Implications of Kidney Disease in the Cardiac Patient

Roger Rear naïve, Pascal Meier, Robert M. Bell naïve, *

INTRODUCTION

Cardiovascular disease (CVD) and chronic kidney disease (CKD) are both encompassing terms that incorporate a spectrum of pathology that in the case of CVD includes arterial atherosclerosis, heart failure, diseases of the myocardium and pericardium, valvular disease, and cardiac arrhythmias. CKD in turn incorporates vascular, glomerular, tubulointerstitial, and obstructive nephropathies that result in a persistent (minimum of 3 months) depression of glomerular filtration rate (GFR) lower than 90 or, more typically, 60 mL/min/1.73 m² (mild and moderate CKD, respectively) and/or the presence of albuminuria. The severity of CKD is classified into 5 categories, as defined by the National Kidney Foundation and the Kidney Disease Outcome Quality Initiative (Table 1).1 Despite the diversity of underlying abnormality in each pathologic condition, there appear to be several etiologic factors shared between CVD and CKD. The non-inheritable, noninfectious CVDs typically incorporate “traditional” cardiovascular risk factors that include age, gender, hypertension, diabetes, dyslipidemia, smoking, and other lifestyle factors including obesity. Given that the most common forms of CKD share a significant number of these risk factors, particularly hypertension and diabetes (Fig. 1),2 it is unsurprising that a substantial proportion of cardiac patients also have significant renal impairment: approximately one-third of patients presenting for coronary angiography will have CKD3–5; in patients with heart failure the prevalence of CKD is estimated at between 32% and 53% (with the highest prevalence in those with acute decompensation)6 and more than half of...
patients with atrial fibrillation (AF) have CKD, increasing to nearly three-fourths of elderly AF patients (>80 years) considered for anticoagulant therapy. 

By contrast, CVDs such as coronary artery disease and heart failure are highly prevalent in the CKD population, and increasingly so with deteriorating renal function: in severe CKD (stage IV), the prevalence of coronary artery disease (CAD) and heart failure reaches 19.0% and 12.5%, respectively. Within this same patient cohort, the prevalence of hypertension and diabetes in individuals with CKD approaches 50% and 20%, respectively. Significantly, these 2 comorbidities represent an increasing worldwide burden: in 2013, 1 billion people were treated for hypertension and 240 million patients for diabetes, with the totals projected to increase to an estimated 1.56 billion with hypertension by 2025 and 380 million with diabetes over the next decade. In these groups, the prevalence of CKD is 37% and 26%, respectively, as reported by the US National Health and Nutrition Examination Surveys. The prevalence of CKD is therefore anticipated to increase significantly worldwide over the coming decades, and although there have been significant improvements in the rates of cardiovascular mortality (particularly with deaths related to CAD, which have fallen by approximately 50% over the last 3 decades), globally the pressure exerted by increasing prevalence of these comorbidities is contrary to the continuation of this positive trend.

CVD and CKD are intricately linked, and their prognoses interwoven. This review discusses how CKD affects common CVD prognosis, and the efficacy of and the adverse events arising from clinical cardiovascular interventions.

### CORONARY ARTERY DISEASE

Atherosclerotic CAD is a prototypical example of the interaction between CKD and CVD. Mild renal dysfunction is increasingly recognized as a nontraditional cardiovascular risk factor for CAD: modest elevations of urinary albumin excretion below the current microalbuminemia diagnostic threshold...
are associated with elevated cardiovascular risk,\(^\text{11}\) which increases proportionately with progressive renal deterioration.\(^\text{12}\) Moreover, CKD, once established, doubles the rates of both CVD progression\(^\text{13}\) and in-hospital death following primary percutaneous intervention (PCI) in comparison with those without CKD.\(^\text{14}\) The accelerated progression of CVD in CKD is likely to be multifactorial, incorporating several nontraditional risk factors that include hyperphosphatemia (and vascular calcification),\(^\text{15}\) oxidative stress and systemic inflammation,\(^\text{16}\) hyperhomocysteinemia, hypervolemia, mineral/electrolyte imbalance, anemia,\(^\text{17}\) thrombogenesis, and malnutrition. Consequently, in the CKD patient cohort, CVD mortality is not only 10 to 30 times higher than in the general population,\(^\text{1}\) but CVD is a also more likely adverse outcome than progressing to end-stage renal disease (ESRD) in these patients.\(^\text{18,19}\) Clinical management strategies therefore must center on the management of the underlying kidney disease and the common causes of hypertension and diabetes; there is emerging evidence that multidisciplinary approaches by nephrologists to control the progression of renal disease pays dividends in diminishing the rates of cardiovascular mortality in these patients.\(^\text{20}\)

**Difficulties in Diagnosis of Acute Coronary Syndrome**

The existence of CKD frequently presents significant diagnostic challenges, not least in the diagnosis of patients presenting with chest pain. The electrocardiogram (ECG) frequently reveals nonspecific abnormalities, so the diagnosis of non–ST-elevation myocardial infarction, a more frequent presentation than ST-elevation myocardial infarction in CKD patients,\(^\text{21}\) requires further supportive diagnostic evidence. Patients with CKD frequently have elevated cardiac enzymes on routine testing, which make interpretation of absolute levels problematic, but a change of these cardiac enzymes over a period of 3 to 6 hours will be discriminatory for acute coronary syndrome (ACS).\(^\text{22}\) However, persistently elevated cardiac enzymes (such as troponin) should not be ignored in CKD: their elevation is an independent risk factor for cardiovascular mortality.\(^\text{23}\) The cause of a chronic troponin increase remains unclear, but is likely to represent myocardial injury potentially relating to microinfarction either secondary to epicardial CAD (53% of patients with advanced CKD will have a coronary stenosis of greater than 50% in 1 or more coronary arteries\(^\text{24}\)) or attributable to microvascular dysfunction/left ventricular hypertrophy, with data showing a strong correlation between left ventricular mass and serum troponin levels.\(^\text{25}\)

Conversely, the diagnosis of ACS may be missed in patients with CAD and CKD, as the presentation is less likely to be with typical chest pain,\(^\text{26}\) potentially reflecting an underlying neuropathy: in the SWEDEHEART register, 67% of CKD patients with ACS had chest pain compared with 90% of those without CKD, and were more likely to present with heart failure.\(^\text{21}\) Moreover, more than half of patients referred for renal replacement therapy (RRT) are found to have clinically significant CAD in the absence of characteristic ischemic symptoms.\(^\text{24}\)

Noninvasive screening methods for CAD can be used in patients with CKD. CKD patients are vulnerable to calcification of the intima-media of the coronary vessels. Cohort studies have demonstrated CKD to be an independent predictor of high computed tomography (CT) coronary artery calcium (CAC) scores in patients with clinically suspected CAD,\(^\text{27,28}\) and CAC scores correlate with the stage of renal dysfunction.\(^\text{29}\) Despite debate as to whether CT CAC scores correlate with luminal narrowing, CAC scores are validated as an independent predictor of future cardiac events, correlating with cardiac mortality in CKD patients.\(^\text{30,31}\) However, the nephrotoxic risk of contrast exposure in CKD patients has meant that there has been little study of CT–coronary angiography in CKD. Of the other noninvasive screening methods, single-photon emission CT has variable and often low sensitivities in the CKD cohort of patients, and although dobutamine stress echo may be helpful in the screening of CAD, interpretation can prove difficult in the presence of left ventricular hypertrophy frequently found in CKD patients.\(^\text{32}\)

Although the diagnosis of CAD in the CKD patient can be problematic, CKD patients have such a high burden of CAD that any cardiovascular presentation should be regarded with considerable suspicion and managed accordingly.\(^\text{26}\)

**Medical Management of CAD in Patients with CKD**

Management of stable CAD consists of a combination of antiplatelet therapy, most commonly with the cyclooxygenase inhibitor aspirin, and aggressive traditional risk-factor management. The coexistence of CKD does not significantly alter this approach.

Aspirin remains beneficial in CKD patients with CAD: in patients with diastolic hypertension, the Hypertension Optimal Treatment (HOT) study found a significant reduction of cardiovascular
events, particularly in those with more advanced CKD (IIlb) managed with 75 mg aspirin, compared with control (reduction of major cardiovascular events by two-thirds, overall death reduced by half), with a nonstatistically significant trend toward higher bleeding rates (hazard ratio 2.81, 95% confidence interval [CI] 0.92–8.84, \( P = .3 \) in the CKD-IIlb group).\(^{33,34}\)

Reduction of traditional cardiovascular risk factors, particularly hypertension and dyslipidemia, has the potential dual benefit of attenuating the progression of both CVD and CKD. Management of hypertension is well recognized and vital; current guidelines provide a target blood pressure of less than 140/90 mm Hg in the general population, but is amended downward to 130/80 mm Hg in those with CKD.\(^{35}\) The antihypertensive agents targeting the renin-angiotensin-aldosterone axis, specifically angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin II receptor blockers (ARBs), are discussed in greater detail in the relevant section herein.

Some controversy has surrounded the effectiveness of 3-hydroxy-3-methyl-glutaryl coenzyme A reductase inhibitors (the statins) in the context of CKD and CAD, but overall the data appear supportive of lipid-lowering agents being helpful in preventing the progression of cardiovascular, if not necessarily renal disease, in both subgroup analysis of existing cardiovascular trials\(^4\) and the prospective Study of Heart and Renal Protection (SHARP).\(^{36}\) Unfortunately, despite the evident benefit of statin therapy in mild to moderate CKD, statins are disappointingly ineffective in preventing death from CVD in dialysis-dependent end-stage CKD.\(^{37}\)

\( \beta \)-Blockers for stable angina remain extremely useful in the symptomatic relief of angina symptoms in patients with CKD, but dose adjustments may need to be considered, particularly for the more hydrophilic agents (atenolol, bisoprolol; see later discussion).

In large part the medical management of CAD in patients with CKD is largely unaltered, and the targeting of cardiovascular risk factors benefits both CVD and CKD, with the possible exception of ESRD, in which the protective benefits of statin therapy on CVD seem to be lost.

**Implications of CKD and percutaneous coronary intervention**

Current interventionalal guidelines are clear in advocating that ACS management of patients with CKD should not differ from that of patients without.\(^{38}\) However, it should be recognized that patients with CKD have a worse short-term outcome and a higher adverse event rate, particularly in regard of major bleeding events, which are nearly double that in the non-CKD population (multivariate odds ratio 1.9, 95% CI 1.22–2.96).\(^{38,39}\) Great care needs to be invested, therefore, to ensure the use of appropriate doses of renal-excreted antithrombotic drugs, such as enoxaparin, fondaparinux, bivalirudin, and small-molecule glycoprotein IIb/IIIa receptor blockers. In severe CKD these drugs may be contraindicated, and unfractionated heparin used in their place.\(^{38}\)

A similar pragmatic approach is used in the management of stable CAD. In a post hoc analysis of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial comparing outcomes of patients with CKD against those without, both patient groups had similar benefits with identical management strategies. Although PCI conferred no survival benefit in patients with CKD,\(^{40}\) there was no adverse signal with any combination of PCI and optimal medical therapy, suggesting that these patients should be managed in an individualized fashion comparable with that for non-CKD patients.\(^{41}\)

In the management of both ACS and stable CAD, there needs to be cognizance of the problems associated with contrast-induced acute kidney injury (CI-AKI). Although CI-AKI is frequently a short-term perturbation of creatinine clearance and is self-limiting, nearly one-fifth of patients may have persistent significant renal impairment\(^3\) and up to 9% will progress to ESRD and dialysis.\(^{42}\) Current guidelines recommend prehydration, cessation of nephrotoxic agents, and minimization of contrast load,\(^{43}\) with much current research interest in the potential beneficial roles of high-dose statin\(^{44,45}\) and remote ischemic conditioning\(^{16,47}\) as renoprotective strategies during angiographic procedures.

**Implication of CKD and coronary artery bypass surgery**

Coronary artery bypass grafting (CABG) in patients with CKD, as with PCI, is associated with higher rates of adverse events, particularly for acute kidney injury (25%–40% increase in CKD-III and CKD-IV, respectively)\(^{48}\) and bleeding events.\(^{49}\) However, in comparison with PCI in patients with complex, multivessel disease, CABG could be considered as an alternative revascularization strategy. In recent data from large cohort studies, CABG has better cardiovascular outcomes, with lower adjusted mortality, a lower rate of recurrent ACS, and a lower requirement for revascularization when compared with PCI.\(^{50,51}\) The presence of CKD may also influence decisions regarding the most appropriate surgical approach. In a cohort study of patients undergoing CABG, the off-pump...
CABG (OPCAB) group had statistically lower rates of in-hospital mortality and incident RRT in comparison with patients undergoing on-pump CABG (ONCAB), with the strongest effect seen with more advanced renal impairment: unadjusted incidence of mortality in patients with a reduced estimated GFR (eGFR; 15–29 and 30–59 mL/min/1.73 m²) was lowest among the OPCAB (vs ONCAB) cohort (3.5% vs 5.2% and 2.2% vs 2.4%, respectively), perhaps reflecting an injurious effect of cardiopulmonary bypass and the potential for transient organ hypoperfusion.

Unfortunately there are no data available from large-scale, multicenter, randomized controlled trials to directly examine management decisions regarding revascularization in high-risk patients with CKD, an area that would certainly benefit from further focused study given the particular problems presented by comitant multivessel CAD and CKD.

**ATRIAL FIBRILLATION**

The Framingham Heart Study identified both valvular and nonvalvular risk factors for the development of AF, with significant differences between the genders: men had 50% greater AF prevalence than women, and women were significantly more likely than men to have a valvular etiology. It is recognized that calcific valvular disease is itself associated with CKD, particularly in dialysis-requiring ESRD. Interestingly the major nonvalvular risk factors for the development of AF, in addition to heart failure, are the traditional risk factors for cardiovascular disease, namely age, hypertension, and diabetes. Moreover, CKD is associated with the development of left ventricular hypertrophy, diastolic dysfunction, and subsequent left atrial dilatation, which increases the likelihood of developing AF. Given the risk-factor overlap between CKD and these recognized risk factors for AF, it is not surprising to discover that the prevalence of AF within the CKD cohort of patients is high. In the Chronic Renal Insufficiency Cohort (CRIC) study, the prevalence of AF is 2 to 3 times greater in patients with CKD compared with the general population, with a prevalence of 16% with an eGFR 60 to 45 mL/min/1.73 m² rising to more than 20% when the eGFR falls to less than 45 mL/min/1.73 m², compared with an estimate of 7.8% in the general population in the REGARDS study. However, whether CKD is a novel AF risk factor is unclear; the increased prevalence of AF within this population may be a simple expression of the presence of several common cardiovascular/renovascular risk factors (hypertension, aging, diabetes) leading to common root disorders such as arterial atherosclerosis, diastolic dysfunction, left ventricular hypertrophy, and heart failure, but the metabolic and electrolyte abnormalities associated with more advanced CKD may nonetheless be unique contributors toward the increased prevalence of AF in the chronic renal impairment cohort.

**Impact of CKD on AF Management**

In patients with persistent or permanent AF, in whom rate control is the preferred strategy, the use of drugs eliminated from the circulation by the kidney present a particular problem, no more so than for digoxin, which has a narrow therapeutic index and is largely (90%) renally excreted. Indeed, digoxin therapy is associated with a 28% increased risk of death, associated predominantly with toxic digoxin levels and the presence of hypokalemia (a common electrolyte imbalance before dialysis). Other rate-control medications are also not entirely problem-free. β-Blockers as a class have varied excretion: hydrophilic agents such as atenolol and sotalol undergo renal elimination, and these drugs, like those with mixed metabolism such as bisoprolol, will require ECG monitoring and dose adjustments; the best rate-control options in CKD may therefore be lipophilic β-blockers such as metoprolol or carvedilol, or the use of a calcium-channel blocker such as diltiazem. Similarly, in pharmacologic rhythm control strategies, many of the preferred therapy options are limited by their dependence on renal excretion, including sotalol and flecainide (reviewed in Ref. 61). However, both dronedarone and amiodarone are safe in patients with renal impairment.

Invasive interventions that can potentially cure the arrhythmia are feasible in the context of CKD, and the limitations to drug therapy imposed by CKD seems to make this approach more attractive. However, it should be noted that the success rate of AF ablation in the CKD population is somewhat lower than that found in the general population, with AF recurrence rates after ablation therapy typically 70% greater in CKD patients than in the general population, with both low eGFR and left atrial dilatation independently adversely influencing the success of catheter ablation. Therefore, the optimal approaches to the management of AF in CKD patients require the weighing of individual risk factors and outcome benefits. However, as in other areas of CVD in the context of CKD, the main problem in making decisions regarding management of AF in CKD patients is the lack of data from prospective randomized controlled trials.
**Impact of CKD on Anticoagulation**

Although the inclusion of CKD as a risk factor does not add to the power of the established predictive systemic embolization CHADS\textsubscript{VASC}\textsuperscript{65} risk-scoring system,\textsuperscript{66} CKD is nonetheless associated with a significant increase in the risk of thromboembolic stroke arising as a consequence of AF.\textsuperscript{67–69} Unfortunately, CKD is also associated with increased bleeding risk, and is recognized in scoring systems such as the HAS-BLED score (Hypertension, Abnormal liver/renal function, Stroke, Bleeding history/predisposition, Labile anticoagulation record, Elderly [>65 years], Drugs/alcohol coadministration/use).\textsuperscript{70} Warfarin undergoes hepatic metabolism using the cytochrome P450 enzyme system, although Limdi and colleagues\textsuperscript{71} found that warfarin requirements were significantly lower in patients with CKD than in the general population (by 10% and 19% in moderate and severe CKD, respectively). Strict monitoring of the international normalized ratio in patients with CKD is therefore mandatory, and CKD patients without close scrutiny of anticoagulation record suffer high bleeding complication rates, particularly soon after initiation of oral anticoagulant therapy.\textsuperscript{72}

There is, however, a general lack of strong data regarding the efficacy of warfarin and its ability to attenuate the rate of thromboembolic stroke in CKD patients, most data being retrospective and nonrandomized.\textsuperscript{69,72–75} Moreover, warfarin is associated with vascular calcification related to vitamin K antagonism, and there are reported risks of warfarin-related nephropathy.\textsuperscript{61} Despite this, current guidance continues to support the use of anticoagulation for thromboembolic risk reduction in the CKD cohort, which until recently has meant the administration and strict monitoring of warfarin. However, the increasing availability of novel oral anticoagulants will provide greater choice in the management of thromboembolic risk in patients with both AF and CKD. The antithrombin dabigatran\textsuperscript{76} and the factor-Xa inhibitors apixaban\textsuperscript{77} and rivaroxaban\textsuperscript{78} all show at least noninferiority to warfarin anticoagulation in preventing thromboembolic stroke in mild and moderate CKD patients, with dabigatran and apixaban showing superior systemic embolism risk reduction and dabigatran lower rates of intracranial bleeding when compared with strictly monitored warfarin therapy. Although all 3 of the novel oral anticoagulants have at least an element of renal elimination (dabigatran is 80% renally excreted; the factor-Xa inhibitors less than one-third), all can be used with dose modifications in patients with mild and moderate CKD. None, however, have been trialed in patients with severe CKD and, consequently, only warfarin can be recommended at present for use in patients with an eGFR of less than 15 mL/min/1.73 m\textsuperscript{2}.

**CHRONIC HEART FAILURE**

Chronic heart failure (CHF) is a complex clinical syndrome resulting from the inability of the heart to maintain adequate tissue perfusion, because of either structural or functional abnormalities affecting the systolic and/or diastolic phase of the cardiac cycle. CKD is highly prevalent in the CHF patient cohort and, despite the usual exclusion of patients with severe CKD, this is reflected in the landmark heart failure trial literature, with prevalence rates estimated between 32% and 50% (Table 2). CKD adversely affects the prognosis of CHF: a recent meta-analysis of 85 CHF trials (comprising 49,890 patients) revealed a doubling of all-cause mortality within this patient population (Table 3).\textsuperscript{6}

The link between CHF and CKD is in part attributable to shared etiologic risk factors, but is also a direct consequence of the interaction of their respective pathophysiology (Fig. 2). For example, low cardiac output and increased venous congestion (predominant in heart failure with preserved ejection fraction) respectively reduce renal arterial blood flow and perfusion gradient,\textsuperscript{79} exacerbating kidney dysfunction, which can be further

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Exclusion Creatinine (\textmu mol/L)</th>
<th>CKD Prevalence (%)</th>
<th>eGFR &lt;60 mL/min/1.73 m\textsuperscript{2}</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOLVD\textsuperscript{109}</td>
<td>Enalapril</td>
<td>&gt;177</td>
<td>32</td>
<td>N/A</td>
</tr>
<tr>
<td>CHARM\textsuperscript{110}</td>
<td>Candesartan</td>
<td>&gt;265</td>
<td>36</td>
<td>N/A</td>
</tr>
<tr>
<td>CIBIS-II\textsuperscript{81}</td>
<td>Bisoprolol</td>
<td>&gt;300</td>
<td>33</td>
<td>N/A</td>
</tr>
<tr>
<td>CARE-HF\textsuperscript{111}</td>
<td>CRT</td>
<td>N/A</td>
<td>50</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*Abbreviations: CHF, chronic heart failure; CKD, chronic kidney disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; N/A, no data available.*
aggravated by the therapies used to manage CHF, through any combination of diuresis-associated hypovolemia, renin-angiotensin-aldosterone system (RAAS) inhibitors, and drug-induced hypotension. By contrast, renal dysfunction leads to neurohormonal dysregulation, anemia, volume overload, and complex inflammatory cascades that negatively affect cardiac function. The bidirectional interaction between 2 failing organ systems can lead to a vicious cycle of progressive cardiac and renal dysfunction, termed cardiorenal syndrome, the classifications of which are summarized in Table 4.80

**Medical Management of CHF in Patients with CKD**

The established canon of CHF management consists of ACE-Is/ARBs, β-blockers, and mineralocorticoid receptor antagonists (MRAs), with 2 decades of landmark mortality outcome data to support their use (Table 5). In patients with normal renal function, all improve prognosis, reduce hospitalizations, and improve mortality rates. The coexistence of CKD, however, introduces particular challenges for the introduction and maintenance of CHF therapy. Perhaps the most innocuous of these drug classes are the β-blockers. β-Blockers have no adverse impact on the progression of CKD, and the efficacy of β-blockade in CHF seems unaltered by the existence of CKD: a retrospective analysis of outcomes in the CIBIS-II study supported preserved relative risk reduction in patients treated with bisoprolol at all stages of CKD,81 data supported from observations in the MERIT-HF trial.82 As discussed earlier, individual β-blockers have variable dependence on renal elimination: hydrophilic drugs (atenolol and bisoprolol) will require dose adjustments and monitoring in CKD, whereas the lipophilic β-blockers (carvedilol and metoprolol), which undergo hepatic metabolism, do not,83 an observation that may help influence the optimal choice of therapeutic agent.

By contrast, drugs that affect the RAAS axis require greater caution when CHF coexists with CKD. The ACE-Is/ARBs are a prototypical example of this. In addition to their role in the management of CHF, ACE-Is and ARBs are also pivotal to the management of CKD, attenuating progression of hypertensive, proteinuric CKD84 and lower mortality rates, as suggested by retrospective population studies.85 However ACE-Is/ARBs are not innocuous in terms of renal function: a modest perturbation of GFR is frequently found following ACE-I or ARB initiation, with an increase of creatinine to a new 10- to 20-μmol/L higher baseline observed in the CONSENSUS study.86 However, although CHF studies excluded patients with severe CKD,
Table 4

Cardiorenal syndrome classification system adopted at the 2010 ADQI consensus conference

<table>
<thead>
<tr>
<th>Type</th>
<th>Inciting Event</th>
<th>Secondary Disturbance</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>Abrupt worsening of cardiac function</td>
<td>Acute kidney injury</td>
<td>Acute cardiogenic shock or acute decompenstation of chronic heart failure</td>
</tr>
<tr>
<td>Acute cardiorenal syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 2</td>
<td>Chronic abnormalities in cardiac function</td>
<td>Chronic kidney damage</td>
<td>Chronic heart failure</td>
</tr>
<tr>
<td>Chronic cardiorenal syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 3</td>
<td>Abrupt worsening of renal function</td>
<td>Acute cardiac dysfunction (eg, heart failure or arrhythmia)</td>
<td>Acute kidney injury or glomerular nephritis</td>
</tr>
<tr>
<td>Acute renocardiac syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 4</td>
<td>Chronic kidney disease</td>
<td>Decreased cardiac function, cardiac hypertrophy, and/or increased risk of adverse cardiovascular events</td>
<td>Chronic glomerular disease</td>
</tr>
<tr>
<td>Chronic renocardiac syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 5</td>
<td>Systemic disease</td>
<td>Cardiac and renal dysfunction</td>
<td>Diabetes mellitus, systemic lupus, sepsis, etc</td>
</tr>
<tr>
<td>Secondary cardiorenal syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cardiorenal syndromes are divided into 5 categories according to triggering event and its consequence.

Abbreviation: ADQI, Acute Dialysis Quality Initiative.


in patients with mild and moderate CKD the cardiovascular mortality benefit of ACE-Is/ARBs appears to be preserved.97–89

With respect to the MRAs, both the RALES90 and EMPHASIS-HF studies91 (in which half and a third of patients had CKD, respectively) demonstrated mortality reductions (30% and 34%, respectively), in addition to reduced symptoms and hospitalizations. Both trials excluded patients with severe CKD (RALES used a cutoff of 221 mmol/L; EMPHASIS-HF an eGFR of 30 mL/min/1.73 m²), but MRAs remain effective therapies in CHF when there is coexistent mild to moderate CKD.92 Unfortunately, the use of aldosterone antagonists in patients with severe CKD can provoke hyperkalemia, especially in conjunction with ACE-Is or ARBs. Current European guidelines recommend that a serum creatinine level higher than 220 μmol/L or potassium level higher than 5 mmol/L is a contraindication, although cautious use is usually well tolerated in mild or moderate CKD.93

Excessive sodium and water retention is usually present in CHF patients with CKD, and should be treated initially with dietary sodium restriction (<2 g salt/d), but may require intensive diuretic therapy using the minimum dose required to achieve a “dry weight”; diuretic overdosing is associated with increased mortality.94 Loop diuretics are more effective than thiazide diuretics, and, if necessary, cautious combination of both agents may be used.95 However, unlike the MRA class of diuretics, there is no prognostic benefit to be derived from loop or thiazide diuretics in the setting of either CHF or CKD.

Management of Anemia

Anemia is a significant problem in patients with CHF and CKD, and often remains overlooked in busy specialist clinics.96 CHF mortality increases with severity of anemia by 50% to 100%97 and the presence of CKD further doubles the mortality.98 Current European guidelines recommend correcting hemoglobin levels to between 10 and 12 g/dL; however, recent systematic reviews and meta-analyses have shown worse outcomes when levels are normalized (>13 g/dL).99,100 Initial correction of iron deficiency with oral or parenteral iron before low-dose erythropoietin-stimulating agents are recommended to minimize the need for blood transfusions.

Device Therapy

Post hoc subanalysis of CARE-HF101 showed that the relative effect of cardiac resynchronization therapy (CRT) was similar among eGFR subgroups, whereas subanalysis of the MIRACLE study demonstrated an improvement in baseline...
renal function. However, another subanalysis of the REVERSE study found that CKD patients treated with CRT had worse left ventricular parameter outcomes, which the investigators attributed to CKD-specific impairment of reverse left ventricular remodeling. For patients who might reasonably be expected to proceed to dialysis, consideration of the site of arteriovenous fistula before device implantation is recommended to avoid complications secondary to pacing wire–associated central venous stenosis.

Patients with CKD have a significantly increased risk of sudden cardiac death (SCD) from ventricular arrhythmia, particularly so during dialysis, and limited evidence suggests they should be offered implantable cardioverter-defibrillator (ICD) therapy if they meet the usual criteria; however, concerns exist regarding the efficacy of ICDs in CKD patients.4 However, another subanalysis of the REVERSE study found that CKD patients treated with CRT had worse left ventricular parameter outcomes, which the investigators attributed to CKD-specific impairment of reverse left ventricular remodeling. For patients who might reasonably be expected to proceed to dialysis, consideration of the site of arteriovenous fistula before device implantation is recommended to avoid complications secondary to pacing wire–associated central venous stenosis.

Patients with CKD have a significantly increased risk of sudden cardiac death (SCD) from ventricular arrhythmia, particularly so during dialysis, and limited evidence suggests they should be offered implantable cardioverter-defibrillator (ICD) therapy if they meet the usual criteria; however, concerns exist regarding the efficacy of ICDs in CKD patients.4 However, another subanalysis of the REVERSE study found that CKD patients treated with CRT had worse left ventricular parameter outcomes, which the investigators attributed to CKD-specific impairment of reverse left ventricular remodeling. For patients who might reasonably be expected to proceed to dialysis, consideration of the site of arteriovenous fistula before device implantation is recommended to avoid complications secondary to pacing wire–associated central venous stenosis.

Patients with CKD have a significantly increased risk of sudden cardiac death (SCD) from ventricular arrhythmia, particularly so during dialysis, and limited evidence suggests they should be offered implantable cardioverter-defibrillator (ICD) therapy if they meet the usual criteria; however, concerns exist regarding the efficacy of ICDs in CKD patients.4 However, another subanalysis of the REVERSE study found that CKD patients treated with CRT had worse left ventricular parameter outcomes, which the investigators attributed to CKD-specific impairment of reverse left ventricular remodeling. For patients who might reasonably be expected to proceed to dialysis, consideration of the site of arteriovenous fistula before device implantation is recommended to avoid complications secondary to pacing wire–associated central venous stenosis.

Patients with CKD have a significantly increased risk of sudden cardiac death (SCD) from ventricular arrhythmia, particularly so during dialysis, and limited evidence suggests they should be offered implantable cardioverter-defibrillator (ICD) therapy if they meet the usual criteria; however, concerns exist regarding the efficacy of ICDs in CKD patients.4 However, another subanalysis of the REVERSE study found that CKD patients treated with CRT had worse left ventricular parameter outcomes, which the investigators attributed to CKD-specific impairment of reverse left ventricular remodeling. For patients who might reasonably be expected to proceed to dialysis, consideration of the site of arteriovenous fistula before device implantation is recommended to avoid complications secondary to pacing wire–associated central venous stenosis.

Patients with CKD have a significantly increased risk of sudden cardiac death (SCD) from ventricular arrhythmia, particularly so during dialysis, and limited evidence suggests they should be offered implantable cardioverter-defibrillator (ICD) therapy if they meet the usual criteria; however, concerns exist regarding the efficacy of ICDs in CKD patients.4 However, another subanalysis of the REVERSE study found that CKD patients treated with CRT had worse left ventricular parameter outcomes, which the investigators attributed to CKD-specific impairment of reverse left ventricular remodeling. For patients who might reasonably be expected to proceed to dialysis, consideration of the site of arteriovenous fistula before device implantation is recommended to avoid complications secondary to pacing wire–associated central venous stenosis.

Patients with CKD have a significantly increased risk of sudden cardiac death (SCD) from ventricular arrhythmia, particularly so during dialysis, and limited evidence suggests they should be offered implantable cardioverter-defibrillator (ICD) therapy if they meet the usual criteria; however, concerns exist regarding the efficacy of ICDs in CKD patients.4 However, another subanalysis of the REVERSE study found that CKD patients treated with CRT had worse left ventricular parameter outcomes, which the investigators attributed to CKD-specific impairment of reverse left ventricular remodeling. For patients who might reasonably be expected to proceed to dialysis, consideration of the site of arteriovenous fistula before device implantation is recommended to avoid complications secondary to pacing wire–associated central venous stenosis.

Patients with CKD have a significantly increased risk of sudden cardiac death (SCD) from ventricular arrhythmia, particularly so during dialysis, and limited evidence suggests they should be offered implantable cardioverter-defibrillator (ICD) therapy if they meet the usual criteria; however, concerns exist regarding the efficacy of ICDs in CKD patients.4 However, another subanalysis of the REVERSE study found that CKD patients treated with CRT had worse left ventricular parameter outcomes, which the investigators attributed to CKD-specific impairment of reverse left ventricular remodeling. For patients who might reasonably be expected to proceed to dialysis, consideration of the site of arteriovenous fistula before device implantation is recommended to avoid complications secondary to pacing wire–associated central venous stenosis.
ESRD. Unfortunately, SCD during dialysis may occur in the absence of typical ICD criteria, owing to complex interactions between hemodynamic, electrolytic, hypertrophic, and electrophysiologic factors, and further prospective studies are required before any specific recommendations can be made.

SUMMARY
Renal disease is a frequent partner of cardiovascular disease, whereby the presence of one accelerates the progression of the other. Moreover, renal disease adversely affects the efficacy and tolerability of a range of medical, interventional, and surgical interventions in CVD. Overall, however, the basic tenets of cardiovascular management remain unchanged by the presence of renal disease, no matter how advanced. Treatment priorities remain the early identification of risk factors, treatment and prevention of CKD and CVD where possible, and, where present, attenuation of the progression of both disease states. Moreover, clinicians should avoid the occurrence of acute kidney injury, through the use of drugs such as ACE-Is, or the minimization of hypotension, nephrotoxics, or contrast agents during invasive or surgical procedures. A key problem in the management of patients with CKD is the lack of prospective, randomized controlled trials. Data from such studies are sorely needed in a variety of areas such as the optimum strategy in patients with moderate and severe CKD and concomitant CAD, CHF, or AF. Therefore, more extensive study is required in this area of cardiovascular medicine to broaden the understanding of the underlying disease processes and to validate medical interventions from drugs through to surgery in the context of kidney impairment, thus ensuring optimal outcomes and preservation of quality of life in this challenging patient cohort.

REFERENCES
Kidney Disease in the Cardiac Patients


41. Sedlis SP, Jurkovicz CT, Hartigan PM, et al. Health status and quality of life in patients with stable coronary artery disease and chronic kidney disease treated with optimal medical therapy or percutaneous coronary intervention (post hoc findings...
Kidney Disease in the Cardiac Patients


93. McMurray JJ, Adamopoulos S, Anker SD, et al, Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure of the European Society of Cardiology, Guidelines ESC Committee for Practice. 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 2012;14:803–69.


Dear Author,

Please check your proof carefully and mark all corrections at the appropriate place in the proof (e.g., by using on-screen annotation in the PDF file) or compile them in a separate list. Note: if you opt to annotate the file with software other than Adobe Reader then please also highlight the appropriate place in the PDF file. To ensure fast publication of your paper please return your corrections within 48 hours.

For correction or revision of any artwork, please consult http://www.elsevier.com/artworkinstructions.

Any queries or remarks that have arisen during the processing of your manuscript are listed below and highlighted by flags in the proof.

<table>
<thead>
<tr>
<th>Location in article</th>
<th>Query / Remark: Click on the Q link to find the query’s location in text Please insert your reply or correction at the corresponding line in the proof</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1</td>
<td>Please approve the short title to be used in the running head at the top of each right-hand page.</td>
</tr>
<tr>
<td>Q2</td>
<td>This is how your name will appear on the contributor’s list. Please add your academic title and any other necessary titles and professional affiliations, verify the information, and OK.</td>
</tr>
<tr>
<td></td>
<td>ROGER REAR, The Heart Hospital, University College Hospitals NHS Trust; The Hatter Cardiovascular Institute, University College London, London, United Kingdom</td>
</tr>
<tr>
<td></td>
<td>PASCAL MEIER, The Heart Hospital, University College Hospitals NHS Trust, London, United Kingdom</td>
</tr>
<tr>
<td></td>
<td>ROBERT M. BELL, The Heart Hospital, University College Hospitals NHS Trust; The Hatter Cardiovascular Institute, University College London, London, United Kingdom</td>
</tr>
<tr>
<td>Q3</td>
<td>Are author names and order of authors OK as set?</td>
</tr>
<tr>
<td>Q4</td>
<td>Please provide professional degrees for all the authors.</td>
</tr>
<tr>
<td>Q5</td>
<td>The following synopsis is the one that you supplied, but edited down to fewer than 100 words. Please confirm OK, or submit a replacement (also less than 100 words). Please note that the synopsis will appear in PubMed: Traditional cardiovascular risk factors, particularly hypertension and diabetes, are common in the disease processes of both renal and cardiac pathology. Unfortunately the coexistence of renal impairment is not an innocent bystander in cardiovascular disease; the addition to cardiac disorder of involvement of a second organ system not only increases the prevalence and severity of cardiovascular disease, it also negatively affects prognostic outcomes and the safety and efficacy of cardiac interventions. This article discusses the role and impact of kidney disease in the cardiac patient in 3 key common cardiovascular processes: coronary artery disease, arrhythmia, and heart failure.</td>
</tr>
<tr>
<td>Q6</td>
<td>Please verify the affiliation addresses and provide the missing information (department name for both affiliations). And please indicate (or confirm) which address is the preferred one for correspondence.</td>
</tr>
<tr>
<td>Q7</td>
<td>As per the editorial remarks, “Please check disclosure statement and change as necessary. Statement was composed by Publisher.”</td>
</tr>
<tr>
<td>Q8</td>
<td>If there are any drug dosages in your article, please verify them and indicate that you have done so by initialing this query.</td>
</tr>
<tr>
<td>Q9</td>
<td>Please provide the volume number.</td>
</tr>
<tr>
<td>Q10</td>
<td>Please provide the volume number.</td>
</tr>
<tr>
<td>Q11</td>
<td>Please provide the volume number.</td>
</tr>
<tr>
<td>Q12</td>
<td>Please provide the volume number and page range.</td>
</tr>
<tr>
<td>Q13</td>
<td>Please provide publisher name and location and also verify the page range.</td>
</tr>
<tr>
<td>Q14</td>
<td>As per the editorial remarks, “Please check the table caption and change as necessary. Caption was added by publisher.”</td>
</tr>
<tr>
<td>Q15</td>
<td>The designators “a &amp; b” are present in Table. Please specify in a footnote what they indicate.</td>
</tr>
</tbody>
</table>

Please check this box or indicate your approval if you have no corrections to make to the PDF file.

Thank you for your assistance.