16.5.4 Cardiorenal syndrome 3421 Darren Green and

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16.5.4 Cardiorenal syndrome 3421 Organization of care Good management requires organization to ensure that appropriate treatment is delivered safely and effectively in order to • gain and maintain clinical stabilization; • recognize when patients are deteriorating, and do something about it before they reach a crisis; • identify patients who need more specialized services. This is greatly facilitated by the use of electronic health records (EHRs), especially if they are enhanced by decision support systems. EHRs and home telemonitoring have a synergistic role in improving healthcare. Increasingly, patients, their carers, and their social net- work are becoming involved with long-term care, and any good or- ganization will use them as part of the care team. Delivering good care requires a care plan that is shared with the patient and all the services that support them. These should provide enough informa- tion about the patient to deliver the treatments and doses specified in the care plan safely and effectively (Table 16.5.3.6). FURTHER READING Burnett H, et al. (2017). Thirty years of evidence on the efficacy of drug treatments for chronic heart failure with reduced ejection frac- tion: a network meta-analysis. Circ Heart Fail, 10, e003529. Kassi M, Hannawi B, Trachtenberg B (2018). Recent advances in heart failure. Curr Opin Cardiol, 33, 249–56. McMurray JJ, et al. ESC Committee for Practice Guidelines (2012). ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail, 14, 803–69. Erratum in: Eur J Heart Fail, 2013, 15, 361–2. NICE guideline (2018). Chronic heart failure in adults: diagnosis and management. https://www.nice.org.uk/guidance/ng106 Yancy CW, et al. (2018). 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: answers to 10 pivotal issues about heart failure with reduced ejection fraction: a report of the American College of Cardiology Task Force on expert consensus decision pathways. J Am Coll Cardiol, 71, 201–30.

Concurrent renal and cardiovascular disease is common. Renal dis- ease is a potent cardiovascular risk factor and consequently cardio- vascular disease is the most important cause of mortality in patients with end-stage renal disease. This increased risk is mediated by vascular disease (coronary calcification, endothelial dysfunction, dyslipidaemia, and others), left ventricular hypertrophy, risk of ar- rhythmias, and left ventricular systolic and diastolic dysfunction. These interactions are further complicated by the presence of an- aemia in advanced renal disease. The coexistence of renal disease and heart failure presents a major therapeutic challenge and requires careful attention to fluid status and renal function. Diuretic resistance is common and the important prognostic benefit of angiotensin-converting enzyme inhibition in this high-risk group is often neglected. Cardiovascular drugs, particu- larly antiarrhythmic agents such as digoxin, sotalol, and flecainide, should be used with caution in patients with renal disease. Patients with severe cardiac and renal disease require a multidisciplinary ap- proach to their management. Instructions • Double carvedilol every 2 wks until target achieved • Delay titration if heart rate <65 bpm or systolic BP <110 mm Hg • Down titrate if heart rate <55 bpm • Add ivabradine 5 mg bd if heart rate remains >70 bpm despite achieving carvedilol target • Double enalapril in one week to achieve target • Reduce dose if systolic BP <90 mm Hg • Check renal function and electrolytes in 10 days. Reduce dose if serum creatinine >180 µmol/litre (c.30% increase). Re-check in 10 days if

> 150 µmol/litre (c.10% increase) • If serum potassium >5.5 mmol/litre stop spironolactone and re-check
> potassium in 10 days. Reinitiate at half-dose if potassium <5 mmol/litre • Stop ferrous sulphate in 3 months and re-check haemoglobin and iron status • Advise on diet and exercise • Increase bumetanide in one month if: • Systolic BP not at target and the patient is not at dry weight • Remains symptomatic and the patient is not at dry weight • Reverse this decision if patient does not like the change • Further cardiology review in six weeks Discharge Target Carvedilol 3.125 mg bd 25 mg bd Enalapril 2.5 mg bd 5 mg bd Spironolactone 25 mg/d 25 mg/d Bumetanide 1 mg/d 1 mg/d Aspirin 75 mg/d stop Clopidogrel — 75 mg/d Metformin 500 mg bd 500 mg bd Lansoprazole 30 mg/d Stop Ferrous sulphate 200 mg tid Re-assess Exercise for 10 min × 3/wks Now Target Symptoms (NYHA class) Recent IV I/II Resting heart rate (bpm) 73 55–65 Systolic BP (mm Hg) 114 110–130 Weight (kg) 68.7 67.0–69.0 Potassium (mmol/litre) 4.5 4.0–4.9 Creatinine (µmol/litre) 134 <150

section 16 Cardiovascular disorders 3422 What is the cardiorenal syndrome? The term ‘cardiorenal syndrome’ was first introduced to describe the frequent finding of worsening renal function in response to acute decompensation of heart failure or the up-titration of nephrotoxic agents used in its treatment. However, this definition is criticized for focusing only on the few patients in whom specific diseases of the heart and kidney lead to concurrent morbidity in the other organs. Indeed, most patients who have evidence of adverse cardiorenal interaction will not fall into this category, and likewise acute kidney injury (AKI) will not be a precipitant of major cardiac morbidity in most patients with this condition. Further attempts to classify different interactions of renal failure and heart disease into subtypes of cardiorenal syndrome have yielded the Acute Dialysis Quality Initiative classification system found in Table 16.5.4.1. This acknowledges the wider spectrum of

cardiac disease that may be precipitated by renal impairment, such as sudden cardiac death and the impact of heart failure on chronic kidney disease (CKD) as well as AKI. However, its use in clinical practice is very limited as it provides no mechanistic, therapeutic, or prognostic guidance, and does not accommodate the complex interactions of acute and chronic illness when coexisting. For this reason, both clinical and experimental terms and definitions relating to cardiorenal syndrome are likely to change as under- standing evolves. In this chapter, rather than simply outlining the purported different types of cardiorenal syndrome (1–5) that have been repeatedly described elsewhere, we instead concentrate on the important structural abnormalities and pathophysiological inter- actions which result from the interplay of diseased kidneys, heart, or both.

Epidemiology of concurrent cardiac and renal disease

Difficulties in classifying cardiorenal syndrome arise from the broad disease categories implicated and their overlapping inter- actions. Cardiovascular mortality is disproportionate in CKD compared to the general population. Annual mortality for dialysis patients is 15% in Europe and 19% in North America, and 46% of these deaths are due to cardiovascular disease. The most common cause of death in dialysis patients is sudden cardiac death, likely due to arrhythmia. The event rate far exceeds that of the general population (70–120 versus 1–2 events per 1000 patient years, see Table 16.5.4.2), and accounts for a greater proportion of all deaths (26% vs. 11%). The period of highest mortality is actually the first 6 months after initiation of chronic haemodialysis therapy. Left ventricular hypertrophy (LVH) is present in 74% of new haemodialysis pa- tients, and reduced ejection fraction is present in 36%. That these abnormalities are already present at the initiation of dialysis in- dicates that the high cardiovascular risk to which these patients are exposed is a function of progression of cardiac disease during predialysis CKD, as well as an effect of dialysis itself. The increased risk of cardiovascular events and death persists after renal transplant, albeit at a reduced event rate. New-onset cor- onary artery disease after transplant occurs at approximately 10 events per 1000 patient years, and cardiovascular death accounts for more than 50% of all post-transplant mortality. This risk is greatest in diabetic transplant recipients, who have a threefold greater risk of cardiovascular disease than their nondiabetic coun- terparts. Indeed, in the latter group, post-transplant infection and malignancy cause more deaths than cardiovascular disease. Renal disorders are also common in patients presenting with car- diac disease. Only 17% of patients seen in heart failure clinics will have normal renal function, and up to 55% will have CKD stage

Table 16.5.4.1 Acute Dialysis Quality Initiative classification of cardiorenal syndrome

Type	Onset	Precipitant	Secondary effect	Examples
1	Acute	CARDIAC	Acute cardiac dysfunction	RENAL AKI	Cardiogenic shock causing rapid rise in serum creatinine, decompensated heart failure leading to AKI
2	Chronic	Chronic cardiac dysfunction	CKD	Chronic heart failure leading to long-term decline in eGFR
3	Acute	RENAL	Acute kidney injury	CARDIAC Acute cardiac event	Acute glomerulonephritis with oliguria leading to pulmonary oedema, AKI causing hyperkalaemia leading to arrhythmia
4	Chronic	CKD	Cardiac remodelling	Renal artery stenosis and CKD leading to LVH, CKD associated vascular calcification with chronic ischaemia
5	Secondary	OTHER	Systemic condition	BOTH Cardiac and renal dysfunction	Diabetes mellitus, hypertension, SLE

AKI, acute kidney injury; CKD, chronic kidney disease; LVH, left ventricular hypertrophy; SLE, systemic lupus erythematosus.

Table 16.5.4.2 Comparison of event rates for sudden cardiac death (SCD) in the general population and high-risk clinical groups including patients with heart failure and receiving dialysis

SCD events (per 1000 patient years)
General population <85 years	1–2
General population >85 years	40
Post-myocardial infarction	40
Heart failure, ejection fraction <35%	90–200
Predialysis CKD	7
CKD on dialysis	70–120

CKD, chronic kidney disease.

16.5.4 Cardiorenal syndrome 3423 3 to 5 (for CKD stages, see Table 16.5.4.3) and mortality risk in- creases as renal function worsens (Fig. 16.5.4.1). Similarly, AKI oc- curs in 27–45% of hospitalizations for decompensated heat failure depending on definition. Inpatient mortality, critical care admis- sion, and total length of stay are all independently associated with AKI in this population. Although definitions of AKI have differed between studies this is a consistent finding, even after a fall in serum creatinine of just 9 µmol/litre. In one study of 1007 nonelective hos- pital heart failure admissions, the relative risks of adverse outcomes if AKI supervened compared to normal renal function were 7.5 for death, 2.1 for major complication, and 3.2 for length of stay greater than 10 days (here, AKI was defined as an increase in serum cre- atinine >26.5 µmol/litre). The predictive power of AKI to recognize adverse outcome in decompensated heart failure has a high degree of specificity (>80%) but is poorly sensitive (<70%). In fact, AKI is as predictive of adverse outcome in acute heart failure as left ventricular ejec- tion fraction and blood pressure. AKI is also most common in heart failure patients with pre-existing CKD. A summary of fac- tors predisposing to AKI after decompensation of heart failure is given in Box 16.5.4.1. Haemodynamic effects of cardiorenal interaction in disease Systemic blood pressure is dependent on the actions of both the heart and kidneys, which regulate body fluid volumes by changes in vascular tone, diuresis, and natriuresis. Dysregulation of one may lead to dysfunction of the other. For example, a fall in blood pressure associated with heart failure will activate the renin–angiotensin– aldosterone (RAAS) pathway to retain salt and water, and increase vascular tone via sympathetic pathways. Subsequent volume expan- sion will help maintain renal perfusion but may paradoxically lead to further decompensation of heart failure. Activation of the RAAS system will also have other deleterious actions such as increasing oxidative stress, inflammation, and tissue fibrosis. Reduced cardiac output may also in turn lead to reduced cardiac filling and increased central venous pressures. Should such pressures increase in the renal vasculature, glomerular filtration may become compromised by a reduction in the pressure difference between af- ferent and efferent vessels. This will lead to CKD or AKI. This vicious cycle of worsening chronic cardiorenal deterioration is summarized in Fig. 16.5.4.2. A specific example of where RAAS overactivation is implicated in cardiorenal disease is the association between atherosclerotic renovascular disease (ARVD) causing renal artery stenosis and acute and chronic heart failure. Renal artery stenosis is classically linked to flash pulmonary oedema, but this phenomenon most probably represents no more than decompensation of heart failure, given that 75% of patients with ARVD have left ventricular hyper- trophy and diastolic dysfunction (far greater than in age and eGFR matched controls). Furthermore, ARVD is common, being found in half of patients attending secondary care heart failure clinics and in one in three hospital admissions with heart failure decompensation. Haemodynamically significant ARVD leads to increases in cir- culating angiotensin II, which as well as promoting salt and water retention contributes to the fibrotic, hypertrophic cardiac remod- elling seen in ARVD by stimulating production of FGF-23, PDGF, Table 16.5.4.3 The stages of chronic kidney disease Stage eGFR (ml/min/1.73 m2) 1

> 90a 2 60–89 3a 45–60 3b 30–44 4 15–29 5 <15 Suffix T = transplant; suffix D = dialysis. a Evidence of damage without change in function (e.g. proteinuria). 40 35 30 25 20 15 10 0.76 2.11 1.03 3.65 4.76 11.29 11.36 21.8 14.14 36.6 5 0 60 45–59 30–44 eGFR (ml/min/1/73m2) Age-standardized event rate per 100 patient years 15–29 <15 Death Cardiovascular events Fig. 16.5.4.1 The

> increasing cardiovascular burden of declining renal function. Adapted from Go SG, et al. (2006). Hemoglobin level, chronic kidney disease, and the risks of death and hospitalization in adults with chronic heart failure. The Anemia in Chronic Heart Failure: Outcomes and Resource Utilization (ANCHOR) study. Circulation, 113(23), 2713–23. Box 16.5.4.1 Risk factors for acute kidney injury in hospital admissions for heart failure • Laboratory parameters • Underlying CKD • Anaemia • Hyponatraemia • Echocardiographic parameters • Diastolic dysfunction • Pulmonary hypertension • Atrioventricular valvular incompetence • Haemodynamic factors • Hypotension on admission • Underlying hypertension • Comorbidities • Older age • Diabetes • Previous acute heart failure admissions • Previous AKI or dialysis • Nephrotoxic polypharmacy

section 16 Cardiovascular disorders 3424 and TGFß. Importantly, renal artery revascularization leads to sig- nificant reductions in circulating angiotensin II, and there is a case report of improvement in left ventricular mass from 161 g before revascularization to 108 g one year after, and in left ventricular end diastolic volume from 193 ml to 124 ml (estimated using cardiac magnetic resonance imaging). On a broader scale, in a case control study of 100 patients with ARVD and heart failure, revascularization was associated with a fivefold reduction in heart failure hospitalization compared to medical management alone. A further study, also of 100 patients, has shown that patients with ARVD and chronic heart failure who have never previously suffered acute pulmonary oedema may also benefit from revascularization. Here, the hazard ratio for death in the revascularization group was 0.76 (0.58–0.99, p = 0.04) compared to medically managed patients. This latter finding may indicate that ‘flash pulmonary oedema’ as the current indication for ARVD revascularization could yet be extended to encompass a broader phenotype of heart failure patients. On a cautionary note, however, these two studies were both conducted in an observational setting, and prospective randomized evidence will be required to justify a change in routine practice. See Chapter 21.10.10 for further discus- sion of atherosclerotic renovascular disease. Other factors implicated in cardiorenal syndrome are the rela- tionship between nitric oxide and reactive oxygen species, both of which affect haemodynamic regulation and endothelial function, and both of which are under partial control by the heart and kid- neys. The relative importance of each factor is unknown and is likely to be different in different cardiorenal syndrome settings. This complexity of pathways leading to cardiorenal syndrome means that the search for biomarkers of cardiorenal syndrome risk or a common signalling pathway, such as interleukin-6, has thus far not been fruitful. Nephrotoxicity and other adverse drug effects The problem of mechanism is further confounded by the effect of external factors, most notably prescribed medication. Perhaps most obviously, AKI may be caused directly by contrast agents used in coronary angiography. This risk can be quantified based on weighted scoring of risk factors for contrast nephropathy, as shown in a cohort study of 8357 patients (Table 16.5.4.4). This is a useful tool in clinical decision-making and for the process of obtaining informed consent. The use of RAAS blockade, particularly angiotensin-converting enzyme (ACE) inhibitors, is associated with improved survival in heart failure. ACE inhibitors are also known to affect glomerular filtration and may lead to AKI during decompensated heart failure Decompensation of heart failure Reduced blood pressure RAAS activation Increased sympathetic tone Vasoconstriction Increased renal perfusion

Preservation of renal function Deterioration of renal function vs. Salt and water retention Relative volume expansion Increased glomerular efferent pressure Increased venous pressure Reduced glomerular filtration Fig. 16.5.4.2 The competing haemodynamic response to heart failure in causing and preventing deterioration in renal function.

16.5.4 Cardiorenal syndrome 3425 with resultant uncertainty as to how best manage these drugs during the episode. However, the extent to which ACE inhibitors are impli- cated in AKI may be overstated. In the Studies of Left Ventricular Dysfunction (SOLVD) trial, 16% of patients treated with enalapril (mean daily dose 16.6 mg) developed a rise in serum creatinine in excess of 44 μmol/litre. However, the figure for the placebo arm was 12%. Also, such studies do not usually report improvements in GFR, but it is estimated that 10% may have comparable improvements in renal function due to improved cardiac output. Furthermore, as demonstrated in Fig. 16.5.4.2, RAAS overactivation may lead to acute worsening of both cardiac and renal function and so cessation of ACE inhibitors is of possible detriment in such cases. Fear of deteriorating renal function is often a reason for underprescribing ACE inhibitors for long-term cardioprotection in CKD patients. However, ACE inhibition is protective against renal deterioration even in CKD stage 4, and deterioration in the pres- ence of renovascular disease is much less common than anticipated at approximately 11%. A rise in creatinine with the introduction of ACE inhibitors in patients with heart failure of up to 50% above baseline or to a creatinine of 200 μmol/litre is accepted in some guidelines provided renal function subsequently stabilizes. What may be required is a different approach to ACE inhibitor dosing for heart failure where CKD is present. The ATLAS trial compared high versus low dose lisinopril in 3164 patients with heart failure (>30 mg per day versus 2.5–5 mg). Overall, there was a reduction in mortality (12%) and heart failure hospitalization (24%) in the high-dose arm. However, in a post-hoc analysis of study patients with advanced CKD (n = 988) there was no difference in mortality or heart failure outcomes, but the high-dose arm suffered significantly more ad- verse effects in respect of hypotension, hyperkalaemia, and decline in renal function. This supports patients with advanced CKD being given ACE inhibitors for heart failure, but at low dose. Long-term monitoring of renal function in patients with CKD on ACE inhibitors is vital, as is adequate counselling about the risk of AKI and the importance of seeking medical advice in the event of a dehydrating illness such as diarrhoea. There are now reports of medico-legal disputes involving such cases, akin to those relating to anticoagulation and chemotherapeutic agents. There is also a reluctance to prescribe high-dose loop diuretics in patients with renal disease. This is based on a fear of renal toxicity and prerenal failure due to intravascular volume depletion. It is fre- quently not appreciated that in fluid-overloaded patients with heart failure the adverse effects on renal function due to an elevated right atrial pressure and renal congestion are greater than the impact of re- duced cardiac output. Inducing a significant diuresis with high-dose diuretics in this situation may result in a significant improvement ra- ther than deterioration in renal function. Key to the assessment of the likely impact of diuretic therapy on renal function in these patients is a careful assessment of the intravascular volume status of the patient. Determining the most appropriate action in respect of these drugs is poorly evidence based, but the key message is that monitoring of renal function is vital in both chronic and acute care of cardiac dis- ease, and although suspension of ACE inhibitors during acute illness is often the safest action, their timely reintroduction is also necessary. As noted earlier, the most common cause of mortality in CKD is sudden cardiac death, and certain drugs commonly prescribed in nephrology clinics have the potential to exacerbate arrhythmia. The three most common pathways for this are (1) electrolyte dis- turbances; (2) drugs affecting repolarization manifesting as QT prolongation; or

(3) altered metabolism of antiarrhythmic drugs leading to toxicity. Table 16.5.4.5 summarizes familiar drugs impli- cated in each of these scenarios. Table 16.5.4.4 Risk prediction for nephropathy after intravenous contrast for coronary angiography Factor Component score NHYA III/IV HF 5 Hypotension <80 mm Hg/invasive support 5 Diabetes mellitus 3 Age >75 years 4 Anaemia (haematocrit <39%[M], <36% [F]) 3 IV contrast (per 100 ml contrast used) 1 eGFR (ml/min/1.73 m2) 40–60 2 20–40 4 <20 6 Combined score Risk (%) Nephropathy Dialysis 0–5 8 0.04 6–10 14 0.12 11–16 26 1.09 17+ 57 12.6 Reprinted from the Journal of the American College of Cardiology, Vol 44, Issue 7, Mehran et al., A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. 1393–9. Copyright (2004) with permission from Elsevier. Table 16.5.4.5 Prescribed medication that may exacerbate cardiorenal disease via arrhythmia Cardioprotective drugs that cause hyperkalaemia Renin–angiotensin blockade Causes hypoaldosteronism and reduced eGFR Digoxin Impairs renal excretion and prevents cellular uptake β-Blockade Supresses cellular uptake of potassium mediated by β2 receptors Unfractionated heparin Hypoaldosteronism Low molecular weight heparin Mechanism not certain Drugs that cause QTc prolongation Indication for use Calcineurin inhibitors Transplant immunosuppression Midodrine Refractory hypotension Quinolones Antibiotics Macrolides Antibiotic Benzodiazepines Anxiolytic SSRIs Antidepressant Potentially arrhythmogenic drugs requiring dose adjustment in dialysis Flecainide Use 50% normal dose Sotalol Avoid in CKD5D, use at 25% normal dose in eGFR <15 ml/min Digoxin Start at 62.5 micrograms daily

 Antiarrhythmic therapy is further complicated in dialysis patients, as many of these drugs are not removed from the body by dialysis. Those that would normally be excreted via the kidneys can there- fore accumulate in such patients, and the timing of dosing of short- acting drugs may need to accommodate the timing of haemodialysis sessions. Managing antiarrhythmic drugs may require the input of a specialist renal pharmacist. Certain drugs, such as sotalol, ought to be avoided completely in dialysis patients where possible. Sotalol may predispose to QTc prolongation and torsades de pointes in toxic doses. It is over 90% absorbed after oral intake, undergoes almost no hepatic first-pass metabolism, and is excreted via the kidneys. Diuretic resistance in chronic renal disease The use of thiazide diuretics in patients with cardiovascular disease is usually limited to hypertension in older people and patients with heart failure. Thiazides are effective in inducing a natriuresis in patients with a GFR less than 30 ml/min. Patients with a GFR below this level will usually require loop diuretics to achieve a satisfactory diuresis. Loop diuretics are progressively less effective at lower GFR and pro- portionately higher doses given in a once-daily regimen are required to induce a diuresis. Activation of the RAAS in conjunction with distal tubular cell hypertrophy induces diuretic resistance. A combination of thiazide diuretic and loop diuretic may be helpful in overcoming diuretic resistance in these patients. Diuretic resistance is particularly prominent in diabetic proteinuric renal disease where protein binding of loop diuretics within the renal tubules reduces bioavailability. Arrhythmia in chronic kidney disease Sudden cardiac death is the most common cause of death in dialysis patients. Although this has been presumed to be predominantly due to ventricular tachyarrhythmia, as for sudden cardiac death in the general population, there is emerging evidence that bradycardia and asystole are implicated more often than is the case in nonrenal pa- tients. In one study, implanted loop recorder devices were used to capture arrhythmia in 50 maintenance haemodialysis patients over 18 ± 4 months. Eight patients (16%) suffered sudden cardiac death, all due to bradyarrhythmia or asystole, and all occurring during the long interdialytic interval. Although arrhythmia was common in this and other similar studies, there was

no prodrome of asymp- tomatic bradyarrhythmia or heart block in such patients during the period of in vivo monitoring prior to the fatal event. This means that the use of such devices does not yet allow for risk stratification in a way that could lead to pre-emptive pacemaker implantation to pre- vent future potentially fatal bradyarrhythmia. Medications commonly prescribed in CKD may also predispose to arrhythmia. These are listed in Table 16.5.4.5. There is also a high prevalence of ECG conduction abnormalities that may indicate risk. In one cross-sectional analysis of 323 prevalent dialysis patients, 34% had QRS duration in excess of 100 ms, 19% first-degree heart block, and 10% atrial fibrillation or flutter. Other studies have shown high rates of QTc prolongation and increased QT dispersion as well as loss of heart rate variability in CKD populations. Such abnormalities are associated with worse outcome. The best ECG predictor of mortality appears to be left bundle branch block, with an increased hazard ratio for death of 4.6 compared to normal QRS morphology. Equally, the impact of supraventricular arrhythmia on mortality cannot be overstated. The absence of sinus rhythm on ECG is associated with an 89% increased risk of death in diabetic dialysis patients, and atrial fibrillation is associated with an 80% 5-year mortality in dialysis pa- tients. Importantly, current evidence suggests that anticoagulation with warfarin leads to worse outcome for dialysis patients with atrial fibrillation, albeit that this evidence comes from observational studies and not randomized trials. The increased risk is thought to result from increased bleeding and vascular calcification. The substrates for arrhythmia in CKD are manifold and Fig. 16.5.4.3 summarizes these. Myocardial ischaemia is likely to play a role via coronary atheroma, medial calcification, and poor coronary perfusion due to diastolic dysfunction and pathological LVH with fibrosis and capillary rarefaction. The process of haemodialysis also induces arrhythmia, but it is not clear whether this is directly due to dialysis-induced myocardial ischaemia, autonomic effects, or the rapid electrolyte and fluid shifts that occur during dialysis. The role of Fig. 16.5.4.3 Potential triggers to sudden cardiac death in chronic kidney disease.

16.5.4 Cardiorenal syndrome 3427 LVH is likely to be an important one as endomyocardial biopsies from dialysis patients demonstrate abnormal remodelling with interstitial fibrosis and myocyte hypertrophy. These changes affect conduction through the myocardium and potentially will lead to arrhythmia. Vascular calcification Although 40% of dialysis patients have coronary artery disease, lipid- lowering drugs are less efficacious in this setting than in the wider population. One reason is that arterial disease in CKD is not typically due to atheroma: 50% of CKD patients have significant diffuse medial arterial calcification at the initiation of chronic dialysis. There is a fivefold increase in calcification of the coronary arteries in dialysis patients compared to non-CKD patients with coronary atheroma where calcification tends to be focal and found in the intimal layer. Calcification in CKD is associated with hyperphosphataemia, hypercalcaemia, and hyperparathyroidism, all of which can stimulate calcification of vascular smooth muscle cells and matrix. CKD also leads to a reduction in endogenous inhibitors of calcification, such as fetuin A. Vascular calcification and renal bone abnormalities are to- gether termed ‘chronic kidney disease–mineral bone disorder’ (CKD-MBD), acknowledging the wide spectrum of associated disease. Aortic stiffness, a surrogate of calcification, can be measured non- invasively with pulse wave velocity (PWV). An increase in PWV is as- sociated with LVH and increased left ventricular myocardial infarction (and with reduced coronary filling), all of which may eventually pre- dispose to heart failure. Indeed, increased PWV has been shown to be more important than hypertension in the development of LVH in CKD. Left ventricular hypertrophy The mechanism of LVH development in CKD is likely to be multi- factorial, but evidence is emerging that the association of vascular stiffness with LVH may be concurrent pathological manifestations of CKD-MBD, as well as demonstrating a cause-and-effect response to increased afterload. Fibroblast growth factor 23 (FGF-23) is pro- duced by osteocytes as renal

function declines. Its role in this setting is to induce phosphaturia and to inhibit hydroxylation of vitamin D to its active form. Elevated FGF-23 levels are independently associ- ated with LVH in CKD, intracardiac administration of FGF-23 leads to LVH in wild type mice, and in vitro administration of FGF-23 to isolated rat myocytes results in pathological hypertrophy. LVH may yet become a therapeutic target in CKD given its high prevalence and implications for worse outcome. The relative risk of cardiac death in dialysis patients with LVH is 2.7 compared to those without. Above a mean arterial pressure of 106 mm Hg, small in- creases in blood pressure are associated with significant increases in the rate of de novo heart failure in CKD. On a more optimistic note, tight control of blood pressure is associated with regression of LVH, slowing progression of CKD may slow progression of LVH, and tight control of CKD-MBD is also likely to positively impact on patho- logical cardiac remodelling. Multidisciplinary approach to renal disease in cardiac patients The high prevalence of coexistent cardiac and renal disease, and the high risk of major morbidity this combination brings, will often necessitate referral to nephrology services outside the usual guidelines. A list of potential circumstances triggering referral is listed in Table 16.5.4.6. Importantly, such referrals provide access to a multidisciplinary team beyond renal physicians, such as an- aemia services, specialist psychologists, dietetic services, pharma- cists, palliative care teams, and dialysis-planning specialist nurses, each of whom can provide care which may improve the quality of life and prognosis for patients. Indeed, being aware of and moni- toring for the possibility of these problems in the likes of heart failure clinics may lead to earlier diagnosis and intervention for significant renal disease in many cases. Table 16.5.4.6 Suggested indicators for referral to renal services for cardiology patients with chronic kidney disease, and investigations to request on referral Problem Diagnosis Investigations Diuretic resistant peripheral or pulmonary oedema/ recurrent acute decompensation of heart failure Renal artery stenosis; consider peritoneal dialysis for heart failure therapy Renal tract ultrasound Unexplained anaemia Renal anaemia Rule out gastrointestinal bleeding, ferritin, Fe/TIBC/B- vitamins, PTH, CRP Electrolyte or acid–base disturbance Tubular or pararenal disease, renal adverse drug effects Serum bicarbonate, chloride, calcium, magnesium,
urine salts Hyperphosphataemia (particularly with valvular annular calcification on echocardiography or radiographic evidence of aortic/arterial calcification) CKD-MBD Serum phosphate, calcium, PTH, food diary Proteinuria or haematuria Nephropathy/glomerulonephritis not cause by vascular disease Urine microscopy, urine culture, urine PCR, renal tract ultrasound, electrophoresis, ESR, HIV, HCV, autoantibody screen if haematuria (ANA, ANCA, GBM, C3, C4) Progressive decline in eGFR Drug effect, renal artery stenosis/occlusion, progressive CKD, approaching dialysis, palliation Send full medication list/dose changes and historical eGFR with referral ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; C3, C4, complement components; CKD, chronic kidney disease; CKD-MBD, chronic kidney disease–mineral bone disorder; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GBM, glomerular basement membrane; HCV, hepatitis C virus; PCR, polymerase chain reaction; PTH, parathyroid hormone; TIBC, total iron binding capacity.

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