKD was detected in 35–70 % of HF patients [12]. For example, in a study by de Silva et al. [13] of 1,216 patients with chronic stable HF, only 7 % had an estimated GFR ≥90 mL/min/1.73 m^2. The presence of CKD is associated with an increased hospitalization rate for worsening HF and all-cause and CV mortality; the hazard ratio for all-cause mortality in HF patients with CKD is about 1.3–2.9 compared to those without CKD [12]. Patients with HF have a 1 % increase in mortality for each 1-mL/min decrease in GFR [14]. Moreover, it was shown that GFR is the most powerful predictor of mortality in patients with HF, ahead of functional status and ejection fraction (EF) [15].

The treatment of HF in patients with CKD is unclear, as there is very little strong evidence to support any recommendations. Guidelines for the management of HF in the general population may not apply entirely to those with CKD, since such patients (particularly those with severe renal impairment) were quite often excluded from most of the RCTs that served as a rationale for these guidelines. The paucity of specific evidence and recommendations may explain why CKD patients with HF are less likely to receive certain therapies that are commonly used in the general HF population. Wang and Sanderson [16] pointed out that the main objectives of HF therapy in CKD (as well as in non-CKD) patients are the

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following: (1) to decrease the preload and afterload and to reduce left ventricular hypertrophy (LVH); (2) to treat myocardial ischemia; and (3) to inhibit neurohumoral hyperactivity, especially the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS).

The rationale for RAAS blockade therapy in CKD patients with HF is supported by many pathophysiological considerations. Excess angiotensin II can accumulate in the heart and promote myocyte hypertrophy, interstitial fibrosis, microvascular disease, as well as cardiac conduction disturbances, QT prolongation, and arrhythmias [17]. Additionally, high serum aldosterone, resulting from activation of renin-angiotensin system or other pathways, can induce myocardial fibrosis, possibly by release of transforming growth factor β [18, 19].

Angiotensin-Converting Enzyme Inhibitors

A subject of many studies, the mechanisms of angiotensin-converting enzyme inhibitors (ACEIs) in HF are complex and still not completely understood. By blocking the conversion of angiotensin I to angiotensin II, these drugs promote vasodilation (by reducing the vasoconstrictive effect of angiotensin II) and renal sodium excretion (by decreasing aldosterone release). They inhibit the cardiac RAAS, which is involved in LV hypertrophy and dysfunction. They also block the degradation of bradykinins, thereby stimulating the synthesis of prostaglandins and nitric oxide, which seem to prevent LVH, as well. Other significant effects of ACEIs include the reduction of sympathetic activity, improvement of endothelial function, decrease of proinflammatory cytokines and prothrombotic factors, and stimulation of fibrinolytic factors. All these mechanisms contribute to the improvement of pulmonary, right ventricular and skeletal muscle function, and the increase of arterial compliance [20].

ACEIs have been evaluated in more than 7,000 patients with systolic HF, in over 30 placebo-controlled clinical trials. Analyses of these studies showed that these drugs can alleviate symptoms, improve functional status, and reduce the risk of death and hospitalization. These benefits were seen in patients with various severity and causes of HF. U.S. and European guidelines recommend prescription of ACEIs to all patients with HF due to systolic dysfunction (LVEF ≤40 %), irrespective of symptoms, unless contraindicated or not tolerated. Treatment should be initiated at low doses and gradually increased thereafter. The most common adverse effects of ACEIs are hypotension, acute kidney injury, hyperkalemia, and cough. During ACEI therapy, serum creatinine and potassium should be assessed periodically, especially in patients with diabetes and/or CKD [21, 22].

The use of ACEIs in patients with CKD and HF seems reasonable, given the well-established simultaneous cardio- and renoprotective effects of these drugs [23]. However, there is little evidence that treatment with ACEIs reduces CV morbidity and mortality in this particular population [18]. Furthermore, clinicians are often concerned about the possibly increased risk of adverse reactions from ACEI use in HF patients with impaired kidney function [23].

Experimental studies in animal models of uremia showed that ACEIs are able to prevent LVH and cardiomyocyte loss [24, 25], whereas administration of a bradykinin receptor inhibitor completely antagonize these effects [25], suggesting that the beneficial effects of ACE inhibitors on the CV system may be mediated through bradykinin.

Several observational studies have suggested a favorable impact of ACEIs on survival in patients with CKD and HF. McAlister et al. [14] analyzed data from a prospective cohort of 754 patients with HF and found significant reductions in 1-year mortality with ACEIs and beta-blockers treatments in patients with eGFR <60 mL/min, as well as in those with eGFR ≥60 mL/min. A retrospective cohort study of 20,902 hospitalized elderly patients with a LV ejection fraction (LVEF) <40 % [26] showed that, after adjustment for multiple confounders, the prescription of an ACEI on hospital discharge was associated with a significant reduction in mortality; notably, this reduction was greater in patients with serum creatinine >3 mg/dL (n = 1,582) than in the rest of the cohort (37 % versus 16 %). Using propensity scores and multivariable-adjusted Cox regression analyses, Ahmed et al. [27] estimated the effect of ACEIs on 2-year outcomes in 1,707 patients with CKD, taken from the 6,800 patients with systolic HF (LVEF ≤45 %) in the Digitalis Investigation Group trial. In this study, CKD was defined as serum creatinine ≥1.5 mg/dL for men and ≥1.3 mg/dL for women. Patients taking ACEIs had significantly lower rates of mortality (hazard ratio = 0.58) and all-cause hospitalizations (hazard ratio = 0.69), compared to those not taking ACEIs.

Moreover, benefits of ACEIs in patients with CKD and HF have been demonstrated by several *post hoc* analyses of RCTs conducted in the general HF population. The Survival And Ventricular Enlargement (SAVE) study was a randomized trial of captopril *versus* placebo in 2,231 patients with acute myocardial infarction and LVEF ≤40 %. Patients with serum creatinine <2.5 mg/dL were excluded. A secondary analysis of this trial showed that captopril was equally efficacious in subjects with CKD (defined as eGFR <60 mL/min/1.73 m^2) and those without CKD. The relative risk reduction in CV events and mortality due to captopril was actually higher in subjects with CKD (31 % *versus* 20 %); however, the interaction between study drug and CKD was not statistically significant [28]. In the Studies of Left Ventricular Dysfunction (SOLVD) Treatment trial, 2,569 ambulatory chronic HF patients with LVEF ≤35 % and serum creatinine ≤2.5 mg/dl were randomized to receive either placebo or enalapril. Of the 2,502 patients with baseline serum creatinine data, 1,036 had CKD (eGFR <60 ml/

min/1.73 m^2). The median follow-up was 35 months. Compared to placebo, enalapril significantly decreased all-cause mortality in non-CKD, but not in CKD patients (hazard ratio 0.82 versus 0.88). However, enalapril did reduce CV hospitalization in both patients with and without CKD (hazard ratio 0.77 versus 0.80). Among patients in the enalapril group, serum creatinine elevation was significantly higher in those without CKD (0.09 versus 0.04 mg/dL) during first year of follow-up, but there were no differences in changes in serum potassium (mean increase, 0.2 mEq/L, in both) [29].

In dialysis patients, observational studies have shown that ACEIs can reduce LVH [30, 31] and improve survival and CV outcomes [32], and these benefits appeared to be independent of their blood pressure-lowering effect. However, a double-blind placebo-controlled RCT in 397 hemodialysis patients with LVH [33] failed to show any significant effect of ACEI fosinopril on a composite CV end-point. The study was, nevertheless, underpowered to estimate the impact of fosinopril on survival. Chang et al. evaluated the effects of ACEI use among hemodialysis patients that participated in the HEMO study [34]. Using proportional hazards regression and a propensity score analysis, the authors found no significant associations between ACEI use and mortality, CV hospitalization, and other CV outcomes. Surprisingly, in the proportional hazards model, ACEI use was even associated with a higher risk of HF hospitalization. A retrospective analysis of the data from the Minnesota Heart Survey [35] revealed that dialysis patients hospitalized with HF had no benefit from ACEI or ARB treatment, for either short-term (30 days) or long-term (1 year) survival, in striking contrast with all of the other HF patients.

Several concerns exist for the use of ACEIs and ARBs in patients with CKD, particularly about the risk of hyperkalemia and worsening of renal function. However, these effects are usually transient and mild.

A meta-analysis of five placebo-controlled RCTs with ACEIs in patients with HF showed that, although the rate of acute kidney injury was higher with ACEIs than with placebo, drug discontinuation was rarely necessary, and renal function returned to baseline in most cases, even without dose adjustment [23, 36]. Furthermore, a systematic review of 12 RCTs with ACEIs for renoprotection in patients with CKD showed that a mild increase in serum creatinine (up to 30 % from baseline) was quite common within the first 2 weeks of therapy; however, this increase was followed by stabilization during the next few weeks [23, 37]. In patients with both HF and CKD, a retrospective analysis of the SOLVD studies has shown that the use of ACEIs was associated with a reduction of mortality, even in those with severe renal insufficiency, and did not have an adverse effect on kidney function [38]. Therefore, ACEIs should not be contraindicated in patients with HF and CKD, and a mild and non-progressive worsening of renal function at the start of therapy should not be considered, *per se*, as an indication to discontinue treatment [23]. However, when the GFR falls by >30 % of the pretreatment baseline, ACEI administration should be halted. Patients should then be evaluated for conditions causing renal hypoperfusion, such as volume depletion (e.g. from diuretics), renal vasoconstriction (e.g. induced by NSAIDs), and severe bilateral renal artery stenosis or stenosis in a single kidney. Unless renovascular disease is found, ACEI therapy can be resumed after correction of the underlying cause of renal ischemia and resolution of the acute kidney injury episode [23]. Reducing the daily diuretic and/or ACEI dose may prevent future worsening of the renal function [39]. It is generally recommended to begin at 15–25 % of the goal dose and, based upon changes in blood pressure and GFR, to increase every 4–8 weeks by 25–50 % until the target dose or the highest tolerated dose is reached [40].

The risk of hyperkalemia associated with the use of ACEIs is also a source of concern. In a retrospective analysis of the SOLVD trials, in patients with HF treated with enalapril the incidence of hyperkalemia ≥5.5 mEq/L was 6 %, overall; it was higher than in the placebo group and it increased progressively with the severity of the renal dysfunction [23, 41]. Careful monitoring of serum potassium is warranted in all patients with GFR <60 mL/min undergoing ACEI therapy. Concurrent use of other potentially hyperkalemia-inducing drugs, such as NSAIDs, ARBs, and potassium-sparing diuretics, should be avoided or minimized, if possible. A low potassium diet, as well as sodium bicarbonate administration in patients with metabolic acidosis, is also indicated [42]. A potassium level over 5.5 mEq/L should prompt a reduction in the ACEI dose. If the potassium concentration remains high despite the above measures, the ACEI should be discontinued [23, 42]. In patients with severe renal impairment, ACEIs should always be used with caution, because of their potential risk for adverse events.

Angiotensin II Receptor Blockers

Experience with ARBs in HF trials is much smaller than that with ACEIs. However, several studies showed that ARBs produce hemodynamic, neurohormonal, and clinical effects similar to ACEIs. The ARBs valsartan and candesartan were associated with a reduction in hospitalizations and mortality in two HF RCTs [43, 44]. Given the existing evidence, ACEIs are currently recommended as the first choice for RAAS inhibition in HF, but ARBs are a reasonable alternative, especially for patients who cannot tolerate ACEIs because of cough or angioedema [22]. Side effects like hypotension, worsening renal function, and hyperkalemia are as common as for ACEIs. Therefore, caution is required, by starting treatment at very low doses, followed by slow,

step-by-step increases. Additionally, blood pressure, renal function, and serum potassium should be closely monitored.

The dual blockade of the RAAS for the treatment of HF, using a combination of an ACEI with an ARB, seems a reasonable approach. It was shown to reduce the LV size more than either agent alone [45]. However, the clinical benefits of this combination are uncertain. A trial in patients with HF post-myocardial infarction showed that combined therapy did not improve outcomes and resulted in more side effects, compared to each of the two drugs [46]. The addition of ARBs to chronic ACEI therapy caused a modest decrease in hospitalization in two studies, with a trend to decreased total mortality in one and no impact on mortality in another [22, 44, 45, 47]. Furthermore, the American College of Cardiology/American Heart Association guidelines suggest that this combination increases the risks of adverse effects [22].

In a study of patients with diabetic nephropathy and CKD stages 3–4, ARBs decreased the risk of developing HF [48]. In a *post hoc* analysis of the Telmisartan Randomized Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease (TRANSCEND) and the Ongoing Telmisartan Alone and in Combination With Ramipril Global End Point Trial (ONTARGET), Tobe et al. [49] examined renal and CV outcomes in renal subgroups, defined by GFR and albuminuria. The main CV outcome was the composite of CV death, myocardial infarction, stroke, or hospitalization for HF. The authors found no CV benefit in any subgroup with either telmisartan versus placebo or with dual therapy (telmisartan plus ramipril) versus monotherapy.

Trials of ARBs in patients with HF and CKD are very scarce. In a recent cohort study of 1,665 elderly patients with systolic HF (LVEF <45 %) and eGFR <60 mL/min/1.73 m^2, followed up for 8 years, Ahmed et al. [50], using a propensity score analysis, found that treatment with ACEIs or ARBs was associated with a significant, but modest reduction in all-cause mortality (hazard ratio 0.86; 95 % confidence interval 0.74–0.996; P = 0.045) and no change in hospitalization for HF. A single RCT has been conducted so far using ARBs in ESRD patients. This multicenter Italian trial [51] included 332 hemodialysis patients with HF (NYHA II–III; LVEF ≤40 %), who were randomized to telmisartan or placebo, in addition to ACEI therapy. At 3 years, telmisartan significantly reduced all-cause mortality (35.1 % vs. 54.4 %; p < 0.001), CV death (30.3 % vs. 43.7 %; p < 0.001), and hospital admission for HF (33.9 % vs. 55.1 %; p < 0.0001). Adverse effects, mainly hypotension, occurred in 16.3 % of the telmisartan group versus 10.7 % in the placebo group.

In conclusion, considering their concurrent CV and renal benefits, we believe that ACEIs should be indicated to all CKD and ESRD patients with systolic HF, unless contraindicated or not tolerated. Alternatively, ARBs can be used, particularly in those who develop cough or angioedema from ACEIs. Dual therapy with ACEIs and ARBs can also be considered, especially in resistant cases, although the advantage over monotherapy is still uncertain and the risk of adverse effects is likely increased. Careful dose titration and clinical monitoring is required to prevent serious side effects, such as hypotension, hyperkalemia, and acute kidney injury. The role of ACEIs and ARBs in patients with CKD and HF with normal LVEF is unknown.

Aldosterone Antagonists

RAAS inhibition with ACEIs and/or ARBs may not be able to maintain adequate suppression of aldosterone production during long-term therapy, because both aldosterone and angiotensin II ultimately can escape the effects of these drugs, resulting in rebound of aldosterone levels [52, 53]. This may be a significant issue in patients with HF, since experimental studies suggest that aldosterone has deleterious effects on the structure and function of the heart, independently of and in addition to those of angiotensin II [22]. Aldosterone stimulates sodium and fluid retention and promotes myocardial remodeling and fibrosis, as well as endothelial dysfunction and atherosclerosis [54, 55]. Aldosterone antagonists (AAs), in addition to ACEIs or ARBs, can provide more complete inhibition of the RAAS, with long-term benefits. However, a higher risk of adverse effects like hyperkalemia and worsening renal function is also to be expected.

Spironolactone and eplerenone were associated with significant reductions in mortality and CV events in patients with systolic HF in the RALES (Randomized Aldactone Evaluation Study) [56] and EPHESUS (Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival) trials [57, 58], respectively. On the other hand, many studies have reported an increased incidence of severe hyperkalemia in HF patients treated with AAs in association with ACEIs [23]. Based on these data, U.S. [22] and European [21] guidelines recommend the addition of an AA to an ACEI or an ARB in selected patients with systolic HF (NYHA class III–IV, LVEF <35 %), but without severe renal dysfunction (serum creatinine ≤2.5 mg/dL in men and ≤2.0 mg/dL in women) and with serum potassium <5.0 mEq/L. Treatment should be initiated at low doses (e.g. 12.5 or 25 mg of spironolactone or eplerenone), followed by a gradual increase (up to a target of 50 mg, if tolerated), under careful surveillance of creatinine and potassium levels. Hyperkalemia and/or worsening of the renal function require dose reduction or even withdrawal of AAs. In men, breast tenderness or enlargement may also occur with spironolactone therapy, in which case switching to eplerenone is indicated. The use of AAs should be avoided whenever

adequate monitoring of potassium and creatinine levels is deemed as not feasible. Furthermore, AAs are contraindicated in association with other potassium-sparing diuretics, with potassium supplements, and with combined ACEIs and ARBs [21, 22].

The effects of AAs on clinical outcomes in patients with HF and moderate or severe CKD are not clear, since both RALES and EPHESUS trials excluded patients with serum creatinine levels >2.5 mg/dL. A prospective RCT in 112 patients with stages 2 and 3 CKD showed a significant improvement in LV mass and arterial stiffness with spironolactone versus placebo, independently of central and peripheral blood pressure changes [59]. In Iran, Taheri et al. conducted a small double-blind RCT of spironolactone 25 mg/day versus placebo, in addition to an ACEI or an ARB, in 16 hemodialysis patients with HF (NYHA class III–IV and LVEF <45 %). After 6 months of treatment, the mean LVEF increased significantly more in the spironolactone group than in the placebo group and the mean LV mass decreased in the spironolactone group, while it increased significantly in the placebo group. The incidence of hyperkalemia was unchanged in both groups [60]. The same research team performed a study with an identical design in 18 peritoneal dialysis patients with HF. They found a significant increase in LVEF in the spironolactone group, but not in the placebo group, and a non-significant increase in serum potassium in both groups [61].

The risk of AA-induced hyperkalemia in patients with advanced CKD has rarely been assessed in prospective studies, but most experts believe that this risk is unacceptably high and may become life-threatening, therefore prohibiting the use of these drugs in patients with severe and end-stage kidney disease. However, it has been suggested that hyperkalemia may be a less serious issue in hemodialysis patients, due to the effective removal of potassium through dialysis, as well as to the ability of these patients to tolerate relatively high levels of potassium without clinical manifestations. Chua et al. recently reviewed 6 RCTs that evaluated the safety of low-dose spironolactone in hemodialysis patients (of which, about 50 % were already on ACEI or ARB therapy). The authors found that the incidence of hyperkalemia with spironolactone treatment was similar to that in control groups; however, all these studies involved small populations of compliant subjects, who were at low risk for hyperkalemia [62].

Large-scale RCTs are required to evaluate the efficacy and safety of AAs in addition to ACEIs or ARBs as a treatment strategy for HF in CKD patients. In stage 3 CKD patients with HF, AAs may be considered, but should be used with great caution, limiting the dose to 25 mg/day, or every other day, and closely monitoring the potassium levels. The AAs should be avoided in patients with CKD stage 4 and 5 [23], although potassium removal by dialysis may lessen the risk of hyperkalemia in patients on renal replacement therapy. The combined use of all three RAAS inhibitors (ACEIs, ARBs, and AAs) cannot be recommended in HF patients, with or without CKD [22].

Future Therapeutic Prospects

Direct renin inhibitors (DRIs) are a newer class of RAAS inhibitors, acting at the first regulatory step of this hormonal system. Initially used as antihypertensive agents, DRIs have more recently been tested in patients with HF. In the ALOFT (Aliskiren Observation of Heart Failure Treatment) Study, which included 302 patients with stable HF, adding the DRI aliskiren to ACEIs or ARBs appeared to be safe and effective in decreasing plasma brain natriuretic peptide (BNP) and urinary aldosterone levels [63]. Two other large trials are underway using aliskiren in HF patients. The ATMOSPHERE (Aliskiren Trial to Minimize Outcomes in Patients with Heart Failure) examines the effect of aliskiren on CV mortality and hospitalization in patients with chronic HF, whereas the ASTRONAUT (Aliskiren Trial on Acute Heart Failure Outcomes) evaluates aliskiren in patients stabilized after acute HF [64]. These studies will shed important light on the role of DRIs in the treatment of HF. However, we should mention here the Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Disease Endpoints (ALTITUDE), which compared aliskiren to placebo, in addition to ACEI or ARB therapy in patients with diabetic nephropathy and CV disease. This study was prematurely stopped, because of the lack of any prospects of showing a treatment benefit, as well as due to safety concerns, including renal dysfunction, hyperkalemia, hypotension, and an unexpected excess of strokes. As a consequence, it has been suggested that dual aliskiren and ACEI/ARB therapy should not be used in patients with hypertension and CKD (eGFR <60 mL/min/1.73 m^2) [63].

BAY 94–8862 is a novel, non-steroidal, mineralocorticoid receptor antagonist with greater selectivity than spironolactone and stronger binding affinity than eplerenone. The very recent MinerAlocorticoid Receptor Antagonist Tolerability Study (ARTS) was a multicentre, randomized, double-blind, placebo-controlled, parallel-group study, aiming to evaluate the safety and tolerability of this new drug in patients with systolic HF (LVEF ≤40 %) and mild-to-moderate CKD (eGFR 30–89 mL/min/1.73 m^2). This study showed that BAY 94–8862 5–10 mg/day was at least as effective as spironolactone 25 or 50 mg/day in decreasing serum levels of BNP and proBNP, as well as albuminuria, but it was associated with lower incidence of hyperkalaemia (5.3 % versus 12.7 %; P = 0.048) [65].

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Erectile and Sex Hormone Dysfunction and Cardiovascular Consequences in CKD

16

Yalcin Solak and Mehmet Kanbay

Introduction

In recent years Erectile Dysfunction (ED) has emerged as an independent predictor of cardiovascular (CV) events. The impact was so great that some attempts have been made to implement ED in well-known CV risk scoring systems. ED has been described as just one manifestation of the generalized atherosclerosis syndrome, similar to angina pectoris. Interestingly ED appears a few years before other clinical manifestations of cardiac disease, particularly in younger patients. Endothelial dysfunction and inflammation were suggested as common denominators of both disorders. Experimental data and clinical studies provided substantial evidence on testosterone deficiency, being associated with worse cardiac outcomes both in the general population and specific patient groups. Hypogonadism was both a cause and also a consequence of traditional cardiovascular risk factors.

Patients with Chronic Kidney Disease (CKD) unfortunately have a high prevalence of ED and CV disease. Inflammation and endothelial dysfunction are rampant in kidney disease. Apart from some small studies, it is not yet clear whether ED offers such a predictive role as in the general population, in patients with CKD. Hypogonadism is also common among CKD patients and to some extent this may be responsible for the unproportionately increased CV disease burden in this population.

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This chapter will discuss ED as a cardiovascular risk factor along with hypogonadism with a particular emphasis on chronic kidney disease context.

What Is Erectile Dysfunction?

Sexual dysfunction in men includes but it is not limited to reduced libido, difficulty reaching orgasm, premature ejaculation and erectile dysfunction. The latter may be the best known/recognized entity by both health professionals and mass media. ED is used almost synonymous for sexual dysfunction in men. ED is defined as the inability to attain or maintain a penile erection sufficient for successful vaginal intercourse [1]. Erectile dysfunction is classified as psychogenic, organic, or mixed. Organic ED may be due tohormonal, neurogenic, vasculogenic (arterial and cavernosal) and drug related [2].

How Common Is ED?

General Population

Erectile dysfunction is a common disorder which primarily inflicts men older than 40 years of age. In an in-depth analysis of prevalence studies, Lewis et al. [3] reported that ED shows an age dependant distribution in the general population. The prevalence of ED varies between 1 and 10 % in men below 40 years, whereas it increases to between 20 and 40 % and 50–100 % in men aged 60–69 and over 70 years, respectively.

Patients with Chronic Kidney Disease

Erectile Dysfunction is a common occurrence in patients with CKD. In a metaanalysis of observational studies [4], the prevalence of ED (of any severity) was found to be 70 %.

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ED prevalence in dialysis patients was higher than that of renal transplant recipients (75 % versus 59 %). On the other hand, there was no difference between hemodialysis and peritoneal dialysis. Notably fewer studies assessed frequency of ED in predialysis CKD patients compared with patients that underwent renal replacement therapies. Mesquita and colleagues [5] evaluated 81 patients with stage 3–5 CKD. The prevalence of ED was 76.5 % in the whole group, 72.3 % in stage 3 CKD, 81.5 % in stage 4 CKD and 85.7 % in stage 5 predialytic CKD patients. In sum, ED is considerably common, both among predialysis CKD and dialysis patients.

Causes and Correlates of ED

Several epidemiologic and observational studies have determined risk factors and correlates of ED in the general population and special patient populations. Among these are diabetes mellitus, hypertension, obesity, smoking, hyperlipidemia, metabolic syndrome, and depression [2, 6–8]. It is evident that many of these disorders are also major risk factors for cardiovascular disease. Main causes of ED are shown in Table 16.1.

Most of the risk factors for ED are also at work for patients with chronic kidney disease. The ESRD population is currently increasingly elderly; moreover diabetes and hypertension are major causes of ESRD requiring dialysis. Older age, hypertension and diabetse mellitus have been found as independent correlates of ED in patients with ESRD [4]. Factors related to ED in uremic patients include risk factors of ED observed in the general population, plus some additional risk factors specific to the CKD population. The latter include anemia [9], and volume overload [10]. Depression has also been determined as a strong independent predictor of ED in dialysis patients.

Table 16.1 Main causes of erectile dysfunction

Metabolic disease
Diabetes mellitus
Chronic kidney disease
Hypogonadism
Hyperprolactinemia
Hypertension
Obesity
Metabolic Syndrome
Dyslipidemia
Liver, Lung and cardiovascular disease
Neurologic disease
Spinal Cord injury
Brain injury
Parkinson disease
Multiple sclerosis
Alzheimer disease
Stroke
Vascular disease
Aging, smoking, and lack of physical exercise
Psychogenic causes
Drug related

Hypogonadism as a Cardiovascular Risk Factor

Epidemiology

Prevalence of testosterone deficiency is estimated between 6 and 9.5 % in the normal population aged 40–75 years [11]. However, the prevalence rises up to 66 % in patients with CKD [12].

Association with Cardiovascular Disease

Male gender has been established as a cardiac risk factor and the culprit has been traditionally attributed to testosterone hormone. However, recent evidence suggest the opposite: deficiency of testosterone may be responsible for increased cardiovascular risk [13]. Epidemiologic data relates testosterone deficiency with increased mortality risk. In a case–control study Khaw and colleagues [14] found that testosterone was inversely associated with all-cause and cardiovascular mortality. Pye et al. [15] evaluated prospective data from the European Male Aging Study (EMAS) on 2,599 community-dwelling men aged 40–79 years in eight European countries. Fifty-five men (2.1 %) were identified as having late-onset hypogonadism. After adjusting for age, body mass index, smoking, and poor general health, men with severe hypogonadism had a 5-fold higher risk of all-cause mortality compared with men without hypogonadism. In a meta-analysis of community-based studies, Araujo et al. [16] found that low endogenous testosterone levels are associated with increased risk of all-cause and CVD death.

Similar trends have been reported among patients with CKD. Yilmaz et al. [17] found that the risk of composite CV events was reduced by 22 % for each 1 nmole/L increment of serum total testosterone level in predialysis CKD patients. In another study conducted on predialysis CKD patients, the presence of stage 3–5 CKD and low testosterone levels were found to be additive risk factors for mortality [18]. Similar findings were also reported for patients undergoing hemodialysis [19].

Pathophysiologic Mechanisms

Hypogonadism is associated with numerous but mild symptoms, hence it is commonly underdiagnosed. Main manifestations of the disorder include, but are not limited to,

reduced energy, mood changes, decreased libido, erectile dysfunction, fatigue, increased visceral fat, loss of muscle tissue. In addition to these protean manifestations, recent studies showed a strong association between hypogonadism and atherosclerosis. The difficulty in evaluation of the relationship stems from sharing of most of the risk factors by the two disorders.

In a population-based cross-sectional study, Svartberg et al. [20] found that lower levels of testosterone in men were associated with higher blood pressure levels and left ventricular hypertrophy. Moreover, replacement of testosterone in hypogonadal men led to decreases in blood pressure. Several mechanisms have been put forward [21].

Epidemiological data suggest that serum testosterone levels are inversely associated with total cholesterol, LDL cholesterol and triglycerides. However, HDL cholesterol also shows a positive correlation with testosterone levels [22]. Some studies reported that testosterone replacement resulted in a decrease in total cholesterol and LDL cholesterol levels, whereas the impact on HDL cholesterol was not that clear [23–25].

Low testosterone levels have been associated with metabolic syndrome and type-2 diabetes mellitus. Stellato and colleagues [26] evaluated the effect of serum testosterone on development of de novo diabetes mellitus. The authors reported that after controlling for potential confounders, diabetes at follow-up was independently predicted by lower baseline levels of free testosterone and sex hormone binding globulin (SHBG). Another study also demonstrated that testosterone and SHBG could predict the development of metabolic syndrome and diabetes in middle-age men [27]. Concentrations of SHBG and total and calculated free testosterone were determined at baseline in 702 middle-aged Finnish men participating in this population-based cohort study. After 11 years of follow-up, men with total testosterone, calculated free testosterone, and SHBG levels in the lower fourth at baseline had a 2.3 odds ratio of developing each for the metabolic syndrome and diabetes mellitus.

SHBG is considered as the probable mediator of this increased risk. Rajala and colleagues [28] found that increased risk of insulin resistance was independently associated with SHBG but not with total testosterone level. Thus the relationship between diabetes mellitus and metabolic syndrome development was stronger for total testosterone than for free testosterone. Moreover, iatrogenic androgen deprivation in patients with prostate cancer is associated with hyperglycemia and metabolic syndrome.

Additional confirmation of this association came from interventional studies. Six-month treatment of hypogonadal men with type II diabetes mellitus and metabolic syndrome with testosterone replacement resulted in improved glycemic control and body composition, compared with the control group [29]. Testosterone replacement therapy reduced HOMA-IR in the overall population by 15.2 % at 6 months and 16.4 % at 12 months. The mechanism of this beneficial effect of testosterone seems to be due to improved insulin resistance rather than direct effects of testosterone on the pancreas.

There is a bidirectional relationship between obesity and hypogonadism. In a population cohort study, Laaksonen et al. [30] showed that men with metabolic syndrome had a 2.6 fold increased risk of developing hypogonadism after 11 years of follow-up, independently of age and other potential confounders. In contrast androgen deprivation studies showed that within a few months after treatment onset, body fat accumulates [31] and there is an increased incidence of new diabetes mellitus type II cases [32].

The relationship between obesity/diabetes and hypogonadism is likely mediated by inflammatory cytokines secreted by the visceral fat tissue. Androgen deprivation therapy is associated with increased levels of proinflammatory and decreased levels of anti-inflammatory cytokines [33, 34]. Schroeder et al. [35] conducted a placebo-controlled study in which they administered oxandrolone to the treatment group for 12 weeks. Compared with placebo treated men, androgen treated cases showed significant and durable reductions in regional abdominal and peripheral adipose tissues along with improved insulin sensitivity. Although the latter study did not measure specific proinflammatory cytokine levels, it may be speculated that level of these markers might have been reduced with the androgen treatment based on the observed reduction in abdominal fat tissue and improved insulin sensitivity since both of which are surrogate markers of increased inflammation.

Endothelial tissue has receptors for androgens. Administration of testosterone results in dilatation of pulmonary and coronary arteries [36]. Oral testosterone treatment resulted in increased myocardial perfusion in hypogonadal men with CAD [37]. Low testosterone level was found to be associated with endothelial dysfunction [38]. In a randomized controlled trial, long-term oral testosterone supplementation in patients with CAD improved brachial artery vasoreactivity [39]. It's believed that testosterone leads both endothelial dependent and endothelial independent vasodilatation (Fig. 16.1) [40, 41].

Hypogonadism in Chronic Kidney Disease: Causes and Consequences

The kidneys are endocrine organ as both a main modulator of endocrine function and major target for hormonal action [42]. Thus chronic kidney disease may affect several hormonal axes. These hormonal changes are depicted in Fig. 16.2. Several factors in addition to hormonal derangements related to kidney dysfunction itself contribute to the

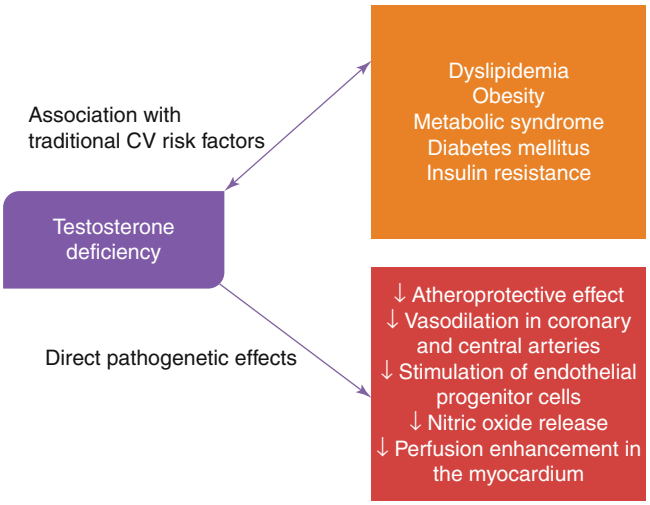

Fig. 16.1 Pathophysiologic effects of testosterone deficiency

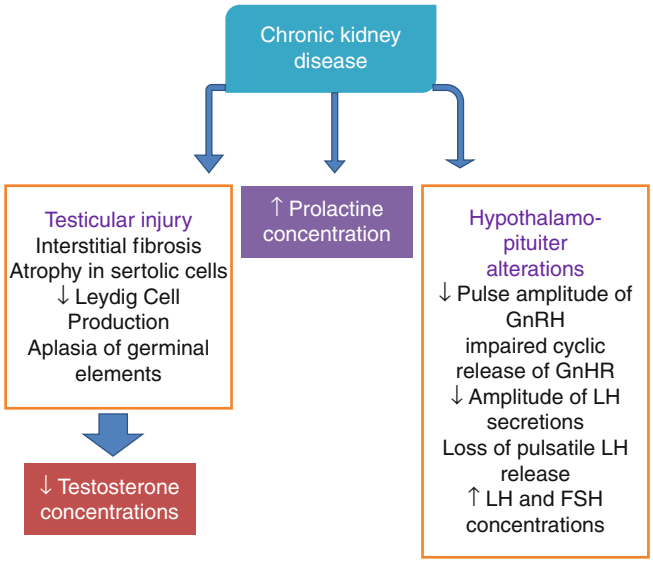

Fig. 16.2 Abnormalities in hormonal functions of HPG axis in patients with CKD

hypergonadotropic hypogonadism seen in CKD. Potential contributor factors are shown in Fig. 16.3.

Testosterone appears to be the pivotal mediator of increased cardiovascular risk in patients with hypogonadism. Plasma total and free testosterone as well as 5α-dihydrotestosterone levels are decreased in ESRD patients. Normalization of serum testosterone and LH levels after successful renal transplantation suggests the central role of uremia in hypergonadotropic hypogonadism [43]. In contrast to renal transplantation, other renal replacement therapies – such as hemodialysis and peritoneal dialysis, do not restore HPG axis. In addition, abnormal gonadotropin responses to GnRH are not corrected by hemodialysis whereas kidney transplantation improves the response [44].

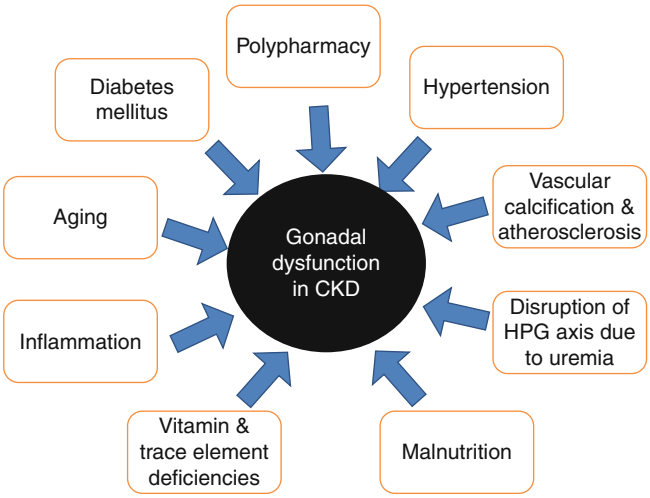

Fig. 16.3 Potential contributory factors of hypergonadotropic hypogonadism of CKD

Hypogonadism in CKD has been implicated in a number of complications. These include anemia, sexual dysfunction and erectile dysfunction, progression of CKD and cardiovascular morbidity and mortality [42].

Erectile Dysfunction-Cardiovascular Disease Nexus

Hypogonadism is just a one contributory factor among many others of erectile dysfunction. Low testosterone levels interacts closely with major atherosclerotic risk factors as described above. On the other hand, ED comprises a wide range of causative factors and associates in addition to hypogonadism. Unsurprisingly, similar to hypogonadism, ED as a whole is independently and strongly related to cardiovascular events. It is likely that endothelial dysfunction and increased inflammation and in many cases hypogonadism are at work leading to erectile dysfunction as well as concomitant coronary atherosclerosis. Compared with difficult to discern and nonspecific symptoms of hypogonadism, ED is apparent and thus, may be used as a early warning sign for simultaneous undiagnosed or future development of cardiovascular disease.

Association of ED with CAD

Several studies investigated frequency of ED in patients with CV disease primarily based on the concomitant risk factors of both disorders. These studies showed an increased prevalence of ED in patients with CV disease. In a seminal study, Montorsi and colleagues [45] reported that 50 % of patients who presented with chest pain and angiographically documented CAD had ED.

Vlachopoulos et al. [46] in a recent meta-analysis evaluated 14 longitudinal studies which looked at the relationship between presence of ED and CV events including mortality (92 757 participants; mean follow-up, 6.1 years). The authors concluded that ED is associated with increased risk of CV events and all-cause mortality. Relative risk was higher at younger ages, and in intermediate-risk groups.

The association between erectile dysfunction and cardiovascular disease has long been recognized. This association was first attributed to sharing of common risk factors for both disorders. Many major CV disease risk factors are at the same time risk factors for ED. These include age, sedentary life-style, smoking, metabolic syndrome, obesity, hypertension, dyslipidemia and diabetes mellitus [47]. However, large epidemiologic and prospective studies established the presence of erectile dysfunction as an independent risk factor for cardiovascular disease. Endothelial dysfunction, inflammation and hypogonadism (or low testosterone levels) have been suggested as the common denominators of both disorders [48–50]. Actually both ED and CV disease share abnormalities in nitric oxide pathway resulting in endothelial dysfunction in the early phase and structural atherosclerotic plaque development in the long-standing disease. It has also been suggested that ED may be the clinical equivalent of angina pectoris, as different manifestations of the same generalized vascular pathology [51].

Normal erectile function is a neurovascular event but modulated also by psychological and hormonal factors. On the other hand, vascular integrity plays a pivotal role in healthy erectile function. The initial abnormal endothelial function transforms into structural changes in small arteries supplying penis just as the case in coronary arteries supplying the myocardium. These structural changes in turn limits the blood supply after a critical occlusion level reached [52]. Montorsi et al. proposed the artery-size hypothesis as a possible explanation of why in some patients ED precedes development of cardiovascular events by 2–5 years [53].

If ED Is Severe, CAD Is Also Severe

The severity of ED has been related to the extent of coronary artery disease by several modalities. A prospective population-based Australian study (the 45 and Up Study) evaluating data of 95,038 men aged ≥45 years found that risk of CVD and death increased steadily with severity of ED. Among men without previous CVD, those with severe versus no erectile dysfunction had significantly increased risks of ischaemic heart disease (adjusted relative risk [RR] = 1.60), heart failure (8.00), peripheral vascular disease (1.92), all CVD combined (1.35), and all-cause mortality (1.93). Moreover, these risks were independent of major traditional cardiovascular risk factors. ED severity assessed by IIEF score was inversely correlated with angiographically proven CAD burden [54]. Multivessel CAD and higher calcification scores were more common among patients with more severe ED [55, 56].

ED and Prediction of CV Events

Erectile dysfunction usually precedes the onset of CAD. Several studies reported this time interval as 2–3 years in CAD symptoms and 3–5 years in cardiovascular events [45]. This relatively early presentation of ED compared with CAD symptoms and CV events has been accounted for by some hypotheses; Artery-size hypothesis suggest early occlusion of smaller penile arteries compared with larger diameter coronary counterparts by the same size atherosclerotic plaque. Another hypothesis suggests that in the younger person with ED impaired vasodilatation of penile arteries is more likely to result in ED than he develops angina due to impaired vasodilatation in coronary arteries [57].

Interestingly, ED is a better predictor of future CV events in younger males aged 40–70 years. In contrast, the prognostic importance of ED in order males >70 years of age is much less powerful.

Inclusion of ED as a risk factor of CAD has been studied in a number of risk prediction models. Incident ED has a predictive value for CV events that is similar or greater than that of smoking dyslipidemia and family history of coronary artery disease [58, 59]. Only one study evaluated addition of ED to Framingham Risk Score (FRS) to date. Araujo et al. [60] found that adding ED to FRS in a population based study including 1,057 males without CVD and diabetes and 40–70 years old did not improve prediction of CV events during 10 year follows up.

Cardiovascular Disease in CKD

Kidney disease is associated with increased CV disease risk. Both proteinuria and reduced GFR are associated with increased risk. A meta-analysis of population based studies reported that compared with eGFR 95 mL/min/1.73 m^2, adjusted HRs for all-cause mortality were 1.18 for eGFR 60 mL/min/1.73 m^2, 1.57 for 45 mL/min/1.73 m^2, and 3.14 for 15 mL/min/1.73 m^2. Similarly albumin to creatinine ratio was also associated with increased risk [61]. This increased risk was also true for specific patient groups such as patients with previous CV disease, hypertension, diabetes or combinations of these [62, 63].

National Kidney Foundation and the American College of Cardiology/American Heart Association to recommend that CKD be considered a CHD risk equivalent [64, 65]. Traditional cardiovascular risk factors such as older age,

hypertension, diabetes, smoking, and dyslipidemia are prevalent in patients with CKD. In addition to these factors some nontraditional or novel risk factors also affect the risk of CV disease in CKD population. These nontraditional risk factors include, but not limited to, uremia, anemia, increased inflammation, endothelial dysfunction, vascular calcification, abnormalities in bone mineral metabolism, and malnutrition-inflammation complex [66, 67]. Several cross-sectional studies have suggested that the Framingham risk scoring is insufficient to capture the extent of CV disease risk in subjects with CKD [68]. This can be explained as effects of nontraditional risk factors and different interaction of traditional risk factors with CV disease risk in CKD patients than general population [64].

Approach to ED as an Harbinger of CV Disease

Since ED has been established as an independent marker of CV disease risk, and can be easily documented with patient interview, ED should be questioned in every patient who is evaluated for overall cardiovascular risk [47]. This is particularly more important in younger patients with seemingly vasculogenic ED.

The Princeton III Consensus offered recommendations for the evaluation and management of cardiovascular risk in men with ED and no known cardiovascular disease, with special emphasis on identification of men with ED who may require additional cardiologic work-up [69]. This report recommends that the initial risk stratification should be based on Framingham Risk Score in patient without prior known CV disease. This initial step stratify patients into three risk groups, namely low risk (≤5 %), intermediate risk (5–20 %) and high risk (≥20 %). High risk patients and symptomatic patients should be referred to cardiologists. Intermediate risk patients are advised to undergo exercise stress test. Patients with an abnormal exercise stress test should be referred to cardiologists. If the test result is negative, carotid intima media thickness, ankle brachial index or coronary calcium scoring can be considered as the next step. All abnormal results should be evaluated by a cardiologist. Patient with low risk and normal noninvasive cardiac workup need risk factor management [47]. Risk factor management and interventions which may prevent CV events are summarized in Table 16.2.

ED at Crossroads Between CKD and CV Disease

Cardiovascular disease is the primary cause of death in patients with CKD. This is so starting from the early stages of the disease. On the other hand ED is also considerably common particularly in patients undergoing dialysis treatment. Since CKD patients suffer from an unproportionately high CV disease burden, early detection and markers which enable us to detect cardiac disease would be invaluable to prevent premature death from CV disease. ED offers such a opportunity in the general population behaving a sort of early warning sign of future CV events. However, it is still not known ED also provides such a predictive data in patients with CKD. This is a paramount clinical need in this vulnerable patient population.

Endothelial dysfunction and increased inflammation are inevitable components of advanced kidney disease. And both of them play fundamental roles in the development of atherosclerosis and erectile dysfunction (Fig. 16.4). What is not known right now is which comes first. Because kidney disease leads to somehow different pathologic consequences in the vascular structures. Dialysis patients with ischemic heart disease may not necessarily have large-vessel occlusive coronary disease. One study [70] showed that up to 50 % of

Table 16.2 Risk factor management and interventions which may prevent CV events in patients with ED

Modification of lifestyle factors
Weight loss
Increased physical exercise
Decreased caloric intake
Management of hypertension, diabetes mellitus, and dyslipidemia
Medication issues
Some medications associated with development or exacerbation of ED
Beta-blockers
Thiazides
Calcium channel blockers
Statins and fibrates
ACE inhibitors
Statins and angiotensin receptor blockers may be associated with improvements in ED

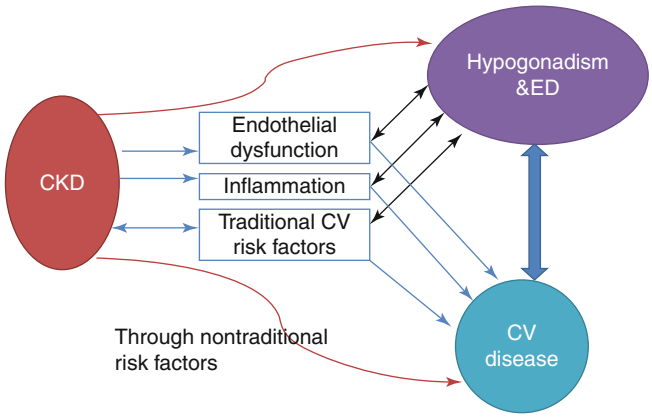

Fig. 16.4 Major pathophysiologic denominators and relationship among CKD, CV Disease and hypogonadism/ED

nondiabetic dialysis patients with symptoms of myocardial ischemia did not have large-vessel coronary artery disease. Thus, The artery size hypothesis which accounts for the time lag between presentation of ED and angina in the general population may not be applicable here in CKD patients. Moreover, these patients also have left ventricular hypertrophy and cardiomyopathy which may make the issues more complicated. In addition, Framingham Risk Scoring has been shown to be not that effective in risk prediction in patients with advanced kidney disease [71]. Thus, efforts which try to implement ED as a major CV disease risk marker into commonly used risk prediction scores may not be adequately feasible in patients with kidney disease.

Patients undergoing hemodialysis also have high rates of depression [72, 73]. Depression is a cardinal cause of psychogenic ED. When we attribute ED of a patient to psychogenic ED primarily, we may have missed an opportunity to investigate underlying silent cardiovascular disease. Although depression is so prevalent, these patients are also subject to traditional and nontraditional CV risk factors which are common in dialysis patients. Thus, what is recommended in the general population in which one first should differentiate psychogenic from organic ED may again be ineffective in dialysis population.

Treatment of Hypogonadism in Context of Chronic Kidney Disease

Treatment of hypogonadism with an aim of reducing cardiovascular morbidity and mortality is an attractive choice. However, adverse CV events related to androgen abuse may seem counter intuitive if testosterone is used in patients at risk for CV disease. However, the doses of androgens are several-fold higher and without medical follow-up when used by an abusive intent [13, 74].

In contrast to general population, patient with CKD are more likely to have hypogonadism mainly due to aggregation of CV risk factors, inflammation, endothelial dysfunction and uremia per se compared with community-dwelling men. In addition, only a portion of patients with ED have hypogonadism compared with CKD patients. Thus, treatment of hypogonadism with testosterone may not automatically improve ED. Indeed some studies in patient with ESRD did not show improvement in erectile function with testosterone supplementation [75, 76]. A subsequent study confirmed the findings of these latter studies. HD patients with hypogonadism were treated with transdermal testosterone. While serum testosterone levels were restored to the normal levels, erectile dysfunction improved [77].

In contrast to the general population, studies investigating potential benefits and harms of testosterone supplementation are scarce in the CKD population. Small studies showed improvements in HPG axis [78] and restoration of serum testosterone with testosterone replacement therapy to normal levels with unsatisfactory sexual functional response [76]. Pharmacokinetic and clinical studies suggested no dose adjustment of testosterone in patients with reduced renal function [42]. Some points which should be taken into consideration while using testosterone supplementation in CKD patients are summarized in Table 16.3. Larger studies are needed to better elucidate potential benefits of testosterone supplementation in terms of sexual function and cardiovascular disease in CKD patient population.

Table 16.3 Potential adverse effects with testosterone supplementation

↑ Prostate cancer risk potential ↑ PSA levels	A meta-analysis refuted this ↑ risk (Caution is advised with regular PSA monitoring)
HDL cholesterol reduction	
Erythrocytosis	In contrast to general population this may be advantageous in CKD population.
Fluid retention	May be problematic in CKD patients
Obstructive sleep apnea	Prevalence is high in ESRD patients and testosterone may worsen the underlying OSAS

In conclusion, in patients with CKD, CV disease is the prime killer. ED has close interrelations both with kidney and cardiac disease and shares common risk factors. The significance of ED in patients with CKD stems from the fact that it may provide early recognition and thus timely management of CV disease in this vulnerable patient population. Large studies must be conducted to test whether ED is an early predictor of future CV disease and if so, take advantage of early predictive ability of ED in CKD population.

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Renal Sympathetic Denervation in the Management of Treatment-Resistant Hypertension

17

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Introduction

Sympathetic Nervous System in Hypertension and Cardiovascular Diseases

The contribution of sympathetic activation to the genesis and progression of hypertension has been well recognised for decades [1]. A step-up has been demonstrated in muscle sympathetic nerve activity from normal to high-normal blood pressure, white coat to borderline to established hypertension, with or without left ventricular hypertrophy [2]. These data are supported by other measures of sympathetic activation in man, specifically spillover of noradrenaline into plasma. A significant increase was noted in essential hypertension patients in comparison to normotensive controls [3] in a study of renal spillover. This increase was particularly prominent in younger hypertensives, aged 20–39 years.

Renal Efferent Sympathetic Activity

Renal sympathetic efferent nerves modulate autonomic control of the kidney. Renin secretion is activated by beta-1 adrenoceptor stimulation, enhanced tubular sodium reabsorption by alpha-1b adrenoceptors and reduced renal blood flow via alpha-1a adrenoceptors [4]. Thus, sympathetic innervation is critical to renal control of regulatory hormones, modulation of total body volume status and effects on the pressure-natriuresis curve. Renal sympathetic denervation shifts the diuresis and natriuresis curves to the left [5], i.e. an increase in water and sodium excretion for the same renal perfusion pressure is achieved in the denervated compared to the innervated animal.

Abrogation or disruption of renal sympathetic efferents therefore represents an attractive therapeutic target in the management of disorders characterised by renal sympathetic nerve activation. This has been supported through the preclinical literature in both low- and high-renin models of hypertension in animals [6].

Renal Afferent Sympathetic Activity

The kidney and pelvic region is highly innervated by mechano-sensitive and chemo-sensitive nerve receptors [7]. Renal afferent nerves transmit this information to the central sympathetic nervous system which in turn modulates activity of key organs including heart, kidney and vasculature. These findings are supported by rhizotomy experiments in animals demonstrating reduced blood pressure in animals with renal disease [8]. These animals demonstrate increased central catecholamine levels compared to healthy controls; such increases are abrogated by renal afferent denervation. In renal transplant patients denervation via nephrectomy of the non-functioning kidney reduced both renal sympathetic efferent activity and blood pressure [9]. Similarly, in renal failure patients receiving renal replacement therapy, removal of the non-functioning kidney has simultaneously reduced MSNA and calf vascular resistance, confirming the kidney as a seminal source of sympathetic stimulation [10].

Carotid Baroreflex Sensitivity

Abnormalities of the baroreflex in the setting of systemic hypertension are well described in the setting of systemic hypertension [11]. Arterial baroreceptors are rapidly reset in response to sustained blood pressure elevations but they also buffer short-term fluctuations in blood pressure [11]. As blood pressure increases there is an increase in firing of baroreceptor afferents. However, in the setting of sustained elevations of blood pressure, despite their adjustment, the baroreceptor response diminishes over time and a new threshold for activation becomes established. Thus, baroreceptors become less sensitive to any given change in blood pressure in the chronic hypertension setting. The reasons for this baroreceptor re-setting are complex but may include both peripheral and central contributions. Thus, attenuation

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of the baroreflex is present in chronic hypertension and the contribution of reduced baroreflex activity to enabling chronic hypertension and its associated multi-organ involvement has been widely described.

Surgical Sympathetic Denervation in the Management of Hypertension

In the era preceding the emergence of modern antihypertensive pharmacotherapy surgical denervation was perhaps the only effective approach to treating patients with significant elevations in blood pressure. Case series comparing this surgical approach to medical therapies (such as existed) demonstrated a roughly 50 % improvement in survival with denervation for the same starting blood pressure values [12]. The magnitude of the blood pressure reduction able to be achieved roughly correlated with the starting pre-operative mean blood pressure. However, unselected sympathetic denervation was accompanied by significant adverse events limiting their clinical utility. In particular, patients experienced impotence, incontinence and, almost invariably, orthostatic hypotension, essentially rendering them unable to achieve upright posture for significant periods of time [13].

Percutaneous and Minimally Invasive Approaches to Renal Sympathetic Denervation

Novel approaches have been developed to specifically achieve renal sympathetic denervation, but to avoid the complications of the earlier surgical approaches, as outlined above. Most of these approaches focus on the sympathetic nerve plexus that surrounds the main trunk of each renal artery. These nerves reside within the adventitia of the main artery or immediately adjacent. These novel approaches include various approaches to radiofrequency (RF) energy application, use of ultrasound waves, direct injection of neurotoxins such as guanethidine and even extracorporeal approaches that are completely non-invasive. By far the most advanced and best investigated of these strategies is that of percutaneous RF ablation [1]. This procedure involves cannulation of the femoral artery and subsequent placement of the tip of the catheter in the distal renal artery where energy is applied targeting adjacent sympathetic nerve trunks. The catheter is then withdrawn 1–2 cm and circumferentially rotated with further RF energy applications performed in this way, such that 4–6 on average (often more) are applied to the individual renal artery . The same procedure then occurs in the contralateral main renal artery.

Published Experience with Percutaneous Renal Sympathetic Denervation

Symplicity Hypertension I Study

Symplicity-HTN1 [14] was a 12 month evaluation of safety and blood pressure-lowering efficacy (without a control group) as a first-in-man experience with the denervation procedure. Inclusion criteria involved patients with a systolic blood pressure greater than 160 mmHg despite three or more antihypertensive medications including a diuretic or confirmed intolerance to medications. Furthermore, estimated glomerular filtration rate (eGFR) was required to be >45 ml/min per 1.73 m^2. The key exclusion criteria included known secondary causes of hypertension, Type I diabetes mellitus, central sympatholytic drug use and critically evidence of renovascular abnormalities, including renal artery stenosis, prior renal procedure and/or dual renal arteries.

Enrolled patients in fact tended to have considerably poorer blood pressure control than the entry criteria cut-off demanded. Mean blood pressure was over 170 mmHg systolic and 100 mmHg diastolic; this was despite on average, five different antihypertensive drug classes being used in an attempt to control blood pressure. Almost all patients were taking ACE inhibitor and/or angiotensin receptor blocker as well as diuretics, 69 % were receiving calcium channel blockers and ¾ beta-blockers.

The key blood pressure results of the non-randomized Symplicity HTN1 study were a 27/17 mmHg reduction in blood pressure compared to baseline at the 12 month end of the formal study evaluation period. This was supported by limited ambulatory blood pressure monitoring (ABPM) data that included an increase in patients shifting from non-dipper to dipper status with the procedure. However the magnitude of the ABPM response to denervation in this study (and Symplicity HTN-2 [15]) was substantially less than that of office blood pressure falls, suggesting a white-coat component may be contributory to the observed office response.

The key mechanistic question was whether sympathetic denervation had in fact been achieved in the kidney. This had been demonstrated pre-clinically where an 85 % reduction in total renal norepinephrine content was observed in the percutaneously denervated kidneys of studied animals (data on file, Ardian). The magnitude of that reduction was similar to that achieved with conventional surgical approaches. In man, evidence of renal denervation was observed with a substantial reduction in renal norepinephrine spillover rate in a published case study where blood pressure was also decreased and muscle sympathetic nerve activity (indicative of efferent sympathetic output) was also progressively reduced out to 12 months [16]. Sympathetic nerve activity reduction following renal denervation has now been confirmed in a

larger series [17]. However, it remains uncertain at the time of the procedure whether denervation has been successfully achieved. The extent of efferent and afferent denervation remains unquantifiable and the importance of complete denervation uncertain; there are as yet no simple clinical tools to address this question.

The Symplicity HTN-1 experience has now been extended out to 36 months in a larger cohort than the initial published 12-month experience [18]. The mean reduction in blood pressure persisted, with a mean 33/19 mmHg reduction compared to baseline at 36 months. This is consistent with the surgical experience where many years of improved blood pressure control are observed following the surgical intervention. There is certainly no suggestion of loss of blood pressure-lowering effect out to 36 months.

Also of interest were the percent blood pressure responders over the 36 month follow-up period. Responders were nominally defined as an office systolic blood pressure reduction of >10 mmHg versus baseline. At 12 months post-procedure, only 79 % had achieved this response in the Symplicity HTN-1 expanded cohort. However, by 36 months all study patients had in fact achieved a "response". Thus, it is possible that short term blood pressure decline is not sensitive to successful renal sympathetic denervation and raises the important issue of what physiological mechanisms may be in play post-denervation regarding achievement of a late (but not early) blood pressure effect. Possibilities include progressive vascular remodelling, resetting of the baroreflex and/or alterations in renal blood flow and sodium excretory status, all of which may take some time to "reset". Whether different energy or ablation modalities could alter the responder rate or the time course of blood pressure reduction remains unknown.

Furthermore, analysis of key subgroups failed to reveal patients with particularly large blood pressure responses (or non-responses). In particular, age greater or less than 65 years, presence or absence of diabetes mellitus, impaired or preserved renal function or high or low heart rate resulted in no heterogeneity in blood pressure response. Thus, it cannot be ascertained from baseline patient characteristics a particular subgroup of patients who may particularly benefit or not benefit from the procedure regarding blood pressure response. However, given the limited numbers of patients in this analysis it is clear that much larger numbers, e.g. from a global registry will be required to fully tease out this important clinical question. Ultimately, pre-procedure measures beyond those that are clinically routine may need to be elucidated (or developed) to improve patient selection and minimise "non-responders". At the present time neither a screening test nor demographic characteristics are able to identify early versus late responders, or hyper- versus non-responders.

Symplicity Hypertension 2 Study

Symplicity HTN-2 [15] used very similar entry criteria to Symplicity HTN-I [14]. The key differences were that there was a 2 week observation period at the end of which baseline systolic blood pressure measures were required to remain above 160 mmHg. In this way concerns about regression to the mean and Hawthorne effect (as per Symplicity HTN-1) could at least be partially overcome. Patients who met blood pressure criteria then underwent anatomical screening via MRA, CTA or duplex scanning and if renal arteries were found to be appropriate for intervention they were then randomised to control or treatment group with a 6-month primary endpoint assessment of safety and efficacy. The initial 6-month results demonstrated acceptable safety and a 32/12 mmHg reduction from baseline in the denervation group (n=49) compared to a 1/0 increase in blood pressure in the control group (n=51). This was achieved despite more patients decreasing their medication and fewer patients increasing their medication in the denervation group compared to the control group.

At the end of the 6-month primary endpoint, the control patients were offered the denervation procedure and all patients were then followed for a further 6 months. The findings of this analysis [19] were that in the initial denervation group (n=47) blood pressure lowering was maintained out to 12-months procedure with a reduction of 28/10 mmHg compared to baseline. In the crossover group (n=35) who were evaluated 6-months post-denervation, mean reduction was 24/8 mmHg compared to their 6 month pre-denervation value of +7/1 mmHg versus baseline.

Symplicity Hypertension 3 Study

The Symplicity HTN-1 and 2 studies provided strong safety and efficacy data to support the utility of this procedure in refractory hypertension patients. However, there were a number of design deficiencies in both of these studies and the United States (US) Food and Drug Administration mandated a definitive US study to overcome some of these design issues. Specifically, Symplicity HTN-3 [20] required more aggressive achievement of target or at least highest tolerated dose of background antihypertensive medications, qualifying blood pressure included a requirement for 24-hour systolic blood pressure of >135 mmHg by ambulatory monitoring (as well as a subsequent office systolic blood pressure >160 mmHg) to be confirmed following initial screening. Additionally, the study mandated a sham procedure performed in the renal artery of control subjects which includes everything but the actual RF energy application. Because the operator was aware of which patients do and do not receive the active procedure, a separate group of investigators performed the endpoint assessments. As with Symplicity HTN-2, the primary efficacy endpoint is office SBP at 6 months at which time patients in the control group could then receive the procedure if they wish.

In contrast to the earlier studies reported above, the Symplicity HTN-3 trial investigators recently reported that their primary efficacy endpoint was not met [21]. The primary efficacy endpoint was change in office systolic blood pressure between the denervation and the control arm, with a superiority margin of 5 mmHg. However, the decrease in systolic blood pressure in the denervation group was 2.4 mmHg versus sham control at 6 months, with a starting systolic blood pressure of approximately 180 mmHg in both groups. There was a non-significant interaction effect ($p=0.09$) in African-American versus non-African-Americans suggesting that these subjects derived less benefit in terms of blood pressure reduction. There were no other pre-specified subgroup interactions of note. There was no significant increase in safety events with denervation.

As mentioned, this RCT had a sham procedure but also a number of other design and logistic features that may have potentially mitigated against a dramatic BP-lowering effect of the active intervention. The type of catheter used by the US operators in Symplicity HTN-3 (Flex) differed from the first generation device used primarily in Symplicity HTN-1 and that may turn out to be relevant to achievement of sympathetic abrogation. There was a broad simultaneous rollout to multiple (88) US sites that had never previously performed the procedure. The level of procedural training and proctoring was considerably less than what occurred in Symplicity HTN-1, where the Ardian engineers (who actually developed the catheter) came to individual laboratories on multiple occasions for intensive hands-on training and live case supervision. Optimisation of background antihypertensive therapy was mandated but up-titration was allowed to continue potentially up to only 2 weeks prior to the procedure. Given that the peak BP-lowering effect of anti-hypertensive drugs may occur anything up to 12 weeks post-commencement, it is possible that BP stability had not been achieved in a significant proportion of Symplicity HTN-3 patients at the time of the procedure. This may have contributed to the significant BP-lowering observed in the sham group, making a further increment achievable by RDN correspondingly more difficult. Furthermore, patients from non-tertiary centres may not yet have exhausted all non-procedural treatment options for their refractory hypertension prior to entering the study.

Additional analysis of the Symplicity HTN-3 dataset, as well as longer term follow up of study patients, which is planned for up to 5 years, will provide important insight into potential reasons for the blood pressure-lowering discrepancies discussed above. Further mechanistic investigation will also be required to sort this out and in particular to develop a simple test to ascertain the achievement and completeness of denervation whilst patients are still on the table during the denervation procedure.

Safety with Percutaneous Renal Sympathetic Denervation

Initial studies focussed primarily on safety of the procedure [14]. From the very first procedure it was noted that diffuse visceral pain occurred in concert with the application of RF energy. These findings suggest that somatic afferent C-fibres travel with the sympathetic nerves which were the targets of the ablation. Subsequent to this observation, patients now routinely receive prophylactic intravenous analgesia and/or sedation. Imaging studies including magnetic resonance angiography (MRA) and computerised tomography (CTA) have indicated absence of atherosclerotic responses to the RF energy application in denervated arteries. This imaging was undertaken both early (1–2 weeks post procedure) and late (approximately 6 months post procedure) in these early studies.

The initial safety experience described one episode of renal artery dissection during the catheter procedure (but before application of RF energy) which was subsequently successfully stented. There have also been a number of cases of impaired haemostasis in the groin but at a rate consistent with other arterial cannulation procedures involving the femoral artery.

A theoretical concern is that of renal artery stenosis. Rare case reports of renal artery stenosis have been documented [22], however it is not clear if the late stenosis is related to mechanical arterial manipulation or the RF denervation. In the reported case, the late stenosis was successfully treated with dilation and stenting. Nevertheless, and as mentioned, alternative technologies have been developed in an attempt to minimise this and other potential local complications. These include use of multi-electrode catheters to minimise time of catheter in the vessel and ultrasound based approaches to minimise endothelial damage. Furthermore, there have been no cases of vessel thrombosis or kidney embolization reported.

Another safety concern has been that of potential of worsening of renal function itself. This has not been observed in early studies or indeed in the published Symplicity-HTN 2 trial [15] versus a control group.

Novel Approaches to Percutaneous Renal Denervation

Radiofrequency Ablation

Newer denervation systems employ multiple RF ablation electrodes mounted on steerable basket-like shaped catheters as in the St Jude Medical EnlighHTN system, spiral shaped catheters as in the Medtronic Multi-electrode Radiofrequency Renal Denervation System, or a balloon cooled RF ablation

as in the Covidian One-Shot. Preliminary 6-month data on the EnlighHTN system (n = 46) has shown efficacious BP reduction, with 76 % of patients achieving systolic BP reduction of >/=10 mmHg at 6 months post procedure. Mean BP reduction at 6 months was −26/−10 mmHg from 176/96 mmHg at baseline, to 150/86 mmHg at 6 months. The Covidien OneShot system employs a saline irrigated balloon catheter, with a spiral RF electrode on the balloon. It permits single RF energy application lasting only 2 min per renal artery with continuous endothelial cooling. The Vessix V2 RSD system is an over-the-wire low pressure balloon catheter with multiple bipolar RF electrodes mounted on the exterior of the balloon. This procedure has programmed treatment times of 30 s. The balloon catheter also accommodates smaller arterial diameters (3.0 mm) which may be particularly relevant to the arteries of CKD patients.

Ultrasound

The ReCor Medical PARADISE RSD system employs a catheter with a cylindrical transducer, within a low-pressure balloon, that emits ultrasound energy circumferentially, effecting renal denervation. It is claimed that this allows complete circumferential denervation and deeper therapeutic penetration which is hoped to be more consistent and effective with improved vascular safety than the standard RF ablation strategy. In a small study (n = 11), this ultrasound RSD method was shown to be a safe and effective treatment for resistant hypertension [23].

All these new devices allow for simultaneous application of ablation energy at multiple different points in the renal artery lumen to denervate the renal sympathetic nerves. This permits a shorter procedure time and thus shorter periods of pain during the application of the ablation energy on the renal sympathetic nerves. There is also a theoretical reduced volume of nephrotoxic contrast used. The newer multi-electrode catheters will also allow smaller and shorter renal arteries to be ablated.

Summary

Hypertension remains a major public health problem, particularly in Western but increasingly in developing countries. Despite effective and largely well tolerated anti-hypertensive pharmacotherapy there exists a population of patients whose blood pressure remains sub-optimally controlled. Provided that appropriate pharmacotherapies and their doses have been adequately explored, new procedures and devices have emerged to assist with blood pressure control in this setting. Renal sympathetic denervation appears to provide significant and durable blood pressure lowering with an acceptable peri- and post-procedural adverse event profile. However, the recent Symplicity HTN-3 experience has challenged the assumptions derived from these earlier data. Furthermore, the number of patients exposed in randomised controlled trials remains relatively low. Further study is clearly required before refractory hypertension patients will have evidence-based procedure or device-based treatment options to reduce their lifetime risk of cardiovascular disease attributed to untreated hypertension.

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Part III

New Ways of Working for the Twenty-first Century: Rising to the Challenge of Comorbid Patients

Future Therapeutic Prospects for Treatment of Cardiorenal Syndromes

18

Peter A. McCullough

Introduction

Acutely decompensated heart failure (ADHF) is one of the most common reasons for adult hospitalizations worldwide and is expected to increase over the next several epidemics as the age structure of the population shifts towards greater numbers of elderly individuals. McCullough and colleagues demonstrated in the Resource Utilization Among Congestive Heart Failure Study (REACH), that there is sharp age dependent increase in the prevalence of heart failure (HF), and that on average the 5 year mortality is 50 % [1]. Approximately 90 % of patients with HF die within 10 years of diagnosis and the final event is accelerated in time for those who have their initial diagnosis later in life. Hence ADHF is a call to arms in terms of disease modifying therapies including angiotensin converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB), mineralocorticoid receptor antagonists (MRA), beta-adrenergic receptor blockers (BB), biventricular pacing, and implantable automatic defibrillators. All of these therapies have been shown to reduce hospitalizations and or prevent or reduce the risks of death in patients with HF. It should be noted that none of commonly used acute therapies for ADHF including loop diuretics, inotropic agents, vasopressors, vasodilators, or mechanical forms of fluid removal have been shown in randomized trials to reduce in-hospital death or a composite of rehospitalization and death after discharge (Table 18.1). Despite the intuitive nature of many of these therapies, in the trials that have been completed, there has been failure. Considerable attention has been brought to the clinical trialist community in ADHF for this global failure and several explanations can be brought forward: (1) conventional therapies used in any combination or management have not differentially influenced outcomes (high versus low dose loop diuretic, inotropic agents), (2) for novel agents there has been either the wrong drug, dose, duration, or wrong outcome (e.g. dyspnea score) and (3) for all randomized trials, there has been inadequate phenotyping of patients with ADHF with the implication that ADHF is a collection of syndromes with different features and has a very narrow therapeutic window for volume management. Thus, clinical and molecular phenotyping may be needed in order to target a therapy for its best opportunity to confer benefit. The best example of this was the milrinone (phosphodiesterase three inhibitor that works to increase the heart's contractility) trials program where The Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) randomized 949 patients with systolic dysfunction and ADHF to receive 48–72 h of intravenous milrinone or placebo [10]. Milrinone-treated patients with ischemic cardiomyopathy had higher rates of the primary end point which was days hospitalized for cardiac reasons at 60 days (13.6 days for milrinone vs. 12.4 days for placebo, $p = 0.055$ for interaction) and the composite of death or rehospitalization (42 % vs. 36 % for placebo, $p = 0.01$ for interaction). In contrast, for those with nonischemic cardiomyopathy, milrinone had significantly lower durations of the primary end point (10.9 vs. 12.6 days placebo) and a reduced risk of the composite of death or rehospitalization (28 % vs. 35 % placebo). Thus in retrospect, it would appear as no surprise that a drug which increases metabolic demand and arrhythmogenesis of the myocardium may have deleterious effects in patients with ischemic heart disease, yet in those where epicardial blood flow is intact, the same drug has a beneficial effect on a clinically meaningful outcome [11]. If the OPTIME trial would have considered an optimal phenotype for this phosphodiesterase inhibitor, only patients with nonischemic cardiomyopathy would have been recruited, and more likely than not, this drug would have been declared a beneficial agent in ADHF and would be in broad use today.

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Table 18.1 Therapeutic agents or strategies and attempts to prevent or treat type 1 CRS

Drug or strategy	Major inference with respect to type 1 cardiorenal syndrome
High dose loop diuretics	↑ AKI, no reduction in rehospitalization or death [2]
Continuous infusions of loop diuretics	↑ AKI, no reduction in rehospitalization or death [2]
Low-dose dopamine infusion (stimulate D1>>β1 receptors)	Improved urine output, but no Δ AKI, no reduction in rehospitalization or death [3]
Nesiritide (recombinant B-type natriuretic peptide) at any dose or infusion protocol	No Δ AKI, no reduction in rehospitalization or death [4]
Dobutamine (β1 agonist)	No high quality trials with CRS outcomes
Milrinone (phosphodiesterase 3 inhibitor)	No high quality trials with CRS outcomes
Levosimendan (myocardial calcium sensitizer)	No high quality trials with CRS outcomes, however, ↓AKI after cardiac surgery [5]
Rolofylline (selective adenosine A1 receptor antagonist)	No Δ AKI, no reduction in rehospitalization or death
Tolvaptan (arginine vasopressin receptor antagonist)	No Δ AKI, no reduction in rehospitalization or death [6]
Programmatic use of invasive hemodynamic monitoring	No Δ AKI, no reduction in rehospitalization or death [7]
Ultrafiltration for diuretic resistance before AKI develops	↓Weight, reduction in rehospitalization and death [8]
Ultrafiltration after AKI develops	No Δ weight, no reduction in rehospitalization or death [9]

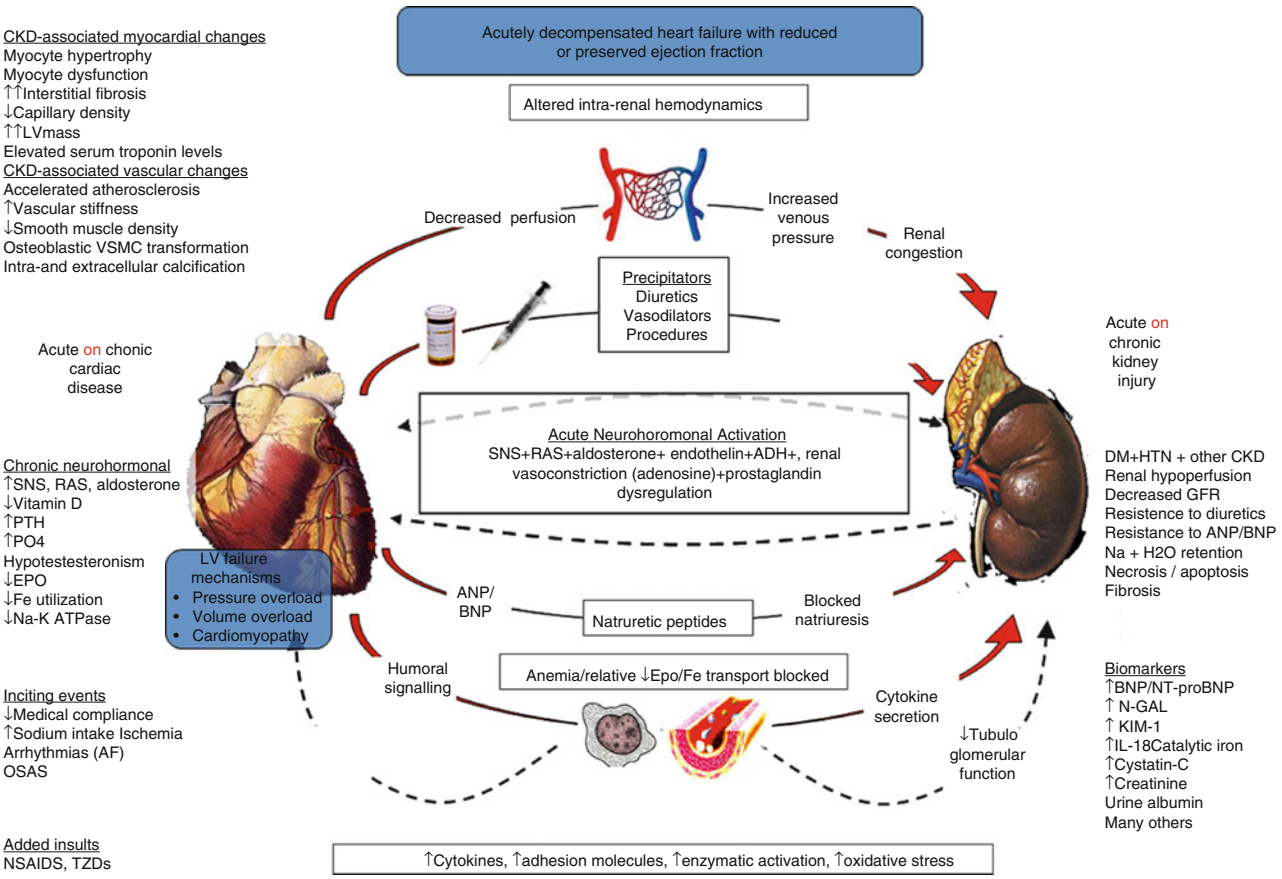

Fig. 18.1 Complicated pathogenesis of acute type 1 CRS

As we look toward novel therapies to prevent or treat type 1 CRS, OPTIME serves as an excellent example of the need to better characterize particular ADHF patients and carefully consider the pathophysiology to best match a specific drug to an individual patient.

The Acute Dialysis Quality Initiative has recently published a consensus on the pathophysiology of type I CRS [12]. This syndrome has established risk predictors including hypertension, elevated jugular venous pressure, pulmonary congestion, and reduced renal filtration function at baseline

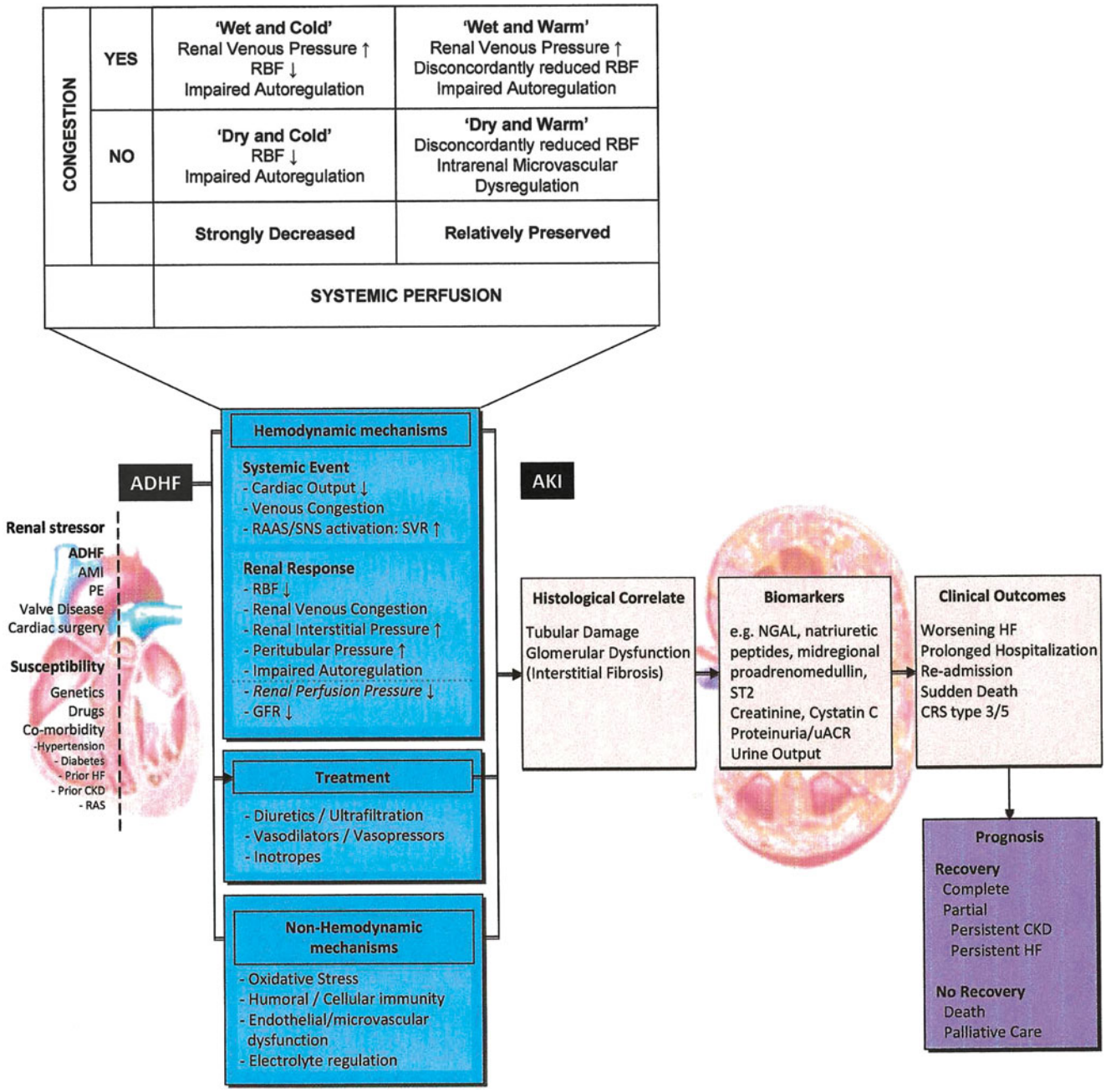

Fig. 18.2 Hemodynamic subsets and their relationship to the pathophysiology of type 1 CRS

(Fig. 18.1). A proposed approach to subset patients according to hemodynamic and pathophysiologic mechanisms is shown in Fig. 18.2. Because it is believed that a very narrow therapeutic window of intravascular volume management exists for the kidney in the setting of ADHF (Fig. 18.3), it follows that some attempt based on clinical exam, chest-x-ray, noninvasive hemodynamic measures, and even invasive pressure measures are needed to adequate select a patient for a specific therapy. For patients who have intact perfusion and little or no congestion, then minimal diuresis and adjustment to baseline medications is a reasonable strategy. For those with impaired perfusion but still little or no congestion, in the absence of ischemic cardiomyopathy, use of a renal-dose adjusted inotropic agent such as milrinone or levosimendan could be a reasonable pathway. If there is intact perfusion but considerable congestion, then use of vasodilator agents such as nitroglycerin or nesiritide could be entertained. Finally, those with impaired perfusion and pulmonary/systemic congestion and the highest risk for type 1 CRS and inpatient mortality, combined use of diuretics and inodilators, and possibly early continuous renal replacement therapy could be considered. It is important to understand in each of these four scenarios, none of the therapies above have been specifically tested in that subset in an adequately

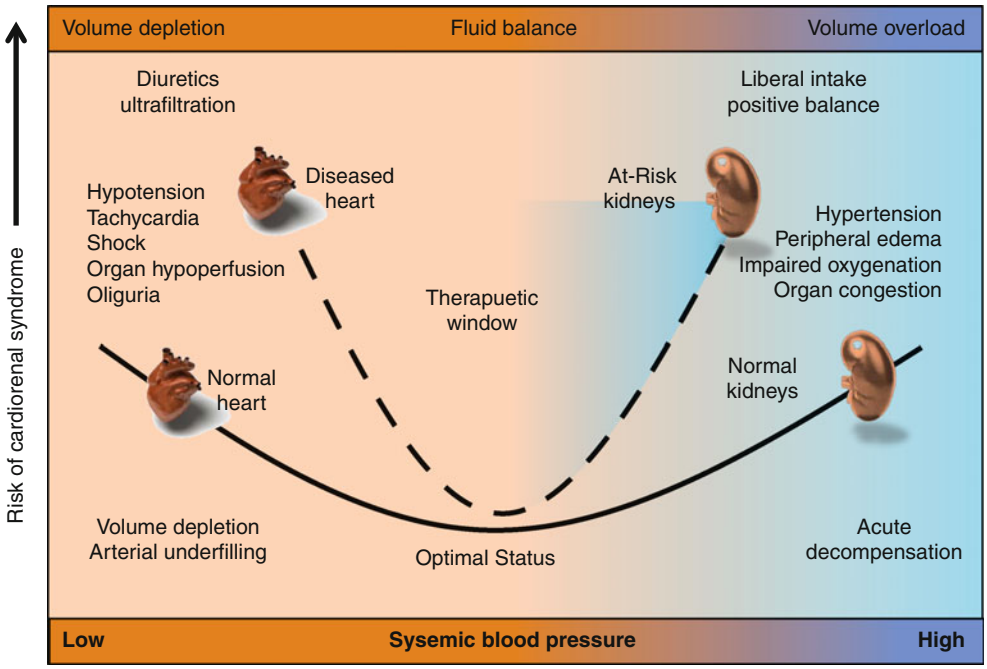

Fig. 18.3 Narrow therapeutic window for intravascular volume management in type 1 CRS

powered, randomized, placebo controlled randomized trial. Hence, novel agents should have the advantage of collective hindsight and be tested in specific phenotypic patients at risk for type 1 CRS in order to give the most valid treatment inferences and help move the field forward.

Conventional Therapies for Acutely Decompensated Heart Failure

The National Institutes of Health, National Heart Lung and Blood Institute Heart Failure Clinical Research Network has sponsored three randomized trials with specific attention on both the cardiac and renal implications of patients admitted with ADHF [3]. The DOSE trial found no benefit of high-dose or continuous infusions of loop diuretics, in fact, there were higher rates of AKI with those approaches [2]. The CARRESS-HF trial found no benefit for ultrafiltration in patients once type 1 CRS had fully developed, and in fact, since the rate of fluid removal exceed the rate of plasma refill, there where greater increases in serum Cr in those undergoing ultrafiltration with no improvement in any clinical parameter (weight loss, rehospitalization, death) [9]. In the double-blind Renal Optimization Strategies Evaluation (ROSE) trial, 360 subjects with ADHF and CKD were randomized in a factorial with 2:1 active treatment: placebo, such that approximately one third of the population received, in addition to standard diuretic-based decongestive therapy, low-dose dopamine (2 μg/kg/min infusion) while another third received low-dose nesiritide (human recombinant B-type natriuretic peptide, 0.005 μg/kg/min infusion for 72 h) [3]. Primary endpoints were total cumulative urine volume and change in serum cystatin-C. While the dopamine and nesiritide strategies both resulted in larger increases in urine output as compared to the placebo control (228 and 278 ml, respectively), these changes were small and not statistically significant. Cystatin C levels were not elevated (~1.1 mg/dl) at baseline, and there were no meaningful changes in this measure. There were no significant differences in symptoms, days alive and free from HF hospitalization at 60 days, or mortality. Of note, the rates of type 1 CRS were ~24 % in the ROSE trial and were unaffected by treatment allocation.

For both dopamine and nesiritide, there have been a significant number of trials and analyses with larger sample sizes showing no benefit in critically ill patients. For low-dose dopamine (<5 μg/kg/min), a meta-analysis of 3,359 subjects in 61 trials showed that, while dopamine resulted in a 24 % rise in urine output, there was no difference in death or the need for kidney replacement therapy [2]. Here, ROSE can add to treatment inferences in that dopamine resulted in a smaller increase in urine output (~3 %) and no impact on cystatin-C or hospitalization or death. For nesiritide, the ASCEND-HF (Acute Study of Clinical Effectiveness of Nesiritide and Decompensated Heart Failure) trial randomized 7,141 patients with ADHF to 24–168 (median 42 h) hours of nesiritide (2 μg/kg bolus then 0.01 mcg/kg/min) or placebo [9]. While nesiritide was associated with minor improvements in symptoms at 6 and 24 h, there were no differences in prespecified primary endpoints including rehospitalization and death. There were no differences in the rates of >25 % reduction in eGFR. Rates of AKI or type 1 CRS were again not reported. For nesiritide, ROSE adds the

understanding that longer durations of a lower dose infusion with no bolus again confers no benefit over placebo.

Where did the NHLBI Heart Failure Trials network fail? Perhaps the lack of phenotyping played a role in failing to identify a population for benefit. Beyond hemodynamic characterization, blood and urine biomarkers should be used to understand the risk for and presence of both subclinical and clinical AKI [13]. The ROSE trial measured N-terminal pro B-type natriuretic peptide, but did not use it to phenotype patients into treatment subsets. In the future, the natriuretic peptides should be used to not only confirm ADHF but also to characterize patients along with other guidelines recommended tests, including galectin-3, troponin I or T, and ST2 [14]. Urine should be tested for tubular cell cycle arrest markers as well as markers of tubular injury, such as neutrophil gelatinase associated lipocalin, kidney injury molecule-1, interleukin-18, L-type fatty acid binding protein, and others [15]. It is possible that combination of these markers could identify ideal subsets for benefit or harm for particular clinical approaches.

A standard Kidney Disease International Global Outcomes (KDIGO) definition of AKI would have been more desirable as a formal primary endpoint in trials of type 1 CRS; since this definition of AKI in the setting of ADHF needs confirmation of translation into hard outcomes such has HF hospitalization and death [4]. Can we find an optimal treatment pathway using conventional therapies which are decades old in randomized trials of ADHF? The DOSE, CARRESS-HF, and ROSE trials suggest we cannot. Thus, future trials will need to target novel therapies and innovative ways (clinical exam, imaging, biomarkers) of identifying patients who are most likely to have the pathophysiology we are targeting with a new therapy.

Ularitide

With the failure of nesiritide to improve clinical outcomes in ADHF, is there a role for any form of natriuretic peptide in the prevention of type 1 CRS? If hemodynamic assessment is important for patient selection, then patients with intact perfusion but pulmonary congestion, possibly with ischemic cardiomyopathy could be an ideal subset for a novel natriuretic peptide which has natriuretic and diuretic properties on the kidneys as well as anti-ischemic and lusitropic properties on the myocardium. Ularitide is the chemically synthesized analogue of urodilatin, a human endogenous natriuretic peptide that regulates renal sodium and water excretion and is expressed in the kidney. After expression in the distal tubular cells, urodilatin is luminally secreted and binds mainly downstream in the inner medullary-collecting duct to specific natriuretic peptide receptors (NPR-A, NPR-B and also to other natriuretic peptide receptors), resulting in the activation of the intracellular guanylyl cyclase domain and generation of cyclic guanosine monophosphate (cGMP). The main pharmacological effects of exogenously administered ularitide are specific vasodilation (of renal, pulmonary, and coronary arteries, and peripheral arteries and veins), bronchodilation, diuresis and natriuresis, modulation of intrarenal blood flow, as well as inhibition of renal sodium reabsorption and of regulatory cardiac neurohormonal systems (sympathetic nervous system, renin-angiotensin system, endothelin).

In the Safety and Efficacy of an Intravenous Placebo-Controlled Randomised Infusion of Ularitide Trial (SIRIUS II), a double-blind phase II trial, 221 patients hospitalized for ADHF and selected for hemodynamic parameters including cardiac index $\leq$2.5 L/min/m^2, and pulmonary artery wedge pressure $\geq$18 mmHg were randomized to a single 24-h infusion of ularitide (7.5, 15, or 30 ng/kg/min) or placebo added to standard therapy [16]. Estimated glomerular filtration rate, serum creatinine, creatinine clearance, were not influenced by ularitide. However at 24 h, 15 ng/kg/min ularitide reduced blood urea nitrogen (BUN) levels (-4.07 ± 12.30 vs -0.20 ± 7.50 for placebo, $P < .05$). Ularitide at 15 and 30 ng/kg/min increased cardiac output. Although 15 ng/kg/min ularitide did not influence the pressure gradient MAP-RAP, 30 ng/kg/min ularitide reduced MAP-RAP by -7.8 ± 10.6 mmHg vs -2.4 ± 9.8 mmHg for placebo ($P < .01$, at 6 h). A strong inverse correlation between MAP-RAP and BUN, $r = -0.50579$, $P = .00015$ was observed. Thus, longer infusions as higher doses of ularitide may work to correct the imbalance between forward perfusion pressure and venous congestion experienced by the kidney in the setting of ADHF. Currently, the Efficacy and Safety of Ularitide for the Treatment of Acute Decompensated Heart Failure (TRUE-AHF) trial is recruiting patients with ADHF and congestion on chest X-ray with B-type natriuretic peptide (BNP) >500 pg/mL or N-terminal pro-brain natriuretic peptide (NT-pro BNP) >2,000 pg/mL and will randomize patients to ularitide 15 ng/kg/min for 48 h versus placebo. There are two co-primary endpoints for this study: (1) a hierarchical clinical composite variable that includes a patient-centered assessment of clinical progress, an assessment of lack of improvement or worsening of HF requiring a pre-specified intervention, and death, and (2) cardiovascular mortality at any time during the trial. Unfortunately, TRUE-HF is very unlikely to give important positive treatment information on type 1 CRS because: (1) it has not followed the positive results of the SIRIUS II with entry criteria based on clinical or hemodynamic exam, (2) is not using the 30 ng/kg/min dose, (3) is excluding patients with a eGFR <30 ml/min/1.73 m^2, (4) is not assessing KDIGO AKI, and (5) is probably giving the infusion for too short of a period of time (48) hours. It takes approximately 10–14 days for a patient with HF to develop ADHF, and then another 3 days in the hospital to have type 1 CRS unfold, thus, it is very optimistic

to think that a 48 h infusion of a neurohormone will reverse this process [4].

Serelaxin

Relaxin is a pregnancy hormone that works through its receptors on vascular smooth muscle as a potent vasodilator of small resistance arteries and modifies arterial compliance in some systemic vascular beds. Thus, relaxin plays a role with many other physiologic changes in pregnancy resulting in an increased blood volume, cardiac output, stroke volume, and decreased systemic vascular resistance and greater perfusion of mesenteric vascular beds via bradykinin-mediated, non-endothelium dependent, enhanced nitric oxide synthesis and release [17]. Recombinant relaxin, known as serelaxin was evaluated as an intravenous infusion at 30 μg/kg/day for 20 h in 71 ADHF patients with pulmonary capillary wedge pressure (PCWP) ≥18 mmHg, systolic blood pressure (BP) ≥115 mmHg, and estimated glomerular filtration rate ≥30 mL/min/1.73 m^2 to serelaxin (n = 34) or placebo (n = 37) within 48 h of hospitalization. Serelaxin modestly decreased PCWP during the first 8 h of infusion (difference vs. placebo: −2.44 mmHg, P = 0.004) and mean pulmonary artery pressure (difference vs. placebo: −5.17 mmHg at 4 h, P < 0.0001). Right atrial pressure, systemic/pulmonary vascular resistance, and systolic/diastolic BP decreased from baseline with serelaxin vs. placebo; however, cardiac output did not change [18]. Serelaxin administration improved eGFR and decreased N-terminal pro-brain natriuretic peptide levels vs. placebo.

RELAXin in Acute Heart Failure (RELAX-AHF-1) Trial randomized 1,161 with ADHF but preserved ejection fraction (HFpEF, 26 %) and reduced ejection fraction HFrEF (74 %) patients to 48-h serelaxin (30 μg/kg/day) or placebo within 16 h from presentation [19]. There was no selection based on hemodynamic or renal presentation. Serelaxin induced a similar dyspnea relief in HFpEF vs. HFrEF patients. No differences were encountered in the effect of serelaxin on short- or long-term outcome between HFpEF and HFrEF patients including cardiovascular death or hospitalization for heart/renal failure through 180 days. Metra and coworkers have summarized combined cardiac and renal effects of serelaxin from several studies, and in general, have shown slightly favorable results with respect to lesser increases in cystatin-C, and lower levels of cardiac troponin after serelaxin infusions [20]. Worsening renal function, defined by a serum creatinine increase of ≥0.3 mg/dl or a cystatin-C increase ≥0.3 mg/l (22 nmol/l) at 48 h (similar to KDIGO AKI), occurred in 167 of 1,086 (15.4 %) in serelaxin and 212 of 1,081 (19.6 %) placebo patients, respectively, p = 0.50. Despite these results, serelaxin was associated with a 38 % reduction 180-day mortality, with similar effects in the phase II and phase III studies (combined studies: n = 1,395; p = 0.0076), with progressively widening survival curves more than 60 days after infusion. With these discordant results, the mortality findings are likely spurious and related to some form of unknown positive confounder(s) at baseline not captured in the baseline variables or a result of alpha error. A large clinical trials program with serelaxin similar to that of ularitide is ongoing and recruiting patients with ADHF, pulmonary congestion on chest x-ray, and BNP ≥350 pg/mL or NT-proBNP ≥1,400 pg/mL. Unfortunately there are no entry criteria based on hemodynamic profile and patients with eGFR <25 mL/min/1.73 m^2 will be excluded. Unlike ularitide, the primary endpoint is mortality assessed at 180 days despite the drug infusion fixed at 48 h, thus, the biologic plausibility of a drug effect on mortality is minimal no matter what the final results indicate.

Conclusions

Type 1 CRS as a complication of ADHF is the most important complication such patients can incur during the acute phase and has the strongest relationships with inpatient outcomes including ESRD, prolonged length of stay, mortality, and rehospitalization [21]. This review has summarized prior approaches with conventional agents (loop diuretics, inotropes, vasodilators, pressors) as well as two new development programs (ularitide and serelaxin). It appears that if progress is going to be made in this field for novel agents, specific patient subtyping will be needed based on hemodynamic and probably biomarker parameters, KDIGO AKI should be positioned as an a priori outcome, and intravenous infusions of novel agents will need to be given for a sufficiently long period of time (5–10 days or longer) to allow positive drug effects on the cellular, vascular, renal, and cardiac pathophysiology in order to have positive clinical outcomes. Such a trials program has not yet been developed, and thus, the future is bright for this field as investigators grow closer to these realizations.

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Novel Combination Therapy to Target Heart and Kidney

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Abbreviations

CKD	Chronic kidney disease
CV	Cardiovascular
CVD	Cardiovascular disease
ESRD	End-stage renal disease
HD	Hemodialysis
IL	Interleukin
IS	Indoxyl sulfate
LVH	Left ventricular hypertrophy
MAPK	Mitogen-activated protein kinase
MW	Molecular weight
OAT	Organic anion transporter
PBUT	Protein-bound uremic toxin
*p*CS	*p*-cresyl sulfate
ROS	Reactive oxygen species
TGF-β1	Transforming growth factor-β1
TNF	Tumor necrosis factor

Cardiovascular disease (CVD) is responsible for 40–50 % of all deaths in patients with chronic kidney disease (CKD) [1]. CKD severity, irrespective of the primary cause of the kidney disease is associated with increasing risk of cardiovascular (CV) mortality [2]. In fact, CKD patients are at greater risk of CV morbidity [3] and mortality [4] than progression to end-stage renal disease (ESRD). Up to 90 % of CKD patients suffer or die of CV complications before reaching ESRD [5].

CVD in the setting of CKD has its own specific characteristics. First, despite the high incidence of accelerated atherosclerosis as well as the high fatality following myocardial infarction observed in these patients [6], only 15–25 % of cardiac deaths are attributable to ischemic heart disease. Approximately half of CKD patients who develop MI or angina pectoris are angiographically negative for significant coronary atherosclerosis [7]. In the CKD population, heart failure is the most common clinical presentation of CVD. Left ventricular hypertrophy (LVH) is commonly used as a predictor for CV mortality, the major causes of which are sudden cardiac death, heart failure and myocardial infarction [8].

Second, striking cardiac interstitial fibrosis, a crucial part of uremic cardiomyopathy, and non-obstructive vascular diseases (such as vascular stiffness, calcification and ossification) are highly prevalent CV pathology in CKD patients, independent of hypertension [9, 10]. Both are predictive of poor CV outcomes [11, 12] and may explain the high incidence of sudden cardiac death and ischemic heart disease in the absence of significant atherosclerosis in this setting.

Lastly, but most importantly, traditional CV risk factors such as hypertension, diabetes mellitus, hyperlipidemia and smoking appear to be of less importance in the CKD population compared to the general population. CV mortality remains high in CKD patients, despite these risk factors being well-controlled in many patients [13]. Increasing evidence suggests that some non-traditional risk factors closely-related/specific to CKD milieu such as uremic toxins and abnormal calcium-phosphate metabolism are strongly associated with the development and progression of CVD, thereby increasing risk for the so-called "cardiorenal syndrome".

CKD is a progressive disorder by nature. Upon reaching ESRD, renal replacement therapy, either dialysis or renal transplantation, is the only approved measures currently used to correct uremic symptoms and prolong life. Successful renal transplantation dramatically improves uremic symptoms and quality of life as well as CV abnormalities [14–16]. However, limitations of renal transplantation are due largely to a shortage of suitable kidney donors. Treatment for ESRD patients is therefore currently dominated by dialysis.

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Hypothesis: Uremic Toxins as a Risk Factor of Cardiorenal Syndrome

Despite tremendous advances in the development of dialysis technology, CV mortality is still unacceptably high in dialysis patients. Rates of all-cause mortality for dialysis patients are 6.3–8.2 times greater than the general population. In contrast, rates for renal transplantation patients are only 1.1–1.5 times greater [8]. Five-year survival probabilities after the initiation of CVD are 0.18 and 0.47 in dialysis and transplantation patients, respectively, compared to 0.64 in the general population [1]. Progression of LVH is still observed in long-term hemodialysis (HD) patients [17, 18], even when high blood pressure and anemia have been corrected [18]. Prevalence of LVH has been reported in up to 76 % in patients on HD for ≥10 years [19]. The severity of cardiac fibrosis increases with time in HD patients but regresses over time after transplantation [20]. Interestingly, the duration of pre-transplantation HD is negatively correlated with the degree of cardiac function recovery following successful transplantation [21].

Current conventional dialysis treatment ineffectively removes a number of organic compounds normally excreted by the kidneys, mainly due to the *high protein affinity* and *large molecular size* [22]. Given some of their reported pathophysiological actions, such non-dialyzable uremic compounds may represent potential additional CV risk factors in CKD patients.

Uremic retention compounds can be divided into 3 groups according to their physicochemical characteristics [23]: (1) small water-soluble compounds (molecular weight (MW) <500 Da), (2) middle molecules (MW >500 up to 32,000 Da) and (3) protein-bound compounds (small molecules, most of which have MW <500 Da, bound to albumin, MW ~66,500 Da [24]). Uremic retention solutes with adverse biological activity are collectively called 'uremic toxins'. Retained uremic toxins are not only a consequence but also a cause of CKD progression and responsible for many uremic symptoms. Protein-bound uremic toxins (PBUTs) appear to be the most clinically problematic because removal is severely limited with current conventional therapy. In the past few years, their negative CV impact has emerged but mostly with incompletely understood mechanisms. [25]

Evidence of Protein-Bound Uremic Toxins in the Development of Cardiorenal Syndrome

Adverse Clinical Outcomes

Among PBUTs, indoxyl sulfate (IS) and *p*-cresyl sulfate (*p*CS)/*p*-cresol have been the most extensively studied with regard to their adverse CV and renal effects. Increased serum levels of IS and *p*CS/*p*-cresol are associated with progression of CKD [26], and CV [27–29] and overall mortality [26–30] in both predialysis and dialysis CKD patients. High serum levels of *p*CS/*p*-cresol and homocysteine are also predictive of CV events [31, 32]. Recently, the presence of *p*-cresol in uremic sera has been found to be an artifact caused by strong acid hydrolysis of the conjugates *p*CS and *p*-cresyl glucuronide during measurement [33]. Therefore the adverse renal and CV effects of *p*-cresol demonstrated in clinical studies or experimental models most likely represent its conjugates, mainly *p*CS (>95 %).

Adverse Cardiovascular Effects

Atherosclerotic Vascular Disease

Evidence of a causative relationship between PBUTs and hallmarks of atherosclerosis has been demonstrated in preclinical studies, as summarized in Table 19.1. Endothelial dysfunction can be induced by IS [35, 39], *p*CS [57] and homocysteine [67]. IS and homocysteine promote proliferation of vascular smooth muscle cells [47, 69], inflammatory activation [68] and increased oxidative stress [39, 67]. In addition, a negative correlation between serum IS and high-density lipoprotein cholesterol has been demonstrated in HD patients [74].

Interestingly, adverse effects of homocysteine can be worsened in the state of folate and vitamins B6 and B12 deficiency [68]. However, putative beneficial effects of folate and vitamin B supplementation on CV outcomes remain controversial. Results from large clinical trials vary from beneficial [75], neutral [76, 77] to even harmful CV effects [78].

Non-atherosclerotic Vascular Disease

PBUTs are implicated in vascular stiffness, calcification and ossification, common CKD-associated vascular abnormalities. Serum IS levels have been demonstrated to correlate with vascular stiffness [27], and both IS and *p*CS circulating levels correlate with vascular/aortic calcification in various stages of CKD [27, 29]. Pre-clinical studies (Table 19.1) have shown that IS [53] and homocysteine [70] promote vascular calcification in association with activation of cell senescence [53]. Both toxins have been demonstrated *in vitro* to be involved in osteogenic differentiation of vascular smooth muscle cell [54, 70].

Cardiac Remodeling and Dysfunction

Study of direct cardiac effects of PBUTs has been extremely rare. It is surprising that investigation of homocysteine on the heart or cardiac cells has never been reported despite its well-known adverse CV outcomes. Recently, pro-fibrotic and pro-hypertrophic effects of IS, cresol and cresol conjugates were investigated in cultured cardiac fibroblasts and myocytes (Table 19.1) [73]. Among the tested compounds,

Table 19.1 Clinical outcomes and direct cardiac, vascular and renal effects of protein-bound uremic toxins

Compounds	Adverse clinical cardiorenal outcomes	Cardiac effects	Vascular effects	Renal effects
Indoxyl sulfate	Progression of CKD [26, 27]	Increased collagen synthesis in NCF [34]	Defective endothelial proliferation and wound repair *in vitro* [35]	Functional impairment [36–38]
	CV mortality [27]	Increased protein synthesis in NCM [34]	Enhanced oxidative stress determined by an increase in ROS production and NADPH oxidase activity, and a reduction in glutathione levels in cultured HUVEC [39]	Renal inflammation with increased pro-inflammatory cytokine gene expression both *in vitro* [40] and *in vivo* [41]
	All-cause mortality [27]	Diastolic LV dysfunction [42]	Promote ROS production and a senescence in cultured HUVEC [43]	Glomerulosclerosis and renal interstitial fibrosis with activation of pro-fibrotic gene and protein expression *in vivo* [36–38, 44], [45, 46]
		Cardiac fibrosis *in vivo* [42, 52]	Promote VSMC proliferation *in vitro* [47]	Enhancing renal oxidative stress, both *in vitro* [48, 49] and *in vivo* [50, 51]
		Increased cardiac oxidative stress *in vivo* [52]	Promote aortic calcification and cell senescence *in vivo* in association with an increased expression of senescence-related proteins such as p16 (INK4a), p21(WAF1/CIP1), p53 and retinoblastoma protein [53]	Renal fibrosis in association with CpG hypermethylation of the Klotho gene (a renoprotective antiaging gene) and decreased Klotho expression in renal tubular cells both *in vitro* and *in vivo* [46]
			Promotes ROS generation and osteoblastic transformation of aortic smooth muscle cell *in vitro* by increasing expression of osteoblast-specific proteins such as core binding factor 1, osteopontin and alkaline phosphatase [54]	Promote cell senescence in the kidneys by down-regulating renal klotho gene and protein expression both *in vitro* and *in vivo*, in association with ROS production and activation of nuclear factor-kB in renal proximal tubular cells [55]
			Enhance leukocyte adhesion and extravasation and interrupt blood flow [56]	
p-cresyl sulfate	Progression of CKD [26, 29]	Increased collagen synthesis in NCF [34]	Promote endothelial dysfunction by inducing Rho kinase-mediated microparticle release from cultured HUVEC [57]	Increased inflammatory gene expression in cultured renal proximal tubular cells [40]
	CV mortality [28, 29]	Increased protein synthesis in NCM [34]	Increased endothelial permeability to albumin *in vitro*, in the presence of *p*-cresyl glucoronide [58]	Glomerulosclerosis and renal interstitial fibrosis with activation of pro-fibrotic gene and protein expression *in vivo* [45]
	All-cause mortality [26, 29]		Enhance leukocyte rolling *in vivo* [56]	Renal fibrosis in association with CpG hypermethylation of the Klotho gene (renoprotective antiaging gene) and decreased Klotho expression in renal tubular cells both *in vitro* and *in vivo* [46]
			Impaired blood flow and cause vascular leakage, in the presence of *p*-cresyl glucoronide *in vivo* [56]	
p-cresol (present in the body as its conjugated forms, mainly p-cresyl sulfate)	CV events [31]	Increased protein synthesis in NCM [34]	Decreased endothelial proliferation and wound repair *in vitro* [35]	Potentially inducing renal tubular adenoma [59]
	All-cause mortality [30]	Abnormal changes in the gap junction in cultured cardiomyocytes [60]	Inhibit cytokine-induced endothelial adhesion molecule expression and endothelium/monocyte adhesion *in vitro* [61]	

(continued)

Table 19.1 (continued)

Compounds	Adverse clinical cardiorenal outcomes	Cardiac effects	Vascular effects	Renal effects
Phenylacetic acid	n/a	Increased protein synthesis in NCM [34]	n/a	Inducing inflammatory cytokine gene expression *in vitro* [62]
Indole-3-acetic acid	n/a	n/a	Induce CD133+ cell apoptosis *in vitro* [63]	Functional impairment [64] Glomerular sclerosis and interstitial fibrosis [64] Enhancing renal oxidative stress *in vitro* [48]
Homocysteine	CV events [32, 65, 66] All-cause mortality [32, 66]	n/a (despite a strong association between homocysteine and poor cardiovascular outcomes demonstrated)	Oxidative stress-induced endothelial dysfunction and damage [67] Increased expression of vascular inflammatory and thrombogenic mediators [68] MAPK-mediated VSMC proliferation [69] Promote calcium deposition and osteogenic differentiation in VSMCs cocultured with THP-1 cells (human leukemia monocytic cell line) [70]	n/a
Hippuric acid	n/a	n/a	n/a	Functional impairment [64] Glomerular sclerosis [64]
Phenol	n/a	suppress contractility of cardiac muscle in *vitro* [71]	n/a	n/a
Hydroquinone	n/a	n/a	n/a	Tumorigenesis of renal tubules in animal models [72]

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CKD chronic kidney disease, *CV* cardiovascular, *HUVEC* human umbilical vein endothelial cells, *MAPK* mitogen-activated protein kinase, *NCF* neonatal rat cardiac fibroblast, *NCM* neonatal rat cardiac myocyte, *n/a* no data available, *NADPH* nicotinamide adenine dinucleotide 3-phosphate, *ROS* reactive oxygen species, *VSMC* vascular smooth muscle cell

IS has strongest pro-fibrotic and pro-hypertrophic effects followed by *pCS* whilst *p*-cresol, *m*-cresol, *m*-cresyl sulfate and phenylacetic acid had little or no effect. IS also enhances gene expression of pro-inflammatory cytokines interleukin (IL)-1β, IL-6 and tumor necrosis factor (TNF)-α in THP-1 cells [34]. The pro-fibrotic, pro-hypertrophic and pro-inflammatory effects of IS are likely mediated *via* activation of p38 mitogen-activated protein kinase (MAPK), p44/42 MAPK and nuclear factor-kappa B (NF-κB). This suggests that IS may be implicated in adverse cardiac remodeling processes. The follow-on *in vitro* study shows indirect evidence of intracellular IS uptake into cardiac myocytes and fibroblasts *via* organic anion transporters (OATs) 1 and 3 [79]. However, further investigation of cellular entry mechanisms of IS may be clinically useful since several OAT inhibitors are readily available and currently used for other indications.

Increased serum IS levels observed in an CKD model of 5/6-subtotal nephrectomy is associated with diastolic left ventricular dysfunction, cardiac fibrosis [42] and increased cardiac oxidative stress [52]; all are prevented by an IS-lowering treatment.

Adverse Renal Effects

High serum *p*CS [26, 29] and IS [26, 27] levels are independently associated with progression of CKD in patients at different stages of CKD.

Most PBUTs are normally excreted in urine by renal tubular cells therefore these cells are likely to be the first injured by accumulated toxins. Among PBUTs, renal toxicity due to IS appears to be strongest, demonstrated both *in vitro* and *in vivo* (Table 19.1) [80–82]. Collectively, IS accelerates the progression of CKD due largely to its pro-fibrotic, pro-inflammatory and oxidative stress-inducing effects. Findings in favor of an upregulation of transforming growth factor-β1 (TGF-β1) and reactive oxygen species (ROS) have been associated with activation of NF-κB [48]. In addition, IS has been recently demonstrated to be implicated in renal cell senescence by reducing expression of an anti-aging gene namely klotho through increased production of ROS and activation of NF-κB in renal proximal tubular cells [55]. Thus, the ROS/NF-κB/TGF-β1 pathway is most likely involved in IS-induced renal toxicity.

Cardiovascular and renal toxicity induced by other PBUTs are listed in Table 19.1 [64].

Novel Treatments Targeting Protein-Bound Uremic Toxins

As previously mentioned, current treatment for ESRD patients is largely based on dialysis. Developments in dialysis technology to remove a whole range of retained uremic solutes has gradually progressed in the past decade but residual uremic symptoms still persist and additional survival years (as achieved with transplantation) are not observed. Increased circulating levels of PBUTs in the setting of CKD are generally explained by impaired renal excretory function. In fact, a number of PBUTs including IS and *p*CS are derived from the colon via microbiotic metabolism. Indoles and phenols, the prototypes of which are IS and *p*CS, are important colon-derived microbiotic compounds originating from dietary tryptophan and tyrosine, respectively. Thus, decreasing circulating levels of colon-derived PBUTs in CKD may be achieved by two means; enhancing PBUTs removal by new dialysis technology and suppressing colonic production (Fig. 19.1).

Enhancing Removal by Dialysis Strategies

The efficacy of dialysis removal generally depends on the permeability and surface area/material of dialysis membrane, frequency of dialysis and time spent on each dialysis session [83, 84]. Removal of middle molecules by conventional dialysis has also been a problem but developments in dialysis technology and protocols have improved their clearance [22, 85]. For instance, compared to thrice a week by conventional HD, nocturnal HD 6 times a week significantly improves clearance of parathyroid hormone, a middle molecule, that is associated with an improvement in LVH [86]. However, the removal efficacy of most PBUTs is not significantly increased with more frequent dialysis, a larger dialyzer pore size (except hippuric acid) [87] or a convective strategy [85, 88]. At present, IS, *p*CS and homocysteine, all of which circulating levels are increased in CKD patients, appear to be most potentially toxic to the CV system. However homocysteine has been demonstrated to be better removed by nocturnal HD compared with a standard thrice-weekly HD [89], by high-flux HD compared with low flux HD [90], and use of convective dialysis [91]. There is currently no approved system for long-term dialysis-dependent ESRD patients to substantially improve removal of circulating IS and *p*CS. Use of protein-leaking membranes offers a better clearance of protein-bound solutes however large amounts (2–6 g/4 h) of albumin loss [92] could worsen the state of protein malnutrition usually present in dialysis patients.

Addition of sorbent system to conventional dialysis has been developed to improve removal of uremic solutes with a large MW or high protein binding capacity. A preliminary study showed promising results for clearance of tested middle molecules and cytokines with a MW range from 12 to 21 kD [93]. Another study using coated carbon hemoperfusion reported a limited removal of protein-bound solutes including IS due largely to the inadequate speed of carbon to take up solutes at low concentration, not the adsorptive capacity [94]. Recently, a dual layer hollow fiber mixed

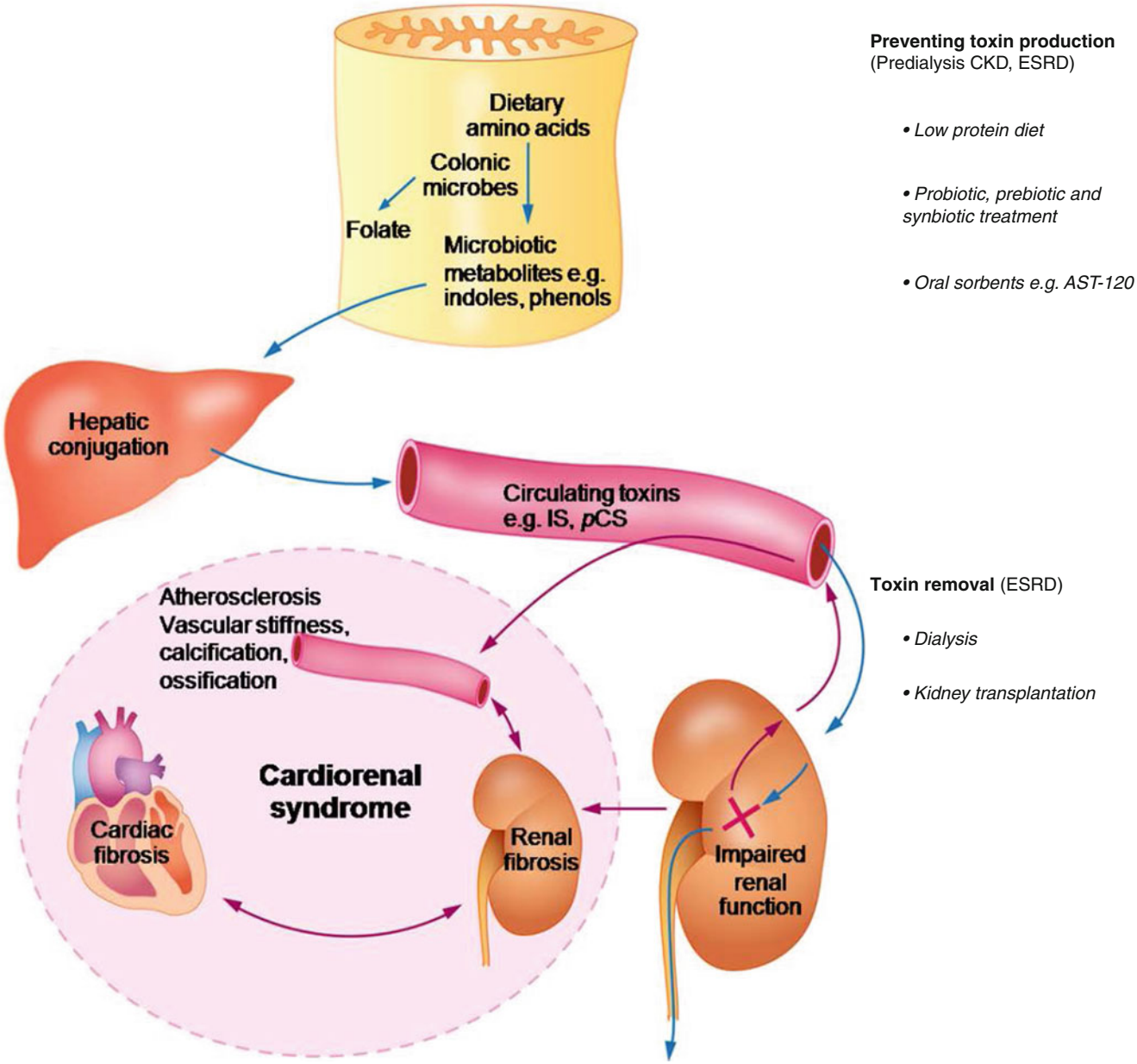

Fig. 19.1 Therapeutic strategies targeting colon-derived protein bound uremic toxins for cardiorenal syndrome. *CKD* chronic kidney disease, *ESRD* end-stage renal disease, *IS* indoxyl sulfate, *pCS* *p*-cresyl sulfate

matrix membrane with embedded adsorptive carbon particles has been demonstrated to effectively remove the daily production of IS, *p*CS and hippuric acid [95].

The optimal sorbent system might augment the efficacy of conventional dialysis in PBUT removal thereby potentially providing clinical benefits, although invention is a big task in terms of its complexity and cost.

Treatment Suppressing Production of Colon-Derived Solutes

Changes in gut microbiome occur in the setting of CKD [96]. Increased amounts of protein delivered to the colon due to impaired intestinal absorption in CKD results in (1) increasing substrates for uremic solute production and (2) a shift of normal colonic bacterial fermentation pattern from a saccharolytic to proteolytic pattern [97]. The increased production of uremic solutes may be further accentuated by a prolonged colonic transit time commonly observed in long-term HD patients [98]. Decreasing colon-derived PBUTs by targeting the colon may be achieved by several means which are much simpler, safer and cheaper than dialysis treatment and could start at the early pre-dialysis stages of CKD.

Probiotic, Prebiotic and Synbiotic Treatment

Use of organisms lactic acid bacilli [99] and *Bifidobacterium longum* [100, 101] to restore the disturbed gut microbiome

milieu or '*probiotics*' reduces serum levels of IS in CKD patients on HD. The oral administration of *Bifidobacterium longum* in a gastroresistant seamless capsule to HD patients is also effective in reducing serum homocysteine levels [101], likely associated with a folate and vitamin B12 producing effect of probiotics. A small prospective, double-blind randomized-controlled crossover trial on probiotic treatment for 6 months in 46 patients with CKD stages 3 and 4 demonstrated a significant decrease in blood urea nitrogen and creatinine levels and an overall improvement in quality of life [102].

'*Prebiotics*', in contrast, uses a non-digestible food ingredient in order to selectively stimulate the activity of some colonic bacteria. Use of non-starch polysaccharides or digestion-resistant starches, considered as dietary fiber, could reverse the ratio of saccharolytic to proteolytic colonic microbial activity back to the normal state thereby limiting production of colon-derived solutes originating from dietary proteins. A non-randomized phase I/II study in maintenance HD patients demonstrated that administration of prebiotic oligofructose-enriched inulin for 4 weeks significantly reduces generation and serum levels of *p*CS but not IS [103].

'*Synbiotics*' is a combination of probiotic and prebiotic treatment. Synbiotic treatment, using *Lactobacillus casei* and *Bifidobacterium breve* as probiotics and galacto-oligosaccharides as prebiotics, for 2 weeks significantly decrease serum *p*-cresol levels in association with an improvement of bowel habits in HD patients [104].

Collectively, probiotic, prebiotic and synbiotic treatments show favorable effects on reducing problematic PBUTs, preserving renal function and improving quality of life. However, the impact of such treatments on major clinical endpoints such as CV events and mortality has not been studied.

Protein Restriction Diet

Protein restriction diet reduces substrates used in the production of colon-derived solutes. A very low protein diet has been demonstrated to significantly lower serum IS levels in predialysis CKD patients [105]. In this study a mixture of ketoanalogue and amino acid supplements was simultaneously administrated to prevent a negative nitrogen balance. In addition, any means that decrease colonic transit time such as laxatives could help suppress the production of colon-derived uremic solutes. Similar to probiotic and prebiotic treatment, study on major renal and cardiovascular outcomes of protein restriction diet is needed to clarify its potential role.

Oral Sorbents

Activated carbon has been widely used to remove various toxins from the gastrointestinal tract. AST-120 is a novel microspherical carbon adsorbent with high porosity and adsorptive capacity selective to low MW molecules (<10 kDa) [106] which therefore does not disturb GI enzymes (high MV) [107] or nutritional status. The kinetic profile of AST-120 is optimized for maximum binding in the lower GI tract where organic compounds including indoles and phenols, are produced. AST-120 is not degraded by digestive enzymes and intestinal bacteria thereby stimulating gastrointestinal excretion of such compounds after being adsorbed [107].

AST-120 effectively adsorbs colonic microbial metabolites and decrease circulating levels of uremic solutes in the setting of CKD such as IS, *p*CS, hippuric acid, phenyl sulfate, 4-ethylphenyl sulfate [108] and advanced glycation end-products [109]. AST-120 does not disturb creatinine and urea nitrogen balance therefore both traditional markers are acceptable for assessing renal function following AST-120 treatment [110].

Preclinical Studies

Renal Endpoints

AST-120 administration in uremic rats significantly reduces serum, renal and urinary IS levels [38, 107, 111] in association with an improvement in renal function and IS-induced renal tubulointerstitial fibrosis and glomerular sclerosis [36, 44, 107, 111–113]. Renal macrophage infiltration observed in failing kidneys is also suppressed by AST-120 [44].

Molecular study demonstrates that AST-120 decreases renal expression of pro-fibrotic (TGF-β1, tissue inhibitor of metalloproteinase-1 and pro-α1 (I) collagen), pro-inflammatory (intercellular adhesion molecule-1, osteopontin, monocyte chemotactic protein-1) and apoptosis-related (clusterin and osteopontin) genes [38, 107]. An antioxidative effect of AST-120 has been demonstrated in uremic rats [52, 112]. Anti-inflammatory, anti-fibrotic and anti-oxidative effects of AST-120 have been associated with attenuation of renal cortical NF-κB activation [44, 48].

Renoprotective effects of AST-120 are not only observed in a severe CKD (5/6-nephrectomy) model but in less severe CKD models 3/4-nephrectomy [44, 114] as well as diabetic nephropathy [107, 111], suggesting that AST-120 could be of benefit in patients with early stages CKD or diabetic nephropathy.

Cardiac Endpoints

Administration of AST-120 in a severe CKD model with high serum IS levels significantly reduces cardiac fibrosis, TGF-β protein expression and NF-κB phosphorylation [42]. Interestingly, a reduction of serum IS levels with AST-120 treatment was positively correlated with extent of cardiac fibrosis. Another study in the same CKD model demonstrated a similar suppressing effect of AST-120 on cardiac fibrosis with a reduction in expression of cardiac oxidative stress markers, 8-hydroxydeoxyguanosine and acrolein [52]. These data suggests that IS-induced cardiac fibrosis may be potentially mediated *via* the ROS/NF-κB/TGF-β1 pathway similar to the proposed mechanistic pathway of IS-induced renal fibrosis [81].

Vascular Endpoints

AST-120 has been demonstrated to alleviate atherosclerosis by limiting plaque extension, inflammation and necrosis in a mice CKD model with apolipoprotein E-deficiency [115]. AST-120 also reduces hypercholesterolemia and plasma very low density lipoprotein in association with improving plasma lipoprotein lipase and hepatic lipase activity and increasing protein expression of lipoprotein lipase and very low density lipoprotein receptor in skeletal muscle and adipose tissue [113].

Clinical Studies

Treatment with AST-120 (>24 months) in pre-dialysis stage CKD patients is associated with a 3.5-fold reduced risk for initiation of dialysis [116]. For HD patients starting AST-120 treatment at the predialysis stage (average treatment duration 15.1 months), 5-year survival significantly improved compared with those with no treatment [117]. AST-120 treatment preserves renal function in diabetic patients with CKD, both early [118] and advanced stage [119]. Benefits on survival and cost reduction are also observed in advance stage diabetic nephropathy [120].

Improved renal function and delayed CKD progression by AST-120 have been associated with a decrease in serum and urinary IS levels [121] and plasma TGF-β1 levels [122]. An improvement of renal function over time was observed after ≥1-year suggesting benefit of long-term AST-120 treatment in pre-dialysis stage CKD patients [123].

Beneficial cardiovascular effects of AST-120 have been reported in CKD patients. AST-120 administration for 2 years (but not at 1 year) in predialysis patients significantly reduces carotid intimal media thickness and pulse wave velocity, a surrogate of vascular stiffness [124]. An improved aortic calcification index is observed in predialysis patients with 6-month duration of treatment [125]. AST-120 treatment for a relatively short treatment period of 6 months shows an improvement in IS-induced endothelial dysfunction by increasing flow-mediated endothelium-dependent vasodilatation in association with a reduction in IS levels and oxidative stress indicated by a decreased oxidized/reduced glutathione ratio [43]. Interestingly, predialysis CKD patients who are on AST-120 for at least 6 months have a significantly lower percentage of left ventricular concentric change compared with the untreated control group with comparable body mass index, systolic blood pressure, pulse pressure, history of coronary artery disease and prescribed medications [126], thereby potentially preventing LVH progression.

Nutritional status is improved with AST-120 by decreasing the free to protein-bound proportion of tryptophan leading to a less serotonin (an appetite suppressor) production and by increasing albumin and transferrin levels [127]. Combining AST-120 with a mild low protein diet shows a comparable effect on preserving renal function in CKD patients to a strict low protein diet [128]. Similarly, a prospective randomized controlled study has demonstrated that combined AST-120 and low protein diet is superior to a low protein diet alone [129].

AST-120 results in decreased serum IS levels and improves uremic symptoms in a dose-dependent fashion without pharmacokinetic drug-drug interactions with concomitant standard CKD medications after a 12-week treatment period in a phase II randomized controlled trial [130]. The magnitude of IS reduction at a AST-120 dose of 9 g/day in this U.S. study was comparable with a dose of 6 g/day (treatment duration of 1 month) in a Japanese study (39.3 % vs 38.5 %) [131]. However, both are approximately the same at 0.1 g/kg/day after body weight adjustment.

The first phase III multicenter, randomized, controlled trial investigated effects of AST-120 on the CKD progression in patients with moderate to severe predialysis CKD (n = 460) [132]. Although, no difference in incipient dialysis or survival between AST-120-treated and control groups was seen within 1 year, a significantly better preservation of renal function (determined by eGFR) was observed. Preliminary results from two large-scale multicenter randomized trials of AST-120 (Evaluating Prevention of Progression In Chronic Kidney Disease, EPPIC) showed no benefit on study endpoints comprising time to initiation of dialysis, doubling serum creatinine levels and death. However subgroup analysis indicated a reduction in CKD progression in patients with >80 % compliance who are at high risk (proteinuria and hematuria) for rapid progression of CKD [133]. Further study is therefore needed to clarify the benefit of AST-120 in CKD. A longer follow-up time with additional CV endpoints especially in patients with early stages CKD may be of clinical importance in terms of early intervention to delay CKD progression as well as to prevent CRS initiation.

Most studies have investigated therapeutic effects of AST-120 on either renal or CV endpoints in isolation. A simultaneous evaluation of both organ systems in patients with established CRS or at high risk for CRS is required to determine whether AST-120 has true cardiorenal protective effects. A small non-randomized before-after trial has reported an improvement in renal function, congestive heart failure signs and symptoms and hospitalizations after AST-120 treatment for 2 years in heart failure patients with moderate CKD [134]. Recently, a reduction in renal fibrosis as well as renal and cardiac expression of pro-fibrosis markers has been demonstrated in a chronic myocardial infarction model with impaired renal function [135]. Given that progressive fibrosis is a final common pathway of the failure of the heart or the kidneys or both regardless of primary cause of injury, any treatment counteracting cardiorenal fibrosis may be of therapeutic importance.

Summary

The hypothesis that uremic toxins (especially non-dialyzable) are a CKD-specific risk factor for development and progression of CRS has recently emerged. Efforts to improve dialysis techniques to better remove these toxins and treatment targeting toxin production has begun to be investigated. The latter, despite selectively reducing some groups of toxins, is generally simple and safe, and may offer additional advantages over dialysis because administration can be given at predialysis stage. The colon, where many uremic solutes including the most problematic PBUTs, IS and *p*CS are produced, is also a potential target of treatment. Strategies either in maintenance of the normal colonic microbiotic milieu or to adsorb microbial metabolites are promising in reducing colon-derived uremic solutes, however their impact on cardiorenal outcomes needs to be further evaluated.

Importantly, many uremic toxins possibly involving in the pathogenesis of CRS may well still be unidentified in terms of chemical composition and mechanisms that mediate adverse biological effects. Increased knowledge of toxins with their negative impact on cardiorenal system is crucial in the development of appropriately-targeted therapeutic strategies.

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Challenging Complex Diseases

20

Jonas Spaak

Co-morbidities: More Common Than Not

Clinical Case Scenario

Sven is a 67 year old obese (BMI 35 kg/m^2) Swedish man who has had type II diabetes for 11 years controlled moderately well on diet and metformin. He has hypertension and high cholesterol levels, responding to blood pressure treatment (Ramipril) and a statin, and microalbuminuria. Five years ago he had a silent anterior myocardial infarction, presenting as breathlessness. Since then he has paroxysmal atrial fibrillation and impaired LV function (LVEF 35 %). He is treated with warfarin, bisoprolol, ramipril and spironolactone. After his myocardial infarction his renal function was found to be abnormal, with an eGFR of 35–40 mL/min which necessitated stopping the metformin and starting insulin, leading to further weight gain and hyperglycaemia. He developed recurrent gout necessitating allopurinol. Three years ago he became anaemic, with an iron deficiency pattern, requiring several courses of intravenous iron, then an erythropoesis stimulating agent (darbepoetin). In the last 12 months he experienced retinal haemorrhages severely reducing his eyesight. Recently he had unstable angina requiring coronary angioplasty and stenting, but leading to further loss of kidney function (eGFR now 18 mL/min) and increasing leg claudication with a non-healing foot ulcer. Currently he attends (a) diabetes clinic, every 3 months, (b) vascular surgical clinic, twice a year, (c) nephrology clinic, every 2 months, (d) cardiology clinic, every 3 months, (e) eye clinic, every 2 months, (f) foot/ulcer clinic, monthly and (g) general practitioner for warfarin dosing, every 1–2 months. His days are filled with appointments, and he does bloods almost every week (one for each specialty clinic). He has noticed that his care seems fragmented, disjointed and poorly co-ordinated, and he wonders why he cannot receive his care at the same place?

Background

Cardiovascular diseases (CVD) are the leading cause of death globally, and if not prevented and treated optimally causing increased morbidity, impaired quality of life and premature death [1]. Hyperlipidemia, smoking, hypertension and diabetes are well established as the most powerful modifiable risk factors for CVD.

About 20 % of the population in developed countries have hypertension, while the prevalence exceeds 50 % in those above age 60 years [2]. The prevalence of chronic kidney disease (CKD), defined by reduced glomerular filtration rate (GFR) or albuminuria, is in the range of 10–13 % in the general population and about 30 % in those above 65 years of age [2]. The prevalence of diagnosed diabetes mellitus in adults ≥65 years is 10–20 % in many European countries, compared to 27 % in North America, and an additional 50 % have pre-diabetes [3]. In addition, data from NHANES 2005–2006 show that 46 % of diabetes cases may remain undiagnosed [4]. Thus, with this high prevalence numbers, the risk of having several of these diseases is high. In fact, in patients 65 years or older, it is more common to have two or more chronic conditions, than just one [5].

Despite that diabetes, CKD and cardiovascular disease (Fig. 20.1) often occur together, related both to interactions between the conditions and to the presence of shared risk factors, this overlap and the interactions remain underappreciated

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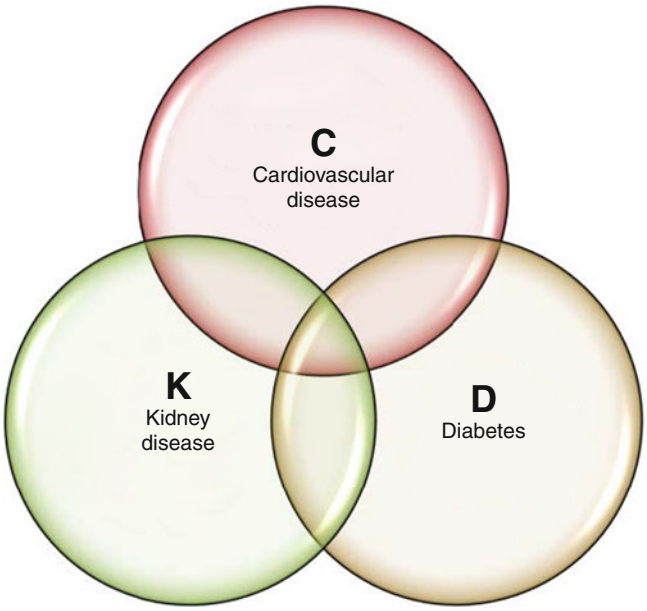

Fig. 20.1 Common and commonly overlapping co-morbidities [6]

by many care providers [6]. A progressively increased subspecialisation has led to that the cardiologists' treats the heart, nephrologists' the kidneys and endocrinologists' diabetes.

Despite the subspecialisation it is vital to take into account comorbidities. For instance a reduced renal function significantly limits available treatment choices in diabetes, and exclude patients from newer oral anticoagulation therapies. Reduced renal function in the setting of heart failure is particularly complex since renin angiotensin aldosterone blockade consistently worsen renal function and increase potassium levels. Several proven therapies may lose their usefulness as renal function decline. Without close co-ordination of treatment, underpinned by good communication and IT systems, it is a recipe for poorer quality, fragmented care, frustrating for patient, family and all medical people concerned. Improved interdisciplinary care and integration are key factors for the future improved management of these common morbidities.

Co-morbidities and Compound Risk

The exact reasons why kidney failure causes heart disease, and vice versa (the cardiorenal syndrome) is still incompletely understood [7], although CKD and diabetes share many of the mechanisms causing accelerated vascular aging [8]. It has been argued that diabetes is a cardiovascular disease [9], and similar arguments apply in the case of CKD [6]. In recent years CKD has emerged as a factor of equal importance as diabetes for future cardiovascular events [10–14]. Furthermore, patients with simultaneous comorbidities have a markedly increased risk. For instance in the Study of Heart and Renal Protection (SHARP), despite similar GFR, patients with diabetes had an adjusted risk of death two-fold higher than that those with cystic kidney disease alone (relative risk 2.35) [15].

In acute coronary syndromes, the single most common cause of death worldwide [1], approximately 40 % of the patients have at least moderate kidney dysfunction with an eGFR below 60 mL/min/m^2 [16]. The 1-year-mortality among these is about 25 %, compared to 5 % in patients with normal renal function [16]. The increased mortality in CKD patients after an acute coronary event is directly related to decreasing kidney function [10, 14]. This may in part be due to the fact that patients with kidney dysfunction are receiving less active treatment, such as with early revascularisation [17], but may also be caused by a range of disturbances in for instance haemostasis and vascular function [8, 18]. The lack of guidelines can be attributed to limited clinical data, as the majority of randomised trials in acute coronary syndromes so far have excluded CKD patients [19].

Thus, patients with concomitant cardiovascular disease, renal dysfunction and diabetes are despite their high risk and high health care consumption often not optimally treated, since an increasingly specialised medical care too often treat these diseases in separate silos. Current studies and guidelines follow the same pattern.

Multidisciplinary and Multi-professional Intervention

In medicine, multidisciplinary care used to refer to physicians in different specialities working together to provide the most comprehensive treatment plan for the patients. The term multi-professional used to refer to different professional categories, such as physicians, nurses, physiotherapists and pharmacists, working together. However, in recent years this distinction has dissolved and the most commonly used term is multidisciplinary. Both involve combining two or more disciplines into the task at hand; *i.e.* the intervention.

Multidisciplinary Intervention: Nephrology

The chronic nature of CKD has led the nephrology speciality to early recognise the importance of multidisciplinary intervention. For instance nurse practitioners have taken a large active part in dialysis treatment since the early days [20].

In dialysis patients, a comparison of outcomes between Canada and Italy suggests that despite equal and long exposure to nephrology care prior to dialysis, there appears to be an association of survival advantage for patients exposed to formalized multidisciplinary clinic programmes in addition to standard nephrologists' follow-up [21]. By multidisciplinary they here refer to a team of a nurse educators, nephrologists, social workers, nutritionists, and pharmacists. In the nephrology setting it is important to note that these integrated clinics are usually instigated with the underlying objective of facilitating and prepare patients for renal replacement therapy.

However it appears they are sometimes also effective in reducing renal decline.

Cohort studies in CKD suggest that similar integrated, multidisciplinary clinics based on a nephrologist and a team with other professions are associated with improvements in metabolic and BP control [22, 23]. Multidisciplinary clinics are also associated with a slower decline in GFR than usual care [24], and a significant reduction in the risk for all-cause mortality [23, 25].

Results from randomised trials are less clear. Barrett and co-workers randomised 474 patients with median eGFR of 42 mL/min to either standard care by a general practitioner, or care by a nurse-coordinated team including a nephrologist. Guided by protocols, the intervention team targeted risk factors for adverse kidney and cardiovascular outcomes. Over a median of 24 months, the nurse-coordinated team did not affect rate of GFR decline or control of most risk factors compared with usual care [26]. In another trial (the MASTERPLAN study), 788 patients with moderate to severe CKD were randomised to receive nurse practitioner support added to physician care, or physician care alone. Median follow-up was 5.7 years, and the intervention reduced the incidence of the composite renal endpoint by 20 %, and decreased the decline in eGFR by 0.45 mL/min per year compared with the control group [27].

Taking these data in consideration, nephrology guidelines state that people with progressive CKD should be managed in a multidisciplinary care setting, with access to education and counselling [28]. Again, these interventions are aimed at facilitating and prepare patients for transplantation and dialysis, but have been shown to delay renal decline on their own. The specific components for CKD models of care should include protocols for laboratory and clinic visits, attention to cardiovascular co-morbidities and CKD-associated co-morbidities such as anaemia, a vaccination program, an education program which includes both general CKD and renal replacement therapy, education, self-management, lifestyle modification including diet, exercise, and smoking cessation, counselling and support for factors such as social bereavement, depression, and anxiety [28–30].

The details on how to best achieve all these components, particularly in patients with multiple co-morbidities is yet to be determined.

Multidisciplinary Intervention: Diabetes

> With proper consideration of the fundamentals of treatment and team-approach, there can be life added to the years and years to the lives of our increasing diabetic population.
>
> W. Pote Jr, California, 1958 [31]

Patients with diabetes are living an average of 8.5–10 years shorter than non-diabetics, and it is particularly cardiovascular disease that leads to premature death [32]. Treatment studies in diabetes have traditionally focused primarily on blood sugar control, and secondarily on the most common risk factors like high blood pressure or lipids. However, it is clear that a multifactorial approach is required to achieve clinically relevant treatment effects [32, 33]. An excellent example of how efficient a multidisciplinary approach can be when implemented rigorously is the STENO-2 study [33]. By multidisciplinary they refer to a combined clinic with an endocrinologist, nurse practitioner, dietician and physiotherapists. The intervention group received aspirin, optimized treatment on glycaemic control, blood pressure, dyslipidemia, and comprehensive lifestyle intervention with both diet and exercise. The intervention not only halved the risk of nephropathy and retinopathy, but also halved the absolute risk of death over 13 years. STENO-2 included only type-2 diabetes patients, and excluded all with concomitant heart disease or kidney failure, notwithstanding their higher risk.

Despite the well established strong link between cardiovascular disease and diabetes, approximately 30–40 % of those with diabetes have undiagnosed cardiovascular disease [32]. It is not uncommon that first when the patient suffer a heart attack or stroke, it is found that they have type 2 diabetes.

Multidisciplinary Intervention: Cardiovascular

More than 80 % of all cardiovascular deaths can be delayed using changes in life-style and commonly prescribed drugs [34]. There is very good evidence for a range of measures to reduce the risk of both morbidity from cardiovascular disease and relapse in established cardiovascular disease [35]. There is consensus that all these measures should be carried out simultaneously. Despite this, many patients never receive the full benefits from these interventions due to frequent under-diagnosis, late presentation and under-treatment [36, 37]. This is particularly an issue for subjects with complex diseases.

In cardiology, the most studied and developed area is integrated heart failure clinics. It was early recognised that nurse-directed, multidisciplinary intervention improves quality of life, reduce hospital use and medical costs for patients with congestive heart failure [38, 39]. Following studies have also shown that multidisciplinary strategies for the management of heart failure patients also improve survival [38, 40]. Multidisciplinary in this setting also refer to clinics with cardiologists, nurse practitioners, physiotherapists, social workers and sometimes pharmacists.

"Holistic management" is currently a class IA recommendation in the European Society of Cardiology. The guidelines specify that the management should include not only optimised medical treatment but also patient education,

social support, exercise training, patient monitoring, and palliative care in a multidisciplinary management programme [41].

The same set of measures, although under somewhat different labels, are also recommended in the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines AHA/ACCF [42]. They further endorse a set of patient-centered practices for care coordination from the National Quality Forum [43]. The statement detail comprehensive specifications for successful care coordination for patients and their families.

Complex, Chronic Disease Management

Patients with concomitant cardiovascular disease, renal disease and diabetes represent a large proportion of all patients in cardiology, nephrology and diabetology. A progressively increased subspecialisation has led to that the cardiologist treats the heart, nephrologists the kidneys and endocrinologists' diabetes. At best, this causes the patient to spend substantial time visiting multiple specialists in each field, and at worst serious under-treatment of co-morbidities. This is not something new; already in 1979 Aldhizer et al. highlighted some of the problems associated with the care of patients with diabetes, with lack of coordination of care, multiple visits, multiple blood works, lack of and sometimes conflicting information, lack of prioritization of treatment goals, redundancy and excessive cost [44]. For the patient, it becomes almost impossible to detail the full medical history and work-up at each visit to a new caregiver, particularly given the shrinking time allotted each visit. Often vital information on previous plans and work-ups are not communicated to all health-care professionals involved in the care for the patient, in many places worsened by flawed IT solutions for medical records.

The amount of healthcare consumed can be phenomenal, as illustrated in Fig. 20.2, showing a not uncommon patient with 480 healthcare contacts during 18 months, not including the assisted living visits. And yet the perceived benefit and care received is not in proportion to the efforts spent [46]. Despite a high indication for optimal treatment, a majority of patients fail to reach basic secondary preventive measures, such as blood pressure [47], and lipid control [46, 48]. Traditional health-care models ascribe this to lack of patient compliance; a term that may imply that the patient and not the physician is at fault. From the patient's perspective, there is a great need for coordination, collaboration, education and improved care to optimize quality of life and reduce risk of disease progression.

Many institutions are developing chronic disease management programs, as detailed in the previous sections in this chapter. However, the majority focus on a single disease and may not recognise the extent of co-morbidities and the complexity of the diseases in many of these individuals. For example, of those patients who survive an acute myocardial infarction, 40 % have decreased kidney function, 30 % diabetes, and another 30 % impaired glucose tolerance [5].

As awareness of the existence of groups of patients suffering from several co-morbidities has spread, new approaches have been suggested for disease management. Instead of treating these patients separately in three different clinics, it may be possible to develop integrated care units which can gather the competence and organise the care around the patient.

Integrated Care Units

As the number of healthcare professionals, care settings, and treatments involved in a patient's care has increased, the coordination of care has become both more difficult and more vital.

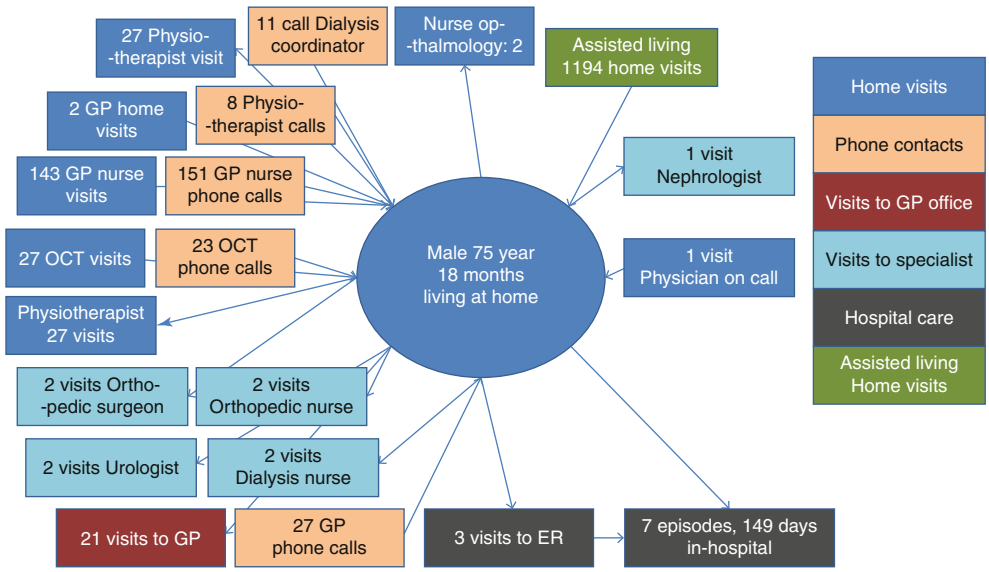

Fig. 20.2 Overview of healthcare consumption during 18 months for a 75 years old man with concomitant cardiovascular disease, CKD and diabetes (Based on data from "Team for the elderly, vision and reality", (in Swedish) [45])

As shown, patients with multiple chronic conditions receive a remarkable amount of health-care recourses. However, in most health-care system, no one is coordinating these interventions [46, 49]. Least of all the patient, who often feel out of control, their daily lives filled with pills, injections, glucose-checks, seeing doctors and nurses, and doing blood works.

Integrated care units is a new way of conducting health care [50]. Pilot studies using this approach have shown potential benefits, but also highlighted many difficulties with changing traditional organisations and physicians way of working [51].

The first multidisciplinary clinic in this area, in the meaning of integrating several specialities, is the Integrated Care Clinic at St. Paul's Hospital in Vancouver [52]. This clinic brings together medical specialists in nephrology, cardiology and endocrinology, as well as a knowledgeable team of nurses, pharmacists, dieticians and social workers. The goals of the Integrated Care Clinic are to increase communication across the traditional boundaries between different health care professionals and different disciplines, to improve coordination of patient care, to reduce medical appointments and duplicate testing for patients, and to provide more integrated education and self-management for the patient.

This clinic have focused on patients already attending a nephrology clinic and one or two of cardiology or endocrinology, and not aiming at those with unrecognized cardiovascular disease or undiagnosed (pre) diabetes [52]. In this setting, patients were randomised (n = 150) to either standard care, or to the integrated clinic. Mortality, hospitalization rates and progression to end-stage renal disease did not differ and a similar proportions in each group achieved clinical and laboratory targets. Their conclusion was that medical care of complex patients may be delivered in a single combined specialty clinic as compared to multiple disease specific clinics without compromising patient care or important health outcomes, with demonstrable outpatient costs savings [52]. This study did not find any difference in the number of specific symptoms patients reported (such as nausea and vomiting, loss of appetite, muscle cramps etc.), but patient reported outcome measures such as quality of life and empowerment were not reported.

In summary, more studies are needed on how to design integrated clinics to maximise patient value, in terms of patient related health outcomes, and efficiency [50]. How to specifically evaluate the difference for patients in terms of outcomes and for the health care system in terms of costs is also not clear, and cost comparisons are often excluded from the evaluation of quality improvement initiatives in general.

Defining Health Related Outcome

From a patients' perspective many more things in life matter than morbidity and mortality, while still many physicians think of CKD patients in terms of creatinine-levels or GFR. The average patient doesn't. That's why we need to change how we evaluate and talk to patients about their health. The objective of a multidisciplinary integrated clinic should be broader than only disease progression and mortality.

In 2006, Porter and Teisberg wrote the book "Redefining Health Care" [53]. Their concept has clear advantages by not selecting a single outcome measure as the only one to focus on, but takes into account all issues that may impact on the patient's life and quality of life. Continuing this work Karolinska Institutet has partnered with Harvard University and the Boston Consulting Group to develop the International Consortium for Health Outcomes Measurement (ICHOM; http://www.ichom.org/). Combined outcome models have been developed for a few common diseases, such as Myocardial Infarction, but not yet for CKD or more complex chronic diseases.

In the value-based health care (VBHC) model, the theory suggests that to maximize value for patients, care should be delivered in integrated care units, also referred to as integrated practice units. These units would involve co-located multidisciplinary teams who provide the full cycle of care for a given condition – inpatient, outpatient, and rehabilitative care as well as patient education, engagement and follow-up [53].

Person-Centered Health Care

Chronic diseases require a different way of providing care than acute, since almost all the actual care is done by the patient him/herself through changes in lifestyle and actively taking medications. This requires a well-informed and involved patient; informed at a level which the patient can take in. A model that in recent years been shown to produce very positive results also in chronic cardiovascular diseases is person centered care [54–56]. Person-centered care can be described as a partnership between patients and professional caregivers, where the patient is seen as a person with resources and abilities to participate in their own care [54]. The prerequisite for being able to provide person-centered care is that health professionals thoroughly understand not only the patient's illness but also the patient's situation in life. After establishing this relationship, a plan with goals and strategies for implementation and short - and long-term follow-up can be made. Realistic short-term successive goals on life-style improvements are usually an important part (Fig. 20.3).

Future Directions

> The good physician treats the disease;
> the great physician treats the patient who has the disease.
>
> Sir William Osler, (1849 Ontario, Canada; † 1919, Oxford)

As these co-morbidities grow more and more common due to lifestyle and an ageing population they are turning

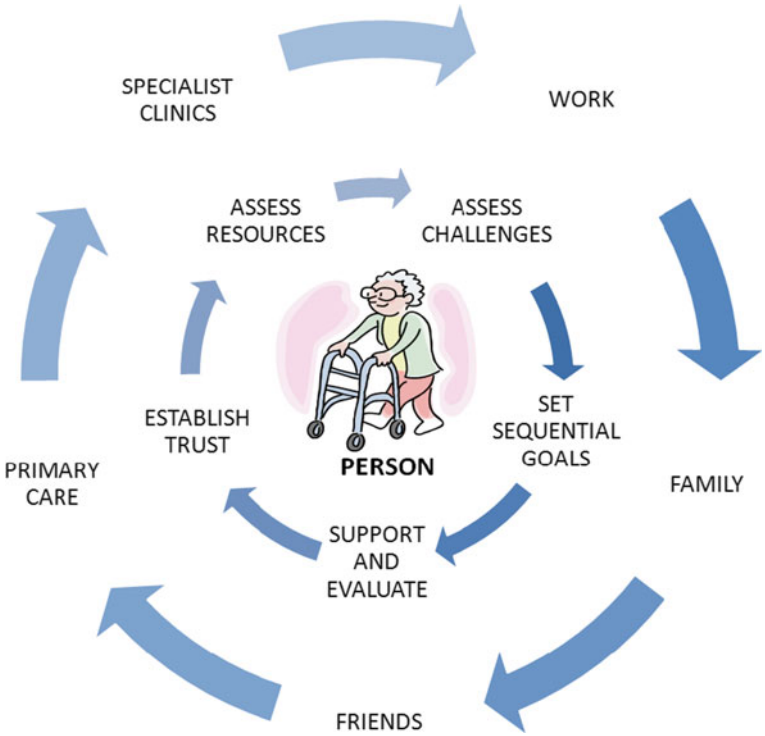

Fig. 20.3 Example of a person-centered approach. The team establishing a relationship and trust between caregiver and the person with the disease(s). The team assess the person's resources and goals, and work together with the person towards both the persons goals, and the evidence based medical goals

into a challenge not only for the individual physician and the clinics, but for the whole health-care system. Improved interdisciplinary care and integration, with a patient-centered approach, are key factors for the future management of challenging complex chronic diseases. However, the importance of prevention and early intervention before the person turn to patient cannot be understated.

Returning to the patient Sven in the introduction. He is a typical patient at the newly opened Heart-, Nephrology-, Diabetes Clinic (HND-centrum) at Danderyd University Hospital in Stockholm. We acknowledge it is a challenge, but believe that integrating cardiologist, nephrologists, diabetologists and specialty nurses into one clinic with a person-centered approach will address some of the issues mentioned above.

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Is "Me, Me, Me" the New "We, We, We"?: Can We Afford (Not) to Take the Plunge into the Personalised, Stratified Medicine Era?

21

David Goldsmith

Introduction

How did it feel just before that fateful comet extinguished the life of the dinosaurs? What were the dialectic currents running through medieval society just at the point the Reformation started to challenge existing dogma in the Christian world? Moving to more modern times, who predicted the epoch-making changes that developing and embracing the world-wide-web have now brought us? Was there any sense of "anticipation"? Were these extra-ordinary, and disruptive, changes presaged in any way? Or did they just arrive, explode, forcing a reactive re-arrangement of the remaining pieces in order to continue?

It's relevant to pose these queries because many would agree that, right now, there is a conceptual, genuine "tipping point" in relation to disease detection, medical intervention, and the relationships between science, medicine and society. If the transition from old to new systems ends up being mishandled not only may be a great, possibly unique, opportunity end up being squandered, but, in so doing, many of the systems which have been so carefully established as a framework for the very successful medical interventions we have increasingly used and relied on since the Second World War may be irretrievably damaged. Our successes to date in terms of medical progress have owed a great deal to "we" medicine. Where we prioritise the improvement of the health and welfare of all using a skilful melange of prevention, sanitation, detection, education, vaccination, and most recently, medication. Priorities for which are decided by public bodies, society and government, with "acquiescence" from the public, who have (so far) put their trust in the medical and scientific communities to deliver solutions to their healthcare challenges. Overall, by and large, it has worked well.

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However, the shortly-arriving "Brave New World" can be reduced to the pithy epithet of "me" medicine. This is where the demand of the individual, with the sovereign "right" to investigation and treatment, regardless of a wider context, is pre-eminent. It is a corollary of the very necessary transfer of information and knowledge about illnesses and treatments across from the professional domain to that of the laity, while information about patients' own biological processes (biomarkers, genomic data) is transferred to specialist repositories in ever-increasing volumes. The internet age allows anyone with a connected computer instant access to realms of information. Dogma-derived decisions will be increasingly challenged as a result. This "information emancipation" is being allied to interventional "personalisation" which it is said will flow from information culled from patients' biomarkers and genes. But, if this approach is now adopted, and thus it supplants "we" medicine, unless it is even more successful than what it is replacing, there is a risk that healthcare disparities will rapidly accentuate and grow. Our startling successes against many (but not all) communicable diseases through eradication programmes heavily emphasising prevention, and some similar, if less impressive, successes against non-communicable disease risk factors (raised blood pressure and tobacco smoking in particular), should in no way leave us any room for the slightest complacency about our future progress and success. Ultimately, we now need a new "contract" or "compact" between insurers-payers, patients and practitioners.

The implications of the marked "greying" or ageing of society in terms of exposure to chronic "medical" conditions – diabetes, arthritis, dementia, cancer – which have become our modern scourges, but without vaccines or "one-off" interventions at our disposal – means that healthcare economies are being seriously stretched, not only coping with this, but also with rapidly mounting costs of new drugs and devices. The chronic management of irreversible conditions is ruinously expensive, as these conditions often reduce active working (tax-paying) life, while partially-successful interventions simply extend the number of years of chronic

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illness and dependency-disability in "retirement". Moreover, along with these changes, we now sit on the cusp of a "genetic revolution" with the siren promises of individual genetic analysis being the fulcrum for individual "life and health plans". One can envisage, in what is a frankly dystopian view, compulsory neonatal genetic and biomarker screening, achieving the "mapping out" of the future susceptibilities and frailties of a whole society comprising countless individuals. In the future this challenge would also be coupled to a well-informed patient population rightly demanding the "best" treatment for them; perhaps seeing that, in return for the voluntary disclosure of their genetic and phenotypic data, they should demand access to the best treatments. The old, communistic, "one size fits all" consensus – which allowed for central control and command – is now under assault as never before. Of course, it is argued by the proponents of this *new world order* that screened cohorts can in fact be given the opportunity to "avoid" risky behaviours, and thus, by so doing, to avoid the diseases that would otherwise then befall them. And those at identifiable risk of developing diseases in later life could also potentially have "preventive" medical interventions before diseases strike – primary prevention. Seductive siren-song reasoning this may indeed be, but, frankly, still very heavy on assertion, and very light on evidence.

How Did It All Begin?

In the 1950s and 1960s most advanced healthcare systems were set up around the notion that cancer, cardiovascular disease (CVD), and infections were the key health challenges to be tackled, and eliminated. Risk factors for all three were detected and measured using epidemiological observations. As an example, data from the life-insurance companies in the 1920s and 1930s clearly described BP change over a lifespan, and showed that higher BP equated to more strokes. Very early (1960s) randomised controlled studies [1], using the simple drugs available at that time to reduce BP, showed a major impact on the development of new strokes where BP fell on treatment. This success was soon mirrored by the impact of lipid-lowering therapy on the development of myocardial infarction and other major adverse cardiac events. The emphasis then fell on "population"-based detection and screening strategies using verified and reliable "risk factors" – such as past medical history, diabetes, kidney disease, cholesterol, smoking, race and age – to determine whom to target. Targets for intervention included diet (less sugar, less fat, less salt and more recently calls for less phosphate), smoking cessation, exercise, and most recently, of course, increasingly many pharmacological agents.

CVD scoring schemes, such as Framingham [2], were also developed based on long-term cohort hard end-point-based follow-up studies using just these parameters. These were used in fresh cohorts in a "predictive" way, allowing those "at the greatest perceived or theoretical risk" to receive intervention before they had ever reached a major adverse event (so marking the transition from secondary or "reactive" prevention to primary "anticipatory" prevention). In the UK, NICE fixed the "CV risk" threshold for targeted CV intervention at 20 % risk over a 10 years period [3]. In part this was done because of the huge perceived costs of major sections of the population receiving expensive interventions – the concept of the Quality-Adjusted Life Year (QALY) was thus spawned, and thus a "cost per QALY saved" could be calculated and used as a economic decision metric [4]. A society could then decide "fairly" which interventions to prioritise – e.g. between cataract operations, hip replacements, gene therapy and immunisations. Patients would often then be told what treatment was "suitable" for them (a decision made which would incorporate some societal affordability parameters). Older nephrologists will be able to remember the practices at the start of dialysis era, in the 1960s, where male-dominated medical panels would sit to decide who should benefit from the new, risky and rarely-available technology of dialysis, and who might not, and thus should die. A candidate's gender, age, race, employment status, and other characteristics, tended to influence the decisions reached. Few patients would have felt empowered to have challenged those decisions 50 years ago. Of course, over time, procedures have become increasingly objectivised by using more medical parameters to help determine the likely benefit of interventions.

However "fair" or objective this more medicalised approach may have seemed, its corollary was that a larger and larger proportion of the older population were perceived to need intervention. This can be seen very clearly with lipid-lowering protocols, based as they are on a composite score for CV risk, which is mostly driven by age. Very few younger patients, unless their risk factor profiling were deeply abnormal, reached "traditional" interventional treatment thresholds. This was Priestly-Bentham utilitarianism philosophy which took for its "fundamental axiom" that it is the *greatest happiness of the greatest number which is the measure of right and wrong.* Even when we know full well that most myocardial infarctions happen in people with normal or mildly elevated cholesterol concentrations, not in the relatively small number with especially high personal risk from severe hypercholesterolaemia. But what a challenge to society it would also be if some biomarkers or genetic analyses suggest "immunity" from smoking-induced cancers, or gluttony-associated diabetes? This is one of the less-thought-through "flip sides" of this new paradigm. A licence to gorge and to smoke with both frequency and impunity, maybe?

Personalised, Stratified, Medicine: Oncology Leads the Way

Although this book is about cardiac and renal interactions, the best illustrations for this new way of thinking actually come from oncology. In cancer, and especially breast cancer (but also other solid organ and lympho-reticular tumours), it is now possible to use specific drugs targeting tumour-specific biological pathways relevant to a particular tumour in a particular patient. It's easiest right now to use the breast cancer example most compellingly to show how this specialisation approach works, but this may well be a perfectly valid paradigm for novel biological drugs targeting organ transplant rejection, for chronic inflammatory conditions such as rheumatoid arthritis, ulcerative colitis and psoriasis, for dementia, and for chronic cardiovascular problems too. I suspect it is only a matter of time for these other areas. We might look back in a few years time and smile indulgently at the naivety of treating all patients the same way. How antiquated and misguided was that?!

Not all patients respond equally to interventions using cancer (or other) therapeutic compounds. Recent advances in high-throughput genomic, transcriptomic, and proteomic technologies with the ever-increasing understanding of the molecular mechanisms of cancers have led to the discovery of some genes that seem to determine personal variations in clinical outcomes or drug responses. Personalised medicine has thus started to revolutionise the healthcare paradigm by integrating personal genetic information, improving drug treatment efficacy, shifting the practice of medicine, and creating (many would say mandating) opportunities to introduce new business and healthcare economic models alongside.

The traditional standard "one-dose-fits-all" approach to drug development and clinical therapy has been ineffective, as inherently it involves risks both of subsequent drug toxicities and treatment failures. The percentage of patients for whom a major drug is effective is never 100 % and often less than 50 % [5]. The average response rate of a cancer drug is the lowest, at around 25 %.

Adverse drug reactions as a consequence of treatment are more of a problem. Among drugs approved in the U.S., 16 % have shown adverse drug reactions [5]; such issues are relevant to many hospitalisation episodes. A frequently cited meta-analysis revealed that 6.7 % of all hospitalized patients are associated with adverse drug reactions in the U.S. and that the number of deaths exceeds 100,000 cases annually [6]. A study conducted in a major hospital identified 2,227 cases of adverse drug effects among hospitalized patients and reported that 50 % of these cases are likely to be related to genetic factors [7].

"Personalised medicine" is thus the ability to segment heterogeneous subsets of patients whose response to a therapeutic intervention within each subset is homogeneous [8]. Under this new healthcare paradigm, physicians can make optimal choices to maximize the likelihood of effective treatment and simultaneously avoid the risks of adverse drug reactions; scientists can improve the drug discovery process, and pharmaceutical companies can manufacture medical devices to forecast patient prognosis, facilitating early disease detection. Shangri-La indeed.

The ultimate goal of personalised medicine is to provide the right treatment to the right person at the right time [9]. The potential impact of personalised medicine is thus contingent upon a systematic discovery of novel biomarkers from genome-wide candidates that account for variations across individuals. A quite colossal effort is now being undertaken to try to achieve this.

But what exactly do we mean by "personalised medicine"? It has been defined in many ways. According to the U.S. National Institutes of Health (NIH), personalised medicine is "an emerging practice of medicine that uses an individual's genetic profile to guide decisions made in regard to the prevention, diagnosis, and treatment of disease" [10]. The U.S. Food and Drug Administration defined personalised medicine as "the best medical outcomes by choosing treatments that work well with a person's genomic profile or with certain characteristics in the person's blood proteins or cell surface proteins" [11]. The President's Council of Advisors on Science and Technology (PCAST) described personalised medicine as "tailoring of medical treatment to the individual characteristics of each patient" [8].

It is important to appreciate that personalised medicine does not literally mean individuality. The idea of personalised medicine has often been exaggerated, as suggested in a headline in Newsweek (June 10, 2005) "Medicine Tailored Just for You." In fact, a new treatment regimen is assessed on a group of carefully selected patients but not yet at the level of individuals [9]. If a new treatment works effectively on a sub-patient cohort, a preventive intervention can then be furnished to those who will benefit, avoiding adverse drug effects and sparing expense for those who will not. It regularly surprises some people that this is not routine, especially as this is indeed just "routine" where say a bacteriological infection (chest, urine) is treated – the "antibiotic sensitivity panel" is regarded as an essential guide to ensuring successful therapies are deployed.

Biomarkers: Powerfully-Poised, Prognostic and Predictive

A biomarker is a reliable and accurate measurement that indicates a normal biological process, a pathogenic process, or a pharmacological response to a therapeutic intervention

[12]. With this broad and general definition, biomarkers include physiological measurements such as lung function, blood pressure or electroencephalography, molecular (DNA, protein, metabolite) or cellular measures from bio-fluids (blood, plasma, serum, csf, and urine), molecular, cellular or histo-pathological measures from solid tissue samples, and measurements from imaging techniques such as magnetic resonance imaging, computed tomography, or positron emission tomography [13].

According to a U.S. NIH Consensus Conference, "a clinical useful prognostic biomarker must be a proven independent, significant factor that is easy to determine and interpret and that has therapeutic consequences" [14]. A prognostic biomarker provides information about the patients overall clinical outcome irrespective of the therapeutic response [15]. Therefore, a prognostic biomarker can be exploited to select patients for an adjuvant systemic treatment but does not forecast the treatment response [10].

Decision-making about adjuvant systemic treatment for breast cancer is usually based on nodal status [16–18], tumour size [19, 20], tumour type/grade [21–24], lymphatic and vascular invasion [25, 26], tumour hormone receptor and human epidermal growth factor receptor 2 (HER2)/*neu*status [27–30], age [31, 32], and ethnicity [33–35]. Prognostic biomarkers that provide better information on relapse risk could prevent many patients from chemotherapy toxicity without compromising survival [35].

In contrast, a predictive biomarker provides information about the effect of a therapeutic intervention [36]. In other words, a predictive biomarker enables screening of a subset of patients that are responsive to a specific therapy where response is defined by any of the clinical endpoints commonly measured in clinical trials [37]. As a predictive biomarker indicates heterogeneous benefits contingent upon sub-patient risk groups classified by the status of the biomarker, a significant interaction between treatment effects and patient categories needs to be statistically validated, ideally in a randomized clinical trial [38].

Predictive biomarkers can help physicians to forecast the effects of a particular treatment. Numerous proteins and genes exist that are specifically associated with for example breast cancer growth, proliferation, and metastasis. The deeper understanding of their roles regarding the responses of various therapies may empower physicians to determine optimal treatments for patients with breast cancer [39].

Some biomarkers are both prognostic and predictive with respect to cancer interventions (see Table 21.1 taken from reference [40] and see [41, 42]). For example, patients with estrogen receptor (ER) and/or progesterone receptor (PR)-positive tumours have longer survival than those with hormone receptor-negative tumours [19, 42, 43]. Additionally, a recent randomised trial reported that high cellular ER and PR expression predicts the benefit from adjuvant tamoxifen [43, 44].

Another example is HER2/*neu* gene amplification which leads to overexpression of its receptor on the cell membrane in approximately 30 % of human breast tumours. This has been shown to be is related to a worse prognosis in patients with node-positive breast cancer due to increased proliferation and angiogenesis and inhibition of apoptosis [27–30]. HER2/*neu* is also the target for the monoclonal antibody

Table 21.1 Personalised chemotherapies for various cancers

Cancer type	Cellular target	Targeted agent	Class of agent
Colorectal [16–18]	KRAS	Cetuximab	Monoclonal antibody against EGFR
Breast [19, 20]	HER2	Trastuzumab	Monoclonal antibody HER2/Neu (EGFR2)
Chronic myeloid leukaemia [21, 22]	BCR-ABL fusion protein	Imatinib	Receptor tyrosine kinase inhibitor
Gastrointestinal stromal tumours [23, 24]	c-KIT	Imatinib	Receptor tyrosine kinase inhibitor
Non-small-cell lung cancer [25–28]	EGFR	Erlotinib and gefitinib	Receptor tyrosine kinase inhibitor
Non-small-cell lung cancer [29, 30]	EML4-ALK fusion protein	Crizotinib	Receptor tyrosine kinase inhibitor
Metastatic malignant melanoma [31, 32]	BRAF V600E	Vemurafenib	B-faf/MEK/ERK pathway inhibitor
Ovarian, breast and prostate cancer (under investigation) [33, 34]	BRCAI, BRCA2	Olaparib	Poly(ADP-ribose) polymerase (PARP) inhibitor)

Taken from Jackson and Chester [40]

Abbreviations: *APC* adenomatous polyposis coil, *CML* chronic myeloid leukaemia, *CRC* colorectal cancer, *EGFR* epidermal growth factor receptor, *EML4-ALK* echinoderm microtubule-associated protein-like 4–anaplastic lymphoma kinase fusion gene, *FAP* familial adenomatous polyposis coli, *GIST* gastrointestinal stromal tumour, *NICE* National Institute for Health and care Excellence, *NSCLC* non-small cell lung cancer, *PARP* poly(ADP-ribose) polymerase, *TK* tyrosine kinase, *TKI* tyrosine inhibitor

trastuzumab from which patients with HER2/*neu* overexpressing tumours benefit in a metastatic and adjuvant setting [45–47].

Non-cancer Paradigms

In cardiovascular disease things are not yet at the same stage of advancement as is seen in cancer therapy, but an important change has taken place all the same. In March 2014, the Joint British Societies (JBS) 3rd Report on CVD (JBS3) was launched [48]. The major change in JBS3 from JBS2 is the recommendation of an approach to risk estimation and management, based not only on traditional models of short-term (10-year) risk, but also on *individual lifetime CVD risk*. Short-term absolute risk estimates are heavily dependent on age and gender so that decisions based on this approach have resulted in drug prescription to a very large number of older individuals. Younger subjects and women have tended to be excluded even if they have substantially elevated modifiable risk factors and are consequently at high lifetime risk. Evidence has accumulated that long-term exposure to CVD risk factors actively drives atherogenesis and that early treatment can modify disease evolution and risk of future CVD events. This represents a real opportunity for 'investment' in future cardiovascular health rather than waiting for people to be unwell, or to get close to their "illness threshold", before intervening. Of course, for both cardiovascular disease, and for cancer, the essential verities of a healthy lifestyle (avoiding excess weight and smoking, restricting sugar, salt, and fat intake, and taking regular exercise) all apply from the moment of birth onwards.

So the new JBS3 CVD risk calculator has been designed to identify the sizeable number of individuals in the population who are at low short-term risk but at high life-time risk [48]. Novel metrics such as 'heart age' and CVD event free survival are displayed together with 10-year risk. The calculator is designed to communicate the long-term consequences of an individual's lifestyle and associated risk factors and the substantial lowering of CVD risk which can be obtained by early lifestyle changes and, where appropriate, by use of evidence based drug therapies. The JBS3 risk calculator should empower individuals to understand why they should start CVD risk reduction, when they should start, and what they should do. It also emphasises the need for long-term maintenance of risk factor lowering to have the greatest influence on CVD risk over lifetime. It will also help clinicians to engage in this important dialogue with their patients. It is thus an "appeal" to the individual, whereas previous health scores were more a means better to marshal scarce healthcare resources.

In terms of other chronic conditions – rheumatoid arthritis, psoriasis, solid organ transplant rejection, inflammatory bowel disease, dementia – in all of these cases there are (or soon will be) panels of biomarkers to predict future susceptibility, and, expensive new biologic agents which claim to be mechanistically-targeted interventions. Dementia in particular is a massive challenge for societies, and so recent advances in science-based predictive imaging [49], in biomarkers of susceptibility [50], and in potential novel therapeutic interventions [51], are very exciting, even at a very early stage. Segmenting the use of these new and inevitably expensive therapies to susceptible/responsive patient cohorts will be the key both to their wise application and affordability. In other words, sparing people who either will not develop the condition, or who will not respond adequately to the treatment, from the toxicity of an inappropriate therapy (the flip-side of choosing a responsive cohort) are just as serious potential gains which should accrue from the new ways of working.

Why Has Personalised, Predictive Medicine Now Become the "Flavour of the Month" in Countries with Already Super-Epensive Healthcare?

The wide-ranging impacts and myriad opportunities provided by personalised medicine can be summarized in reference to its four major attributes – which conveniently enough, all start with the letter "P" [9].

P Is for Personalised

Personalised medicine integrates personal genetic or protein profiles to strengthen healthcare at a more personalised level, particularly with the aid of recently emerging "-omic" technologies such as nutritional genomics, pharmacogenomics, proteomics, and metabolomics [52]. Personalised medicine targets what has a positive effect on a patient's disease and then develops safe and effective treatments for that specific disease [9]. In fact, genetic biomarkers that may be specifically associated with a disease state are the foundation and cornerstone of personalised medicine. Knowledge of a patient's genetic profile leads to the proper medication or therapy so that physicians can manage a patient's disease or predisposition towards it using the proper dose or treatment regimen [10].

P Is for Predictive

Personalised medicine enables physicians to select optimal therapies and avoid adverse drug reactions. Molecular diagnostic devices using predictive biomarkers provide valuable

information regarding genetically defined subgroups of patients who would benefit from a specific therapy. These complex diagnostic tests can be used to classify patients into subgroups to inform physicians whether patients would be treated successfully with hormone therapy alone or may require more aggressive chemotherapy treatment.

P Is for Preventative

Personalised medicine pursues not reaction but reaction. With the ability to forecast disease risk or presence before clinical symptoms appear, personalized medicine offers the opportunity to act on the disease through early intervention. In lieu of reacting to advanced stages of a disease, preventive intervention can be life-saving in many cases. For example, females with genetic mutations in the *BRCA1* or *BRCA2* genes have a higher chance of developing breast cancer compared to those in the general female population [53–55].

P Is for Participatory

Personalised medicine might and indeed should lead to an increase in patient adherence to treatment. When personalised healthcare assures its effectiveness and can minimize adverse treatment effects sparing the expenses, it can be expected that patients will be more likely and willing to comply with their treatments. Of course, to "qualify" for entry into the new treatment club, one first has to agree freely to share all relevant information from personal genetic and other analyses.

And P Is Also for Perhaps?

Perhaps we can find reliable predictive biomarker and genetic panels to tell us susceptibility and response? Perhaps the information from genome-wide screening, and individual genomic analysis, will provide us with novel mechanistic targets for interventions? But perhaps also this is an overhyped paradigm, derived from enthusiastic extrapolation from a small sub-set of oncological conditions to the whole of medicine? Will society accept this "new deal"? We shall all find out 'ere long'.

Statistical and Logistical Challenges Which Still Need to be Overcome

The critical component to success in personalised medicine is the discovery of gene signatures that drive individual variability in clinical outcomes or drug responses. Without these, there is unmanageable uncertainty. A number of systematic approaches have been proposed to identify "molecular fingerprints" that are predictive of patient prognosis and response to cancer treatments. In the data-driven approach, biomarkers associated with tumour characteristics are objectively searched in genome-wide analysis using data-mining tools. Unbiased biomarker discovery is the merit of this approach. A downside is that gene signatures identified by the data-driven approach are often difficult to interpret due to limited knowledge about their biological functions. In contrast, the knowledge-driven approach attempts to select candidate genes using prior knowledge or surveying the literature for evidence of linkage to either cancer pathological processes or pathways important in drug responses. As such, genes that are unknown to be involved in a process cannot be included.

Biomarker discovery begins by collecting molecular data in a drug response experiment. A large amount of genomic or genetic characteristics on cell-lines are experimentally determined using high-throughput technologies. The drug's patterns of activity in cells are measured on a continuous (percent of cell survival or death) or discrete scale (responsive or resistant).

After narrowing down candidate genes to a few hundred, a statistical classification modelling technique is then used to construct a multivariate prediction model. Single biomarkers are less likely to furnish sufficient sensitivity and specificity for most applications. Several classification methods have been utilised, including a variant of linear discriminant analysis [56], support vector machines [57–59], Bayesian regression [60], partial least squares [61], principal component regression [62], and between-group analysis [63].

The ultimate evidence of the usefulness of a prediction model in a clinical setting remains randomised, prospective validation in clinical trials [64]. This is absolutely pivotal as it would underpin with robust evidence the assertion that this approach was of true benefit both to individuals and to wider society.

Several key challenges must be overcome before this tsunami of personal profile data can be successfully translated into clinically relevant opportunities for patients. Improved knowledge obtained using advanced profile technologies will not be sufficient for this purpose, but all stakeholders involved in personalised medicine will need to work together to take responsibility. Regulatory authorities will need to provide clear guidelines for evaluating and approving newly developed "personalised" drugs and should independently and rigorously validate the capabilities of the diagnostic devices that predict patient prognoses or drug responses. Medical educational institutions should prepare the next generation of physicians to use and interpret personal genetic information appropriately and responsibly. Public and private insurers need to evaluate the clinical and economic utility of "personalised" drugs and devices to facilitate reimbursement.

As an example of the new challenges facing this field, take the colossal task of storage, retrieval and expeditious analysis of the massive amount of data we shall need to acquire to achieve these goals. A whole new way of archiving and working using massive super-computer arrays has been developed [65]. In the era of "big data", biomedical databases are brimming with protein structures, image collections and genomic sequences. As the data mount, new 'cave automatic virtual environments', or CAVEs, are being built to help researchers pick through the files. One such is the largest currently in the world, CAVE2 at Australia's Monash University in Melbourne, Australia. What appears to be an enormous electronic billboard encircles the space, forming a cylindrical room with a 24-ft diameter. The images displayed on the 80, high-definition, liquid-crystal display panels beam out at a staggering 84-megapixel resolution. And with a pair of stereo glasses, they emerge out of the eight-foot-high display wall in three dimensions. Science fiction? No, science fact.

CAVE2 is the state of the art in electronic engineering and computer visualization technologies—and Monash's CAVE2, which opened its doors only late last year (2013), is one of just two such facilities in the world. The first, slightly smaller CAVE2, with 72 panels instead of 80, started accepting scientists at the University of Illinois at Chicago (UIC) in October 2012. The circular CAVE2 design of both facilities is the latest immersive virtual environment to emerge from UIC's Electronic Visualization Laboratory (EVL) – see [65].

Conclusions: "Back to the Future" – Is Personalised Medicine Coming Soon to a Hospital Near You?

Personalised medicine has received and continues to attract a growing amount of attention for its tremendous potential opening up a myriad new opportunities. The ultimate promise of personalised medicine depends on the discovery of the personal genetic causes of many common diseases. The remarkable advent of current high-throughput technologies in combination with improved knowledge of the molecular basis of malignancy, provides a solid base for identifying novel molecular targets driving drug-discovery programmes. The use of high-throughput technologies is expected to increase massively in the next few years driven largely by the fact that the cost of technologies will continue to drop sharply. Genomic sequencing and its interpretation will have to be further developed and standardised for routine clinical practice to develop efficient and effective methods for discovering and verifying new biomarkers and enabling personalized medicine technologies. In particular, efforts to standardise existing technologies will need to lead to more reproducible and robust identification of biomarkers. This revolutionised paradigm in healthcare is already beginning significantly to affect both research and clinical practice. And what has already started to happen in oncology will surely soon start to happen in other disease areas?

So, personalised healthcare — or what Professor Donna Dickenson calls "me" Medicine [66] — coupled to increasing patient "choice" through information emancipation – is now starting radically to challenge and then to transform our longstanding "one-size-fits-all" system model. Technologies such as direct-to-consumer genetic testing, pharmacogenetically developed therapies in cancer care, private umbilical cord blood banking, and neurocognitive enhancement, all claim to cater to an individual's specific biological character, and, in some cases, these technologies have shown significant potential. Yet in other areas they have produced negligible, or even negative, results to date [66]. Whatever is behind the rise of "me" Medicine, it doesn't seem to be the quality of the science which is driving it alone – there is also a healthy dose of "economics" as well. So if it is indeed the case that "me" Medicine is now about rapidly to edge out "we" Medicine, will our commitment to our collective health have suffered as a result? Increasingly knowledgeable patients, prepared to use and share more of their own private data, are directly investing in their own health – this is a challenge in particular to systems which can be characterised as publically-funded, centralised, socialised healthcare.

Well before this amazing "Brave New World" healthcare paradigm has been shown to be both effective, and cost-effective, it is now being vigorously adopted. This is because it is a "Big New Idea". The new concepts are taking physical form – in several places in the United Kingdom there have sprung up new "ivory-tower institutes", often with titles as grandiose and otiose as their porticos and atria, emphasising (amongst other things) their scale, ambition and reach. As an example, it was announced by the United Kingdom's Business Secretary Dr Vince Cable in August 2013 that a "Diagnostics for Stratified Medicines Catapult" would be established, joining several other Catapults, or "technological accelerators" [67]. A number of partners (including the Technology Strategy Board and the Medical Research Council) have committed to spend over £200 m over a 5 year period to promote the development of stratified medicine, providing the tools, processes and systems for identifying the right therapy for the right patient, at the right time and at the right dose. Presumably also from the right doctors in the right hospitals?

In February 2014 there was a report of one of the first attempts systematically to personalise/stratify breast cancer treatments [68]. Fabrice Andre and colleagues undertook the SAFIR01 breast cancer trial, which has provided important insights into the logistical, scientific, and clinical challenges of implementing national cancer genomic assessment. The primary purpose of SAFIR01 was to investigate the

feasibility of molecular screening to identify potential candidates for entry into phase 1 and 2 trials, rather than to assess the direct clinical benefits of the therapies for patients. 18 centres in France used a common screening protocol and sent metastatic biopsy samples comprising at least 50 % tumour cells for molecular testing at five sites. A genomic review board that included bio-informaticians, biologists, and clinicians, made treatment decisions based on genomic data. Samples were analysed with comparative genomic hybridisation (CGH) array and Sanger sequencing for *AKT1* and *PIK3CA*. Recruitment of patients was rapid, with 423 patients recruited within 13 months. 407 (96 %) enrolled patients underwent tumour biopsy. However, only 55 (13 %) of 423 biopsied patients received treatment directed by genomic alterations. Just four (9 %) of 43 assessable patients who received therapy directed against *EGFR*, *AKT2*, *IGF1R*, or FGF pathway amplifications had partial responses. These results indicate that even in the domain of breast cancer, and with the participation of a highly organised collaborative group, achieving notable clinical benefit for a significant number of patients is currently associated with very substantial challenges.

Is this then really going to be the correct approach for medical screening and intervention for the remainder of the twenty-first century? Can we find the evidence to sustain our faith in this new route? Can we change diagnostic services, drug design, trial design, re-imbursement decisions, all to be aligned perfectly with this new model? Who will also be involved in providing regulatory advice, integrating stratified medicines into health technology assessments, developing business models and assembling the case for reimbursement and deployment in our traditional, "conservative" (i.e. change-resisting) healthcare services? How will this be communicated to people – while they are well, and, after they fall ill? Will a population meekly submit all of their most personal and intimate genetic, epigenetic and phenotypic information to "Big Brother", that widely-trusted, beneficent, wise custodian they know so well (whose stewardship of their other personal data is of course beyond criticism)? How will the institutions, or practices, of life insurance, employment, marriage and procreation respond?

All of these remain forbidding, pertinent, and very pressing challenges for patients, carers, scientists, politicians, healthcare economies, and countries alike. The CDC's National Center for Chronic Disease Prevention and Health Promotion says that common, health-damaging but modifiable behaviour-sets – tobacco use, insufficient physical activity, poor eating habits, and excessive alcohol use – are collectively responsible for much of the illness, disability and premature death related to chronic diseases. People with three or more chronic disease conditions generally fall into the costliest one percent of patients who account for 20 % of all healthcare spending in the U.S.A [69]. Is it not likely still to be more cost-effective to invest in population disease prevention, rather than in the micro-personalisation of treatment?

We need to decide just what we do want. Everyone knows the phrase "be careful what you ask for". Do we want, with our rapidly ageing population, to have better and longer disease-free survival (yes, of course we do)? Then better predictive modelling, and targeted selective primary prevention interventions (as much a part of "public health" as are our personal choices), are key. Do we want, at any cost, to extend lifespan for its own sake, regardless of the mechanisations and medicalisations involved? Probably no, we do not. Let us not forget the chilling saga of Tithonus, of Greek legend, the son of Laomedon, king of Troy, and of Strymo, daughter of the river Scamander. Eos (Aurora) fell in love with Tithonus and took him to Ethiopia, where she bore Emathion and Memnon. According to the Homeric *Hymn to Aphrodite*, when Eos asked Zeus to grant Tithonus eternal life, the god consented. But Eos forgot to ask also for eternal youth, so her husband grew old, increasingly frail and withered, but could never succumb to mortality. The poem "Tithonus" by English poet alfred, Lord Tennyson [70], begins:

The woods decay, the woods decay and fall,
The vapours weep their burthen to the ground,
Man comes and tills the field and lies beneath,
And after many a summer dies the swan.
Me only cruel immortality
Consumes; I wither slowly in thine arms.

The Muses were said to have "frolicked about the Pierian springs soon after their birth". The springs were believed to be a literal and metaphorical fountain of knowledge that intellectually inspired and nourished whomsoever drank from them. Let us all hope this does not run dry any time soon as we need a clear head to chart our forward course from where we are now – at the dawn of the era of personalised medicine, which without doubt has now arrived [68, 71].

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Psychological Distress in Physical Long-Term Conditions

22

Joanna L. Hudson and Joseph Chilcot

Overview

Psychological distress including depression, anxiety, and disease specific distress is common in people with physical long-term conditions (LTCs). This chapter focusses on psychological distress in four LTCs associated with the cardiovascular and endocrine systems, specifically: coronary heart disease (CHD), cerebrovascular disease (CVD), end-stage renal disease (ESRD), and diabetes. The co-occurrence of psychological distress alongside each of these LTCs is associated with increased morbidity [1–5], mortality [6–9], poorer quality of life [10, 11], and higher health care costs [12]. Underlying mechanisms as to why psychological distress is associated with poorer physical health outcomes remain unclear, but there is evidence implicating both biological and behavioural mechanisms. Such uncertainty generates difficulties for the development of effective treatment interventions for the management of psychological distress in the context of physical illness. In addition, it is likely that the mechanisms underlying the association between psychological distress and health outcomes are LTC specific. This chapter provides a brief overview of: (i) the conceptualisation and prevalence of psychological distress in LTCs, (ii) the aetiology of psychological distress in LTCs and its proposed mechanisms of action for contributing to poorer physical health outcomes, and (iii) existing treatment interventions for the management of psychological distress in people with LTCs.

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Conceptualisation and Prevalence of Psychological Distress in People with Long-Term Conditions

How psychological distress is conceptualised often depends on the empirical question. In the context of physical LTCs psychological distress can be conceptualised as either:

(i) A clinically diagnosed (categorical) mood disorder that meets psychiatric diagnostic thresholds used to define, for example, the presence of major depressive disorder. This approach provides discrete categorical boundaries to distinguish, the depressed from the non-depressed. It allows the generation of prevalence estimates but is also useful for identifying individuals most likely to benefit from clinical intervention [13]. For diagnostic criteria used, see the Diagnostic and Statistical Manual of Mental Disorders (5th Edition; DSM-V) [14].

Using this approach, the presence of a mood disorder is identified using either a diagnostic clinical interview, administered by a trained professional (i.e. Composite International Diagnostic Interview; CIDI) [15] or a continuous self-report measure (i.e. The Patient Health Questionnaire; PHQ-9) [16] with cut-points applied to categorise those individuals likely experiencing a clinically meaningful mood disorder. It is important to note however, that cut-points used in most self-report measures of depression and anxiety often inflate estimated cases of psychopathology [17], and should be used as proxies of "caseness" and not as diagnostic tools.

(ii) The occurrence of distressing symptoms outlined in psychiatric mood disorder classification systems but instead of applying categorical boundaries these symptoms remain on a continuum, which ascends based on the number of symptoms experienced [13]. This conceptualisation assumes that all distressing symptoms contribute to impairment but the degree of impairment

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experienced is proportional to the number and severity of symptoms present [18]. Indeed, depressive symptoms that would not meet the criteria for a clinical diagnosis of depression contribute to negative health outcomes in people with LTCs [19]. Because of the dimensional nature of this conceptualisation of distress it is typically measured using continuous self-report measures. This is a useful approach to apply when exploring the impact of severity of psychological distress on health outcomes.

(iii) The manifestation of disease specific distress whereby negative emotions are experienced, but their occurrence is contextually dependent on the presence of disease specific stressors. For example, feeling overwhelmed by treatment demands or treatment related side-effects. Arguably, this area of research is most developed in the diabetes population. Preliminary findings suggest that diabetes specific distress operates independently from the emotional state depression to impact negatively on health outcomes (i.e. higher glycosylated haemoglobin levels, HbA1c). Please see Esbitt et al. [20] for a detailed critical review.

The above three conceptualisations capture the heterogeneity of psychological distress in people with LTCs. Acknowledging these differences is important when critically interpreting research findings, but it also has clinical relevance. It encourages the practice of personalised medicine, whereby practitioners tailor their treatments in response to the type of psychological distress their patient predominantly presents with (i.e. diagnosable depression vs subthreshold depression vs disease specific distress) [21].

Prevalence estimates for psychological distress in people with LTCs vary considerably. Estimates from meta-analytic reviews [22–28] and observational studies [29–32] across our four disease groups of interest are summarised in Table 22.1. The wide variation in prevalence estimates is not a consequence of differences in the underlying physical health condition because consistent patterns of variation occur both within

Table 22.1 Prevalence estimates of psychological distress in people with long term conditions

Study	Long-term condition	Design (location)	Psychological distress assessment method	Number of participants (n) or studies (k)	Prevalence (95 % confidence intervals)
Depression					
Moussavi et al. [29]	Coronary Heart Disease	Observational (worldwide, 60 countries)	Diagnostic clinical interview conforming to the International Classification of Disease (ICD-10) criteria	n = 245,404	Angina: 15.0 % (12.9–17.2 %)
Gunn et al. [30]	Coronary Heart Disease	Observational (Australia)	Self-report measure: Centre for Epidemiologic Studies Depression Scale (CES-D)	n = 6,864	Hypertension: 24.0 % (Not reported) Heart disease: 29.0 % (Not reported)
Rutledge et al. [25]	Coronary Heart Disease	Systematic review with meta-analysis (NA)	Both diagnostic clinical interviews and self-report measures of depression	k = 27	Heart Failure: 22 % (18–26 %)
Gunn et al. [30]	Cerebrovascular disease	Observational (Australia)	Self-report measure: Centre for Epidemiologic Studies Depression Scale (CES-D)	n = 6,864	Stroke: 37.7 % (Not reported)
Hackett et al. [26]	Cerebrovascular disease	Systematic review with meta-analysis (NA)	Both diagnostic clinical interviews and self-report measures of depression	k = 51	Stroke: 33 % (29–36 %)
Palmer et al. [22]	End stage renal disease	Systematic review with meta-analysis (NA)	Both diagnostic clinical interviews and self-report measures of depression	n = 198 (independent sample populations on dialysis)	On-dialysis, Clinical Interview: 22.8 %, (18.6–27.6 %) On-dialysis, Self-report: 39.3 % (36.8–42.0 %)
Anderson et al. [23]	Diabetes mellitus (Type 1 and 2)	Systematic review with meta-analysis (NA)	Both diagnostic clinical interviews and self-report measures of depression	k = 42	Type 1 and 2: 25.3 % (Not reported)
Anxiety					
Tully et al. [27]	Coronary Heart Disease	Systematic review with meta-analysis (NA)	Both diagnostic clinical interviews and self-report measures of GAD	k = 12	10.9 % (7.8–14.0 %)
Campbell Burton et al. [28]	Cerebrovascular disease	Systematic review with meta-analysis (NA)	Both diagnostic clinical interviews and self-report measures of all anxiety disorders and symptoms	k = 44	Clinical Interview: 18.3 % (8.1–28.5 %) Self-report: 24.3 % (20.5–28.1 %)

Table 22.1 (continued)

Study	Long-term condition	Design (location)	Psychological distress assessment method	Number of participants (n) or studies (k)	Prevalence (95 % confidence intervals)
Cukor et al. [31]	End stage renal disease	Observational (US)	Diagnostic clinical interview (SCID). All anxiety disorders	n = 70	Haemodialysis: 27 % (Not reported)
Preljevic et al. [32]	End stage renal disease	Observational (Norway)	Diagnostic clinical interview (SCID). All anxiety disorders	n = 109	Haemodialysis and peritoneal dialysis: 16.5 % (Not reported)
Grigsby et al. [24]	Diabetes mellitus (Type 1 and 2)	Systematic review with meta-analysis (NA)	Both diagnostic clinical interviews and self-report measures of all anxiety disorders and symptoms	k = 18	Type 1 and 2: Meta-analysed prevalence estimates ranged from 1.3 to 39.6 % depending anxiety disorder studied and symptoms measured

CES-D Center for epidemiologic studies depression scale, *GAD* Generalised anxiety disorder, *NA* Not applicable, *SCID* Structured Clinical Interview

and between each physical LTC. Inconsistencies therefore, are largely an artefact of differences in the conceptualisation (contributing symptoms/pathologies) and measurement of psychological distress (diagnostic clinical interviews vs self-report measures). Indeed, there are numerous self-report measures of distress to choose from and the extent to which they adhere to diagnostic criteria outlined in the DSM-V [14] varies considerably. Shafer [33] identified seven depressive symptom factors across four of the most popular self-report depression measures, of which only three factors were common across two or more of the self-report measures.

Detecting the presence of mood disorders in people with physical LTCs is complicated further by somatic symptoms associated with the mood disorder (i.e. reduced energy and weight loss) overlapping with the symptoms that occur because of the physical LTC [34]. Unique diagnostic criteria and/or adjusted diagnostic thresholds are recommended to determine the presence of a mood disorder in the context of a physical LTC. Sultan et al. [35] suggest excluding somatic symptoms from self-report measures of distress to prevent wrongly diagnosing mood disorders, a position supported by others [36]. The measurement of psychological distress in physical LTCs remains contentious. A more consistent approach to measurement is needed. This will allow greater comparisons across studies, to explore the impact of disease specific stressors (i.e. treatment regimens and underlying disease physiology) and socio-demographic factors on physical and emotional health outcomes.

Aetiology of Psychological Distress and Its Mechanisms of Action

Understanding the factors that contribute to the aetiology and exacerbation of psychological distress in people with LTCs will help to identify treatment targets for clinical intervention. Furthermore, a detailed examination of the mechanisms through which psychological distress leads to poorer physical health outcomes and vice versa will pinpoint intervention targets that have potential for simultaneous improvements in a person's physical and mental health.

Do LTCs Cause the Onset of Psychological Distress or Vice Versa?

Evidence from observational studies show that among people with physical LTCs the odds of psychological distress occurring is two to three times greater compared with people in which, LTCs are absent [37, 30, 23]. Thus the presence of a physical LTC appears to be a key driver for the development of distress. Conversely, studies exploring the reverse direction of effect show that among people with a diagnosed mood disorder, there is a 34–81 % increased risk of developing a physical LTC [38, 1, 39], relative to people without a mood disorder. In sum, the relationship between psychological distress and LTCs appears to be bi-directional.

However, the above studies have largely focussed exclusively on depression and overlooked anxiety and more general symptoms of distress. In addition, definitive causal conclusions cannot be made because of potential confounders that may better explain the relationship between LTC onset and the development of depression and vice versa, for example, personality traits or genetic factors. Nevertheless, quantitative findings complement those observed in the qualitative literature. Adults with diabetes and co-morbid depression described their causal beliefs about the aetiology of their conditions [40]. Some perceived their depression to be a causal consequence of their diabetes, others felt that their depressive disorder triggered the onset of their diabetes, and a third group felt that there was no connection between their physical and mental health. An understanding of both actual and patient perceived causes of their psychological distress will help to refine treatments further by offering individuals treatments that are consistent with their perceived causal triggers of their distressing symptoms.

How Do LTCs Impact on Psychological Distress Outcomes?

Biological Pathways

Inflammatory responses which often occur in the context of physical LTCs can stimulate a series of hormone responses in the body to promote the secretion of pro-inflammatory cytokines. Studies have shown increased cytokine secretion to be linked to a response known as "sickness behaviour". Sickness behaviour presents with symptoms akin to depression and includes loss of motivation, energy, and appetite. This response is adaptive for acute episodes of illness as it encourages the preservation of energy, but in the context of LTCs it can exacerbate physical symptoms further [41]. The person specific genetic factors that determine this response is currently being explored in the literature. In a study of people with ESRD, Holtzman et al. [42] identified greater depressive symptoms among people with a genetic predisposition for heightened inflammatory responses. To elaborate, people who were low producers of a genotype for anti-inflammatory responses (A/A genotype for IL-10 1082 polymorphism) had greater depressive symptoms compared with intermediate (G/A) and high (G/G) genotype producers. Thus there are likely specific subgroups of individuals more susceptible to the development of distress in the context of LTCs because of their pre-disposing genetic factors. But this area of research is in its infancy.

Cognitive Pathways

A person's unhelpful (cognitive) appraisal of their LTC (i.e. perceiving they have little control over their illness) and its perceived or actual limiting effects on their day to day functioning (i.e. self-care behaviours needed for the management of their condition and its effects on other roles including work and family) can engender feelings of helplessness, hopelessness, and worry about future health consequences [43, 44]. These thinking styles are core features that trigger and sustain depression and anxiety [45].

How Does Psychological Distress Impact on LTC Outcomes?

Biological Pathways

The experience of psychological distress can activate the hypothalamic-pituitary-adrenal (HPA) axis, sympathetic nervous system (SNS), and increase cytokine secretion. Their activation can promote insulin resistance in diabetes [46] and atherosclerosis and platelet activation in vascular conditions [47]. These pathophysiological mechanisms are correlates of both objective health outcome measures (i.e. glycosylated haemoglobin) [46] and the onset of physical health complications (i.e. increased risk of myocardial infarction) [46]. These pathways have yet to be explored extensively among people with ESRD. Nevertheless studies are emerging identifying important relationships between depression and cytokine secretion in people with ESRD (see Chilcot et al. [48] for a review).

Behavioural Pathways

The somatic features of distress (i.e. loss of energy) and its affective elements (i.e. feelings of hopelessness, fear of confronting the illness) disrupt a person's ability to adhere to necessary self-care behaviours by (i) lowering their motivation to engage in treatment behaviours AND/OR (ii) promoting avoidance of threatening illness related environments (i.e. dialysis). Indeed, studies show that psychological distress in the context of LTCs is associated with lower adherence to: lifestyle behaviours (diet, exercise, and smoking), [49–51], medications [52, 53, 49], and appointment attendance [54, 55].

Interventions to Manage Psychological Distress in LTCs

Because we have an awareness of the likely causal pathways that trigger and sustain psychological distress in the context of LTCs we can apply existing evidence-based treatments used to manage psychological distress [56] to target these pathways specifically. Figure 22.1 summarises the pathways that maintain psychological distress and perpetuate poorer LTC outcomes described above. Mapped onto these pathways are treatment interventions that can target the antecedents of psychological distress. These interventions are described below, although a degree of caution is required. Effective mental health treatments may be antagonistic to effective LTC management [43]. Figure 22.1 therefore, also highlights potential antagonistic relationships (see Detweiller-Bedell et al. [43] for a full review).

Targeting Cognitive and Behavioural Pathways

Cognitive behavioural therapy (CBT) is a psychological talking therapy used to manage depression and anxiety [56]. Two meta-analyses exploring the effectiveness of psychological talking therapies (including CBT) for the management of depression in people with coronary heart disease [57] and diabetes [58] showed that these types of interventions improve depressive symptoms. However the size of improvements in depressive symptoms was small. This likely reflects the need to refine psychological treatments further to manage illness specific beliefs and challenging treatment demands and health consequences that present uniquely for each LTC. However, components of CBT can

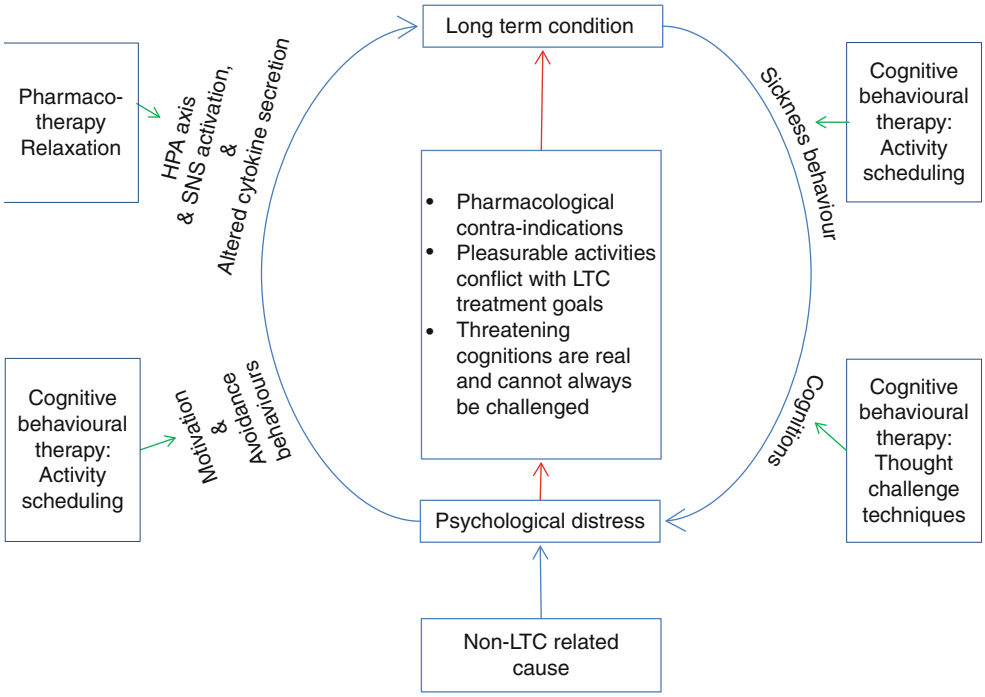

Fig. 22.1 Pathways linking the vicious cycle between long term conditions and psychological distress and potential treatment interventions. Curved arrows with text show the hypothesised mechanisms of action for the onset and exacerbation of both psychological distress and long-term conditions, boxes outside the vicious cycle linked with straight arrows show potential intervention techniques for targeting specific mechanisms, arrow through the centre of the vicious cycle shows the potential for psychological distress treatments to conflict with LTC management. *HPA* hypothalamic-pituitary-adrenal axis, *LTC* Long-term condition, *SNS* sympathetic nervous system

address the more generic mechanisms of action that perpetuate distressing symptoms and physical health outcomes in LTCs (See Fig. 22.1).

Activity scheduling can address sickness behaviour and its consequential effects on motivation. It encourages the planning of pleasurable activities into a person's day to day routine to allow them to experience positive mood states. For example, a patient receiving dialysis may plan to go to the theatre with a friend. But also, activity scheduling encourages the explicit planning of necessary tasks (i.e. attending for dialysis treatments). It allows a person to gain a sense of achievement when necessary tasks are completed. By thoroughly planning pleasurable and necessary activities, a person can better incorporate LTC management challenges into their lives, whilst sustaining opportunities to experience pleasurable events. But caution is required to ensure that people's pleasurable activities do not conflict with LTC management strategies. To elaborate, eating out with friends may generate challenges for people who are on restricted diets because of their condition; indeed it may trigger further distress because it reinforces the impact of the LTC on their day to day living.

Thought challenge techniques is another approach used in CBT. It encourages people to question the validity of their pessimistic thoughts. For example, a person may feel distressed because they perceive they have little control over their condition. Thought challenge techniques help people to identify situations where they have successfully managed their condition and encourage them to re-evaluate their initial pessimistic thoughts that are sustaining their distress. Skill building may also be used to encourage greater confidence in LTC management [59]. But not all pessimistic and distressing cognitions are amenable to thought challenge techniques. They are accurate perceptions about the seriousness of a LTC such as ESRD. Use of acceptance based approaches may be more appropriate for these types of beliefs [60] because it encourages people to distance themselves from their thoughts. But the efficacy of these approaches in people with LTCs has received little research attention to date. The interested reader should refer to Westbrook et al. [61] for a more thorough introduction to the principles of CBT and to McCracken [62] for examples of the application of acceptance based approaches in people with LTCs.

Targeting Biological Pathways

Pharmacotherapy can be used to treat clinically significant distress in LTCs [56]. According to the National Institute of Health and Care Excellence (NICE) depression [63] and generalised anxiety disorder guidelines [64], pharmacotherapy should only be used to treat patients who meet diagnostic criteria [14] for moderate to severe symptoms of distress. Currently, however there are no evidence-based guidelines with detailed pharmacotherapy algorithms for managing distress in the context of specific LTCs. Generating such algorithms is perhaps unfeasible given the heterogeneity of the patient population and high prevalence of multi-morbidity. Indeed, in England alone it is estimated that by 2018, 2.9 million people will have two or more LTCs [65].

When prescribing drug treatments to manage distress in people with physical LTCs the following factors need to be considered: (i) the potential for drug-drug interactions, (ii) the likely side effects of the medication, (iii) the patient's previous history of pharmacotherapy treatments, (iv) patient preference, and (v) the toxicity of the drug and the risk of overdose among patients with suicidal ideation. NICE recommend selective serotonin reuptake inhibitors (SSRIs) as a first line treatment for depression and generalised anxiety disorders. However, SSRIs should be prescribed with particular caution among older patients because of increased risk of bleeding.

The US TEAMcare trial [66, 67] in primary care generated a medication treatment algorithm to manage depression in people with diabetes and/or coronary heart disease as part of a complex intervention (see website [68] for detailed treatment manual and medication algorithm). Consistent with NICE guidelines, patients were offered the SSRI citalopram. An initial dose of 10 mg per day was used, with doses gradually titrated upwards until a clinically meaningful improvement in depressive symptoms was observed. Citalopram was used as a first line treatment because of a decreased likelihood of drug-drug interactions with diabetes and/or coronary heart disease medications. If patients had tried SSRIs on two or more previous occasions and observed no improvements in their depressive status then they were offered the dopamine-noradrenaline reuptake inhibitor (DNRI) bupropion SR at a starting dose of 100 mg per day. Likewise to citalopram their dose was titrated upwards where necessary until a clinically meaningful response in their depressive symptoms was observed. Buproprion SR was chosen as an alternative first line drug treatment to citalopram because of: (i) its decreased potential for hepatic enzyme inhibition, (ii) fewer sexual functioning side effects, and (iii) evidence of weight loss when used in people with diabetes, which may indeed promote synergistic gains in physical and mental health.

Patients' progress was managed by diabetes nurses who received training and weekly supervision from a liaison psychiatrist and primary care provider. During supervision individual patient needs were discussed. Patients who failed to respond to either of the first line treatments either switched to a different anti-depressant (typically another SSRI if feasible) or had their existing anti-depressant treatments regimens augmented with additional anti-depressant medications. This trial effectively reduced depressive symptoms and improved health outcomes also (glycosylated haemoglobin, low-density lipoproteins, and systolic blood pressure. No adverse events were reported.

More trials are needed to determine the efficacy and safety of prescribing anti-depressant medications to patients with LTCs. Generating pharmacotherapy evidence-based treatment algorithms in specific LTC populations like in the TEAMcare trial would provide clinicians with a useful framework to default to. When considering pharmacological interventions in patients with complex multi-morbidity, consultation with a liaison psychiatrist is suggested [63]. At present, clinicians can only use generic depression and generalised anxiety disorder treatment guidelines and initiate treatment with SSRIs unless the patients' medical history would deem this to be unsuitable.

There is also *potential* for specific drug treatments to mutually improve physical health outcomes by decreasing the activation of the SNS and HPA axis, the pathophysiological pathways described earlier that are activated when people are distressed and have known associations poorer LTC outcomes. However, pharmacotherapy agents with the most appropriate properties to target specifically the HPA axis and SNS remain unclear. This may account for why in the diabetes literature studies show that anti-depressants improve depressive symptoms, but overall no improvements in HbA1c outcomes are observed [46]. These null effects can equally be accounted for by methodological weaknesses rather than absence of these pathophysiological processes (i.e. lack of statistical power, inappropriate timing of outcome measures). Alternative non-pharmacological treatments that target biological pathways include arousal reduction techniques such as mindfulness based cognitive therapy [69]. Mindfulness encourages the use of meditative practices to allow a person to disengage from maladaptive coping processes (i.e. dwelling on LTC health consequences) to improve mood. There is a hypothesised link between the practice of mindfulness and decreased HPA axis activation [70] and thus the potential to improve physical health also .

Summary

Different conceptual frameworks are used to explore the experience of psychological distress in the context of LTCs. This heterogeneity is reflected in the wide ranging prevalence estimates of distress in people with LTCs. Nevertheless, acknowledging these varying presentations of psychological distress is a useful step towards offering more personalised medicine to patients. It allows us to more appropriately match people with a specific psychological distress profile (i.e. major depressive disorder, sub-threshold depression, disease specific distress) to treatments most appropriate for targeting these symptom clusters.

Pharmacotherapy and CBT have evidence of effectiveness for managing psychological distress in people with LTCs. However, more prospective cohort studies are needed to tease apart the precise biological, cognitive, and behavioural mechanisms of action that cause and sustain each specific type of distress, including the timespans over which these relationships occur to refine our treatments further. Indeed, because mechanisms of action are likely to be disease specific the development of disease specific models of distress

is advocated [71]. These models must also acknowledge the potential for conflicting physical and mental health treatment demands. Furthermore, we need to establish genetic and socio-demographic factors that modify the activation of these pathways to further tailor treatments and allow cost-effective application of limited health care resources.

We must ensure that emerging evidence based treatments are supported by an appropriately resourced and effective health service delivery framework. Collaborative care is a health service delivery model typically applied in primary care. It puts in place structures to support the implementation of evidence-based treatments for depression and anxiety by promoting multi-disciplinary working, regular monitoring of patient progress, and appropriate supervision from a mental health specialist. Collaborative care models improve depressive and anxious symptoms [72], but also evidence is emerging showing that this framework promotes improvements in both mental and physical health outcomes also [66].

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