Screening and Diagnosing Cardiovascular Disease in Chronic Kidney Disease

12

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Before You Start: Facts You Need to Know

- Cardiovascular disease is a leading cause of morbidity and mortality in patients with chronic kidney disease as determined by reduced estimated glomerular filtration rate and/or albuminuria.
- Atherosclerosis is both accelerated in development and in calcification in patients with chronic kidney disease.
- Heart failure is the most common symptomatic manifestation of cardiovascular disease requiring hospitalization in patients with chronic kidney disease.
- Blood B-type natriuretic peptide, N-terminal pro B-type natriuretic peptide, galectin-3, and soluble ST-2 are approved tests as these aid in the diagnosis, prognosis, and management of heart failure; however, caution should be exercised in the interpretation of these markers in the setting of chronic kidney disease.
- Aortic valve sclerosis and mitral annular calcification are common valve pathologies associated with chronic kidney disease.
- All forms of arrhythmias are more common in chronic kidney disease, especially sudden death which is markedly increased in risk in dialysis patients.

12.1 What Are the Approaches to Screen for Coronary Artery Disease?

All adult patients including those with chronic kidney disease (CKD) should undergo an assessment for coronary artery disease (CAD) risk using a standard risk assessment such as that proposed by the Framingham investigators [1]. Variables in the Framingham risk calculation include age, total (or low-density lipoprotein [LDL-C]) cholesterol, high-density lipoprotein, smoking, and systolic blood pressure [2]. A 20 % 10-year risk (2 % annual risk) of nonfatal myocardial infarction or

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cardiovascular death is considered high risk and is a call for full prevention measures in the general population. Most patients with CKD (67 %) will be in Framingham moderate- or high-risk groups; however, as shown in Fig. 12.1, patients with Stages 3–5 CKD in these groups will have a 10–20 % annual risk of cardiovascular events (tenfold that of subjects in Framingham) [1]. Since the risk connoted by traditional risk factors is markedly amplified in CKD, it is reasonable to use exercise stress testing for exercise prescription and prognosis in high-risk individuals. Because of high rates of abnormal baseline electrocardiogram (ECG), left ventricular hypertrophy, and conduction abnormalities, exercise stress testing combined with either echocardiographic imaging or nuclear scintigraphy is reasonable. For those who cannot exercise, both dobutamine and dipyridamole/adenosine/regadenoson can be used as a pharmacological means of achieving myocardial perfusion imaging. Large areas of ischemia (>10 % of the left ventricular myocardium) usually call for invasive assessment of coronary lesions and consideration for revascularization. In the setting of diabetes and multivessel disease, coronary artery bypass surgery is the preferred method of revascularization [3]. Coronary computed tomographic angiography in patients with CKD is not advised given the very high rates of coronary calcification which causes "bloom" artifact which works to make lesion severity difficult to assess [4]. However, if vascular calcification is detected incidentally on computed tomography or roentgenography, it is indicative of advanced atherosclerosis, and attention should be paid to both atherosclerosis risk factors and the elements of CKD mineral and bone disorder (phosphate retention, hyperparathyroidism, and relative hypocalcemia) (Fig. 12.2) [5, 6].

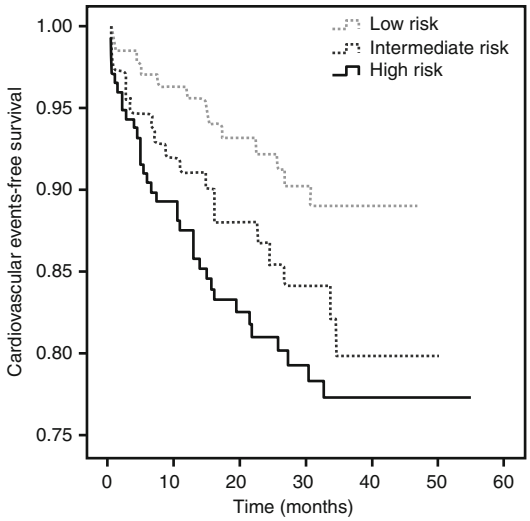


Fig. 12.1 Event-free survival from major cardiac events according to the Framingham risk score applied to a population of patients with chronic kidney disease

12.2 Should Patients with Chronic Kidney Disease Undergo Routine Echocardiography?

Because of the very high incidence of left ventricular hypertrophy, risk for Stage A and Stage B heart failure, and known associations between

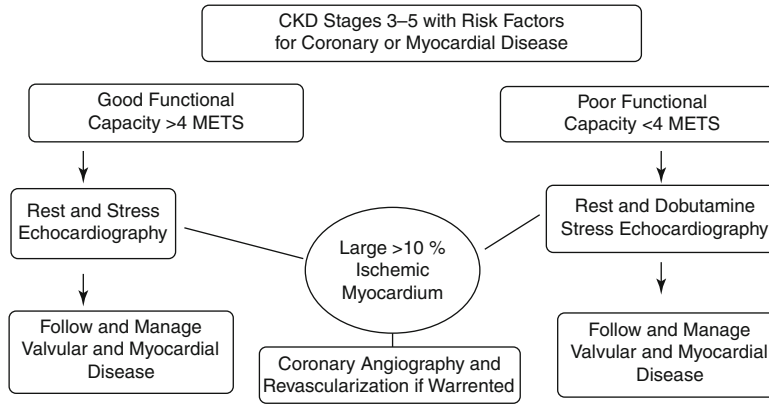


Fig. 12.2 Coronary artery disease screening algorithm (*METS* metabolic equivalents of functional capacity)

Box 12.1. Five Cardiorenal Syndromes and Their Common Clinical Scenarios

Cardiorenal Syndrome* (*CRS*) *General Definition

A pathophysiologic disorder of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other organ

***CRS Type I* (*Acute Cardiorenal Syndrome*)**

Abrupt worsening of cardiac function (e.g., acutely decompensated congestive heart failure) leading to acute kidney injury

***CRS Type II* (*Chronic Cardiorenal Syndrome*)**

Chronic abnormalities in cardiac function (e.g., chronic congestive heart failure) causing progressive and permanent chronic kidney disease

***CRS Type III* (*Acute Renocardiac Syndrome*)**

Abrupt worsening of renal function (e.g., acute kidney injury) causing acute cardiac disorder (acute heart failure)

***CRS Type IV* (*Chronic Renocardiac Syndrome*)**

Chronic kidney disease (diabetic nephropathy) contributing to decreased cardiac function and cardiac hypertrophy and fibrosis and/or increased risk of adverse cardiovascular events

***CRS Type V* (*Secondary Cardiorenal Syndrome*)**

Systemic condition (e.g., sepsis) causing both acute cardiac and renal injury and dysfunction

CKD and valvular heart disease, all patients with CKD should be considered for echocardiography at the time CKD is determined by the presence of reduced estimated glomerular filtration rate (eGFR) <59 ml/min/1.73 m^2 or evidence of kidney damage manifest by an increased urine albumin: creatinine ratio or imaging evidence of kidney disease such as polycystic kidneys by ultrasound [7]. Importantly, cardiovascular disease including coronary disease and heart failure occurs at much earlier ages than in the general population [8]. The presence of combined heart and kidney failure is now considered a "cardiorenal syndrome" and should be considered in the context of the more antecedent abnormality with respect to both diagnosis and management [9]. Five subtypes of cardiorenal syndromes are displayed in (Box 12.1). The current Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines recommend echocardiograms for all CKD 5D patients 1–3 months after renal replacement therapy initiation and at 3-year intervals thereafter [10] (Boxes 12.2 and 12.3). Echocardiography with complete Doppler assessment reliably estimated left ventricular ejection fraction (normal 55–75 %), left ventricular hypertrophy (left ventricular mass index >115 and >95 g/m^2), and assesses both the morphology and flow characteristics of all four cardiac valves. Findings suggesting reduced ejection fraction, diastolic dysfunction, or regional wall motion abnormalities may prompt an evaluation for chronic cardiac ischemia as discussed above [11]. Diastolic dysfunction is ideally graded according to the European Association of Echocardiography/American Society of Echocardiography criteria as normal, Grade I (impaired relaxation), Grade II, and Grade III (most severe) with evidence of restriction and increased left atrial pressure. Echocardiographic evaluation of left ventricular diastolic dysfunction can be complicated. It consists of measuring E/è and E/A ratios to determine impaired relaxation as well as restrictive patterns and LV filling pressures. E and A represent velocities of the rapid early and late transmitral diastolic flow, while è is a measurement of mitral annulus recoil velocity. Chronic kidney disease is associated with a form of uremic or CKD cardiomyopathy as shown in Fig. 12.3. The cardiomyopathy associated with CKD is characterized by the presence of left ventricular hypertrophy, evidence of diastolic dysfunction, and, in more severe cases, superimposed systolic dysfunction with reduced ejection fraction.

A finding of significant valvular or pericardial disease warrants clinical correlation and

Box 12.2. What the Guidelines Say You Should Do

- Patients with chest pain should receive a complete history and physical examination to assess the probability of coronary disease before additional testing.
- A resting ECG is recommended in patients without an obvious, noncardiac cause of chest pain.
- Assessment of resting left ventricular function and evaluation for abnormalities of myocardium, heart valves, or pericardium are recommended with the use of Doppler echocardiography in patients with known or suspected coronary disease and a prior MI, pathological Q waves, symptoms or signs suggestive of heart failure, complex ventricular arrhythmias, or an undiagnosed heart murmur.
- Standard exercise stress testing is recommended for risk assessment in patients with stable coronary disease who have an interpretable ECG and no disabling comorbidity. Pharmacological stress with nuclear myocardial perfusion imaging or echocardiography is an alternative in those who are incapable of exercising to an accepted workload.
- Coronary computed tomography angiography is reasonable for patients with a low to intermediate pretest probability of ischemic heart disease who have a disabling comorbidity.

Source: Data from Refs. [16–18].

Box 12.3. Relevant Guidelines

1. *American Heart Association Guidelines*:
   - 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: executive summary. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Circulation. 2012;126:3097–137 [16].
   - 2011 ACCF/AHA/SCAI guideline for Percutaneous Coronary Intervention: executive summary. A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. Circulation. 2011;124:2574–609 [17].
2. *National Kidney Foundation Guidelines*:
   - National Kidney Foundation. K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. Am J Kidney Dis. 2005;45 Suppl 3:S1–154 [18].

follow-up. Most patients with moderate or more aortic stenosis/regurgitation or mitral regurgitation will require annual echocardiography and cardiology consultation for surveillance. In general, severe symptomatic aortic stenosis (Fig. 12.4) and/or regurgitation is an indication for valve replacement [5].

Pericardial disease may develop in kidney failure as pericarditis, pericardial effusion, or chronic constrictive pericarditis. BUN elevations over 60 mg/dl may lead to inflammation in the pericardial membranes causing uremic pericarditis. Fluid overload can also lead to pericardial inflammation without uremia. Typical symptoms include fever and pleuritic chest pain that is relieved by sitting up or bending forward. Platelet function impairment may cause a hemorrhagic pericardial effusion and possibly tamponade depending on the

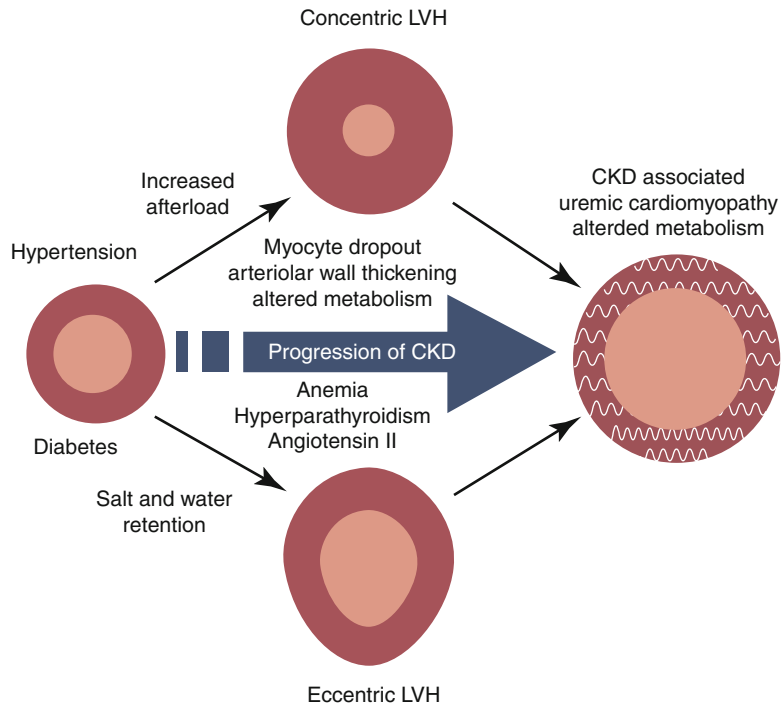


Fig. 12.3 Hypertension, diabetes mellitus, and the development of chronic kidney disease cardiomyopathy

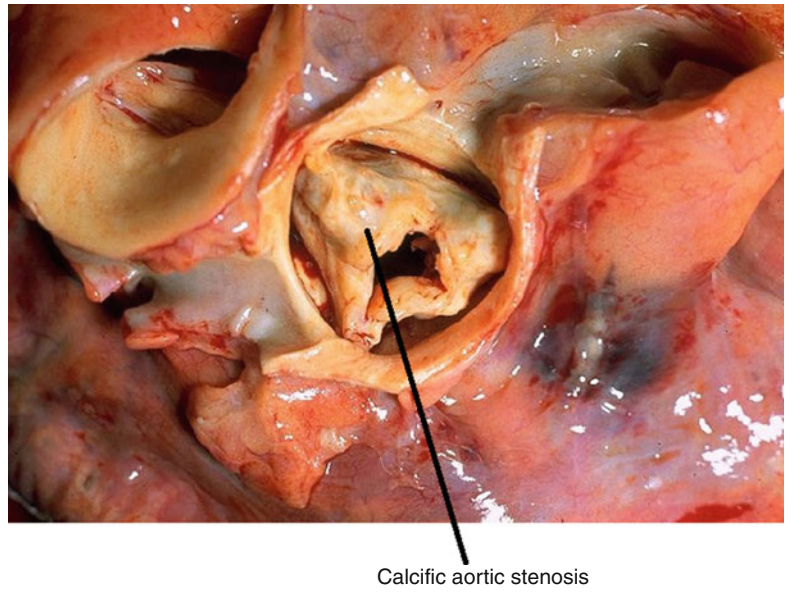


Fig. 12.4 Calcific aortic stenosis

rate of fluid accumulation. Typical diffuse ST elevations observed with acute pericarditis are generally not shown when uremia is the cause [12]. Echocardiography is able to exclude silent effusions and useful in determining associated myocarditis and altered ventricular function.

12.3 What Blood Biomarkers Are Useful in Heart Failure?

Both blood B-type natriuretic peptide (BNP) and N-terminal pro B-type natriuretic peptide (NT-proBNP) have been approved, guidelines

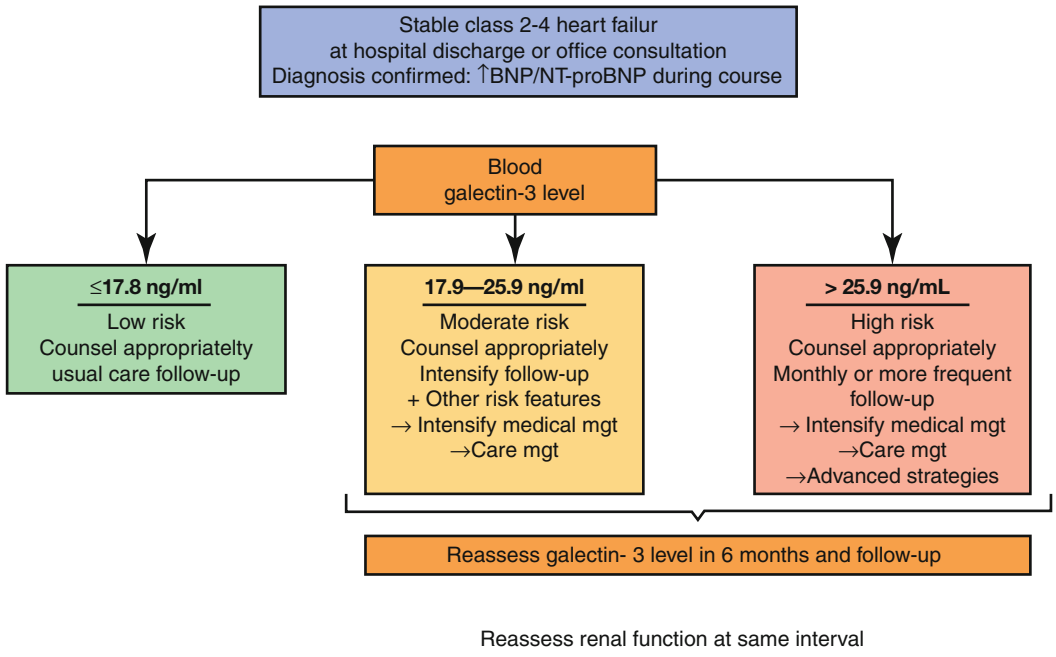


Fig. 12.5 Suggested algorithm for the management of heart failure patients using galectin-3 levels measured in blood

recommended, and are commercially available for several years. When measured in blood, they are indicated as diagnostic aids for the evaluation of patients with acute shortness of breath, prognostic indicators for death and heart failure hospitalization, and aids in the management of patients particularly with respect to the titration of chronic medications. In general, when BNP >200 pg/ml and NT-proBNP >2,000 pg/ml, there is increased myocardial production even in the presence of reduced clearance by the kidneys. The higher the levels, the greater the positive predictive value for heart failure and the worse the prognosis for hospitalization or death. Chronic use of angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, aldosterone receptor blockers, and beta-adrenergic receptor antagonists and use of biventricular pacing have been shown to reduce BNP/NT-proBNP over time. In approximately 25 % of patients with preserved renal function, natriuretic peptides can be normalized (BNP <100 pg/ml, NT-proBNP <150 pg/ml) with therapy for heart failure. In the setting of CKD, it is rare for natriuretic peptides to normalize; however, relatively lower levels (~50 % reduction from prior levels) are associated with a favorable prognosis. Conversely, a doubling of levels over a time frame of 6 weeks or more portends a high rate of future hospitalization and death, both from pump failure and arrhythmias.

Galectin-3 is a paracrine substance produced by macrophages that are participating in myocardial fibrosis. Increased levels of galectin-3 (>25.9 ng/ml) are strongly prognostic for short-term death and hospitalization in patients with either diastolic or systolic dysfunction. There have been no published studies evaluating the clinical value of galectin-3 in patients with CKD; however, many subjects in the heart failure studies where it was measured met the criteria for CKD according to an eGFR < 60 ml/min [13]. A suggested algorithm for the management of heart failure using galectin-3 is shown in Fig. 12.5.

Soluble ST2 (ST2) and interleukin-33 compete for the transmembrane protein ligand (ST2L) and induce production of T helper type 2 cytokines. In heart failure, serum ST2 is elevated and indicates increased abnormal immune cell signaling related to myocardial dysfunction. ST2 aids in prognostication in patients with acute and chronic heart failure, particularly when at very high levels (ST2 >36.3 ng/ml). However, an elevated concentration of serum sST2 is found in CKD patients and correlates with the severity of renal disease. Serum sST2 may be also associated

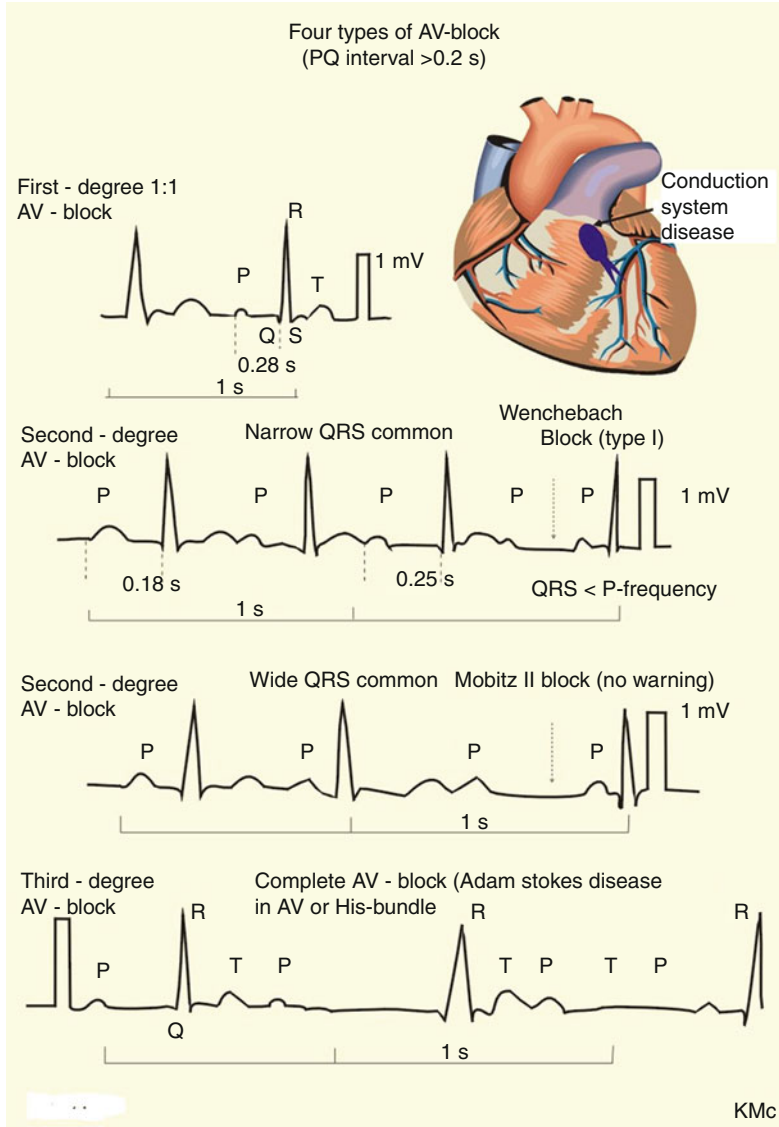


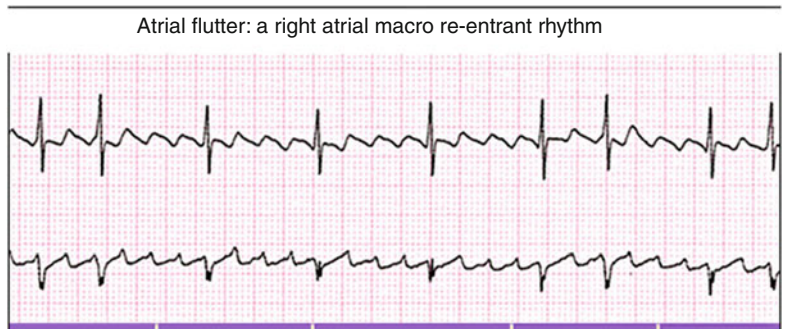
Fig. 12.6 Types of atrioventricular block as identified by electrocardiography

with secondary hyperparathyroidism. The sST2 may have an important role in the development of CKD or as a marker of disease severity, particularly in those with incipient heart failure. Future research in this area is warranted.

12.4 Should Patients with Renal Dysfunction Have Arrhythmia Surveillance?

Maintenance of normal sinus rhythm can become progressively more difficult in patients with CKD who develop left ventricular hypertrophy, left atrial dilatation, right ventricular strain and hypertrophy, and right atrial dilatation. With activation of factors that promote cardiac fibrosis, the conduction system of the heart can show signs of failure at all levels. Thus, at the minimum in an asymptomatic patient with CKD, a 12-lead electrocardiogram should be obtained on an annual basis and with any change in cardiac symptoms. Failure of conduction at the level of the sinus node can lead to sick sinus syndrome (episodes of sinus pauses and tachycardia), atrioventricular node block (Mobitz Type II second degree and complete heart block (Fig. 12.6), and bundle branch blocks. These lesions in symptomatic

Fig. 12.7 Atrial flutter



Heart Rate	Rhythm	P wave	PR interval (in seconds)	QRS (in seconds)
A: 220–430 bpm V: <300 bpm	Regualr or variable	Sawtoothed appearance	N/A	<.12 Winder if BBB

A=atrial, V=ventricular
BBB=bundle branch block

patients are indications for permanent pacemaker implantation.

Right atrial dilatation can create a macro reentrant circuit which facilitates atrial flutter. This rhythm is recognized by sawtooth atrial depolarization waves and ventricular conduction typically in a 2:1 or 3:1 ratio (Fig. 12.7). Atrial flutter is easily managed by radio-frequency ablation and deserves electrophysiology referral. Left atrial dilatation and left ventricular hypertrophy as well as advanced age and hypertension are strong determinants for the development of atrial fibrillation (AF). Atrial fibrillation is the most common dysrhythmia among the general and CKD populations. Because the disorganized rhythm leads to stasis of blood in the left atrial appendage, thrombi can form and be ejected into the left circulation resulting in stroke and systemic cardio-embolism (Fig. 12.8). Thus, AF presents multiple management dilemmas including rhythm versus rate control, anticoagulation, and heart failure prevention. Any patient who presents with palpitations, tachycardia, or stroke symptoms should be assessed for AF with inpatient monitoring, 24- or 48-h outpatient Holter monitoring, or patient-triggered event monitoring. For difficult cases, an implantable loop recorder can be placed subcutaneously in the infraclavicular region and give information about cardiac rhythm for several years using noninvasive computer interrogation. In the setting of cryptogenic stroke, use of intensive rhythm monitoring has shown that approximately one third of cases can have the stroke be attributable to paroxysmal AF that was previously unrecognized.

The leading cause of death in CKD and ESRD is sudden arrhythmic death. The details surrounding these cases are often difficult to pull together since many occur in the home and out of hospital. Presumably heart block, electromechanical dissociation, pump failure, or ventricular fibrillation is the terminal scenario. Patients with left ventricular ejection fractions <35 %, those with a history of a prior resuscitated cardiac arrest, and spontaneous sustained ventricular tachycardia on monitoring should all be considered for implantable cardio-defibrillators. These devices reduce cardiac mortality in the general population but have not definitively been shown to prolong survival in patients with CKD or ESRD. The two major therapies delivered by implantable cardio-defibrillators are antitachycardia pacing and defibrillation as shown in Fig. 12.9. Because of increased myocardial interstitial matrix in CKD and left ventricular hypertrophy, CKD and ESRD patients can be expected to have higher defibrillation thresholds and should undergo more frequent monitoring by the electrophysiologist using noninvasive programmed stimulation [14].

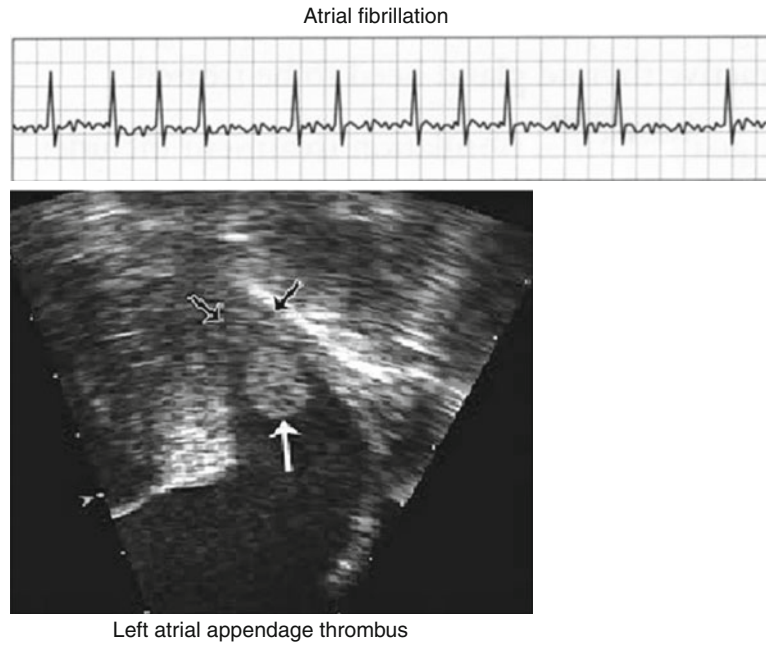


Fig. 12.8 Atrial fibrillation on electrocardiography and a left atrial appendage identified by transesophageal echocardiography

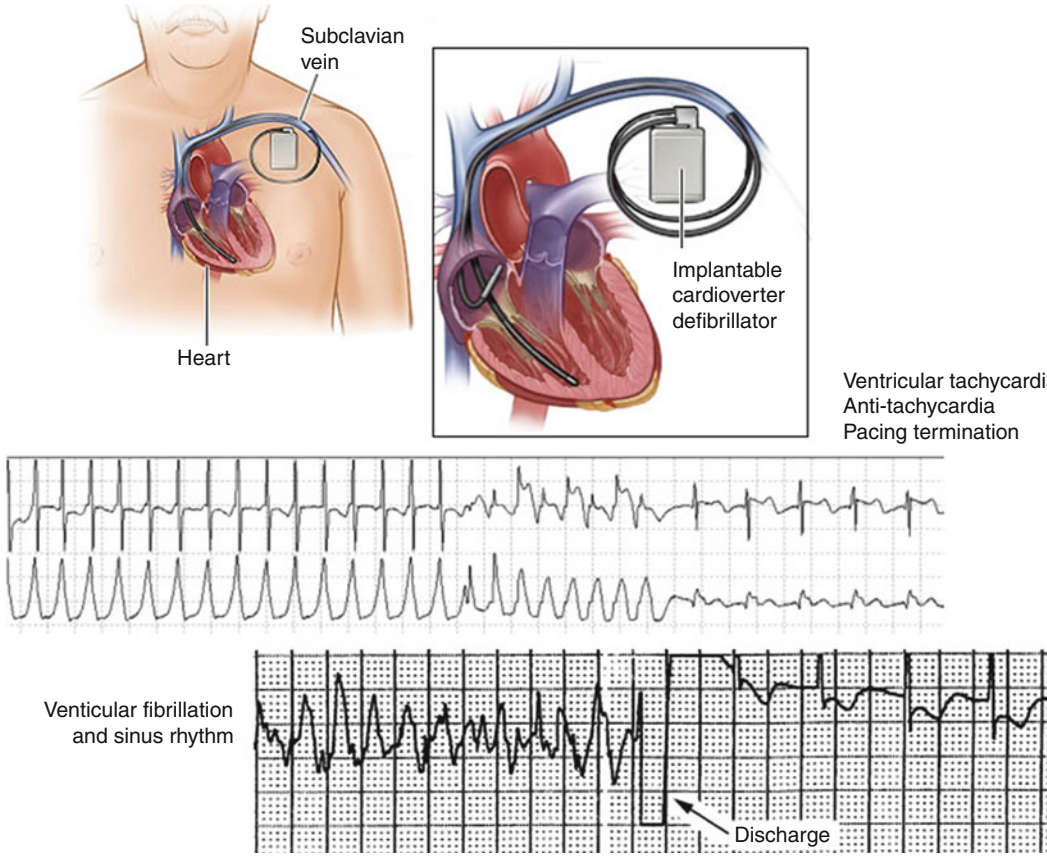


Fig. 12.9 Implantable cardio-defibrillator and demonstration of its two major forms of therapy: (1) anti-tachycardia pacing termination of ventricular tachycardia and (2) defibrillation for ventricular fibrillation

12.5 Summary

High rates of serious cardiovascular disease in patients with CKD and ESRD call for a more attentive approach to both routine and responsive testing in patients at risk or with potential cardiac symptoms [15]. The nephrologist needs a basic understanding of electrocardiographic interpretation both on routine single-lead monitoring and with 12-lead electrocardiography. Use of stress imaging, echocardiography, and continuous forms of rhythm monitoring provide an approach for the diagnosis and management of cardiovascular disease. Early detection and prompt management offer the hope for prevention of myocardial infarction, heart failure, valvular-induced structural damage, stroke, and fatal arrhythmias.

Before You Finish: Practice Pearls for the Clinician

- Assess atherosclerosis risk factors on all patients and work to manage them to optimal levels.
- Diagnose significant cardiac ischemia with stress imaging. Large amounts of ischemia (>10 % of the left ventricle) deserve coronary angiography and consideration of revascularization.
- Obtain routine 12-lead electrocardiography and have a low threshold to obtain more advanced forms of monitoring in patients with palpitations, near syncope, syncope, and stroke.
- Consider echocardiography for all patients with CKD and ESRD for assessment of myocardial function and valvular disease. Patients with considerable abnormalities need cardiology consultation and surveillance.
- In acute or chronic dyspnea, or when heart failure is suspected, elevated levels of BNP, NT-proBNP, galectin-3, and ST2 are supportive of the diagnosis of heart failure and can portend decompensation and death.
- Resuscitated sudden death is an indication for an implantable cardio-defibrillator.

References

1. Chen SC, Su HM, Tsai YC, Huang JC, Chang JM, Hwang SJ, et al. Framingham risk score with cardiovascular events in chronic kidney disease. PLoS One. 2013;8(3):e60008.
2. McCullough PA. Cardiovascular disease in chronic kidney disease from a cardiologist's perspective. Curr Opin Nephrol Hypertens. 2004;13(6):591–600.
3. Keeley EC, McCullough PA. Coronary revascularization in patients with coronary artery disease and chronic kidney disease. Adv Chronic Kidney Dis. 2004;11(3):254–60.
4. McCullough PA, Agrawal V, Danielewicz E, Abela GS. Accelerated atherosclerotic calcification and Mönckeberg's sclerosis: a continuum of advanced vascular pathology in chronic kidney disease. Clin J Am Soc Nephrol. 2008;3(6):1585–98.
5. McCullough PA, Agarwal M, Agrawal V. Review article: risks of coronary artery calcification in chronic kidney disease: do the same rules apply? Nephrology (Carlton). 2009;14(4):428–36.
6. KDIGO clinical practice guidelines for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). Kidney Int. 2009;76(113):S1–S130.
7. McCullough PA, Jurkovitz CT, Pergola PE, McGill JB, Brown WW, Collins AJ, KEEP Investigators, et al. Independent components of chronic kidney disease as a cardiovascular risk state: results from the kidney early evaluation program (KEEP). Arch Intern Med. 2007;167(11):1122–9.
8. McCullough PA, Li S, Jurkovitz CT, Stevens L, Collins AJ, Chen SC, KEEP Investigators, et al. Chronic kidney disease, prevalence of premature cardiovascular disease, and relationship to short-term mortality. Am Heart J. 2008;156(2):277–83.
9. Ronco C, McCullough PA, Anker SD, Anand I, Aspromonte N, Bagshaw SM, et al. Cardiorenal syndromes: an executive summary from the consensus conference of the acute dialysis quality initiative (ADQI). Contrib Nephrol. 2010;165:54–67.
10. National Kidney Foundation. K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. Am J Kidney Dis. 2005;45:S1–153.
11. Vanhecke TE, Franklin BA, Soman P, Lahiri A, Mieres JH, Sias T, et al. Influence of myocardial ischemia on outcomes in patients with systolic versus non-systolic heart failure. Am J Cardiovasc Dis. 2011;1(2):167–75.
12. Grunukula SR, Spodick DH. Pericardial disease in renal patients. Semin Nephrol. 2001;21:52.
13. McCullough PA, Olobatoke A, Vanhecke TE. Galectin-3: a novel blood test for the evaluation and management of patients with heart failure. Rev Cardiovasc Med. 2011;12(4):200–10.
14. Wase A, Basit A, Nazir R, Jamal A, Shah S, Khan T, et al. Impact of chronic kidney disease upon survival among implantable cardioverter-defibrillator recipients. J Interv Card Electrophysiol. 2004;11(3):199–204.

15. Best PJ, Reddan DN, Berger PB, Szczech LA, McCullough PA, Califf RM. Cardiovascular disease and chronic kidney disease: insights and an update. Am Heart J. 2004;148(2):230–42.
16. Fihn SD, Gardin JM, Abrams J, Berra K, Blankenship JC, Dallas AP, Douglas PS, Foody JM, Gerber TC, Hinderliter AL, King 3rd SB, Kligfield PD, Krumholz HM, Kwong RY, Lim MJ, Linderbaum JA, Mack MJ, Munger MA, Prager RL, Sabik JF, Shaw LJ, Sikkema JD, Smith Jr CR, Smith Jr SC, Spertus JA, Williams SV, American College of Cardiology Foundation. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: executive summary. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Circulation. 2012;126:3097–137.
17. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, Chambers CE, Ellis SG, Guyton RA, Hollenberg SM, Khot UN, Lange RA, Mauri L, Mehran R, Moussa ID, Mukherjee D, Nallamothu BK, Ting HH. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: executive summary. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. Circulation. 2011;124:2574–609.
18. National Kidney Foundation. K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. Am J Kidney Dis. 2005;45 Suppl 3:S1–154.