Cardiovascular disease in chronic kidney disease. A clinical update from Kidney Disease: Improving Global Outcomes (KDIGO)

Charles A. Herzog[1,2], Richard W. Asinger[1,2], Alan K. Berger[2], David M. Charytan[3], Javier Díez[4], Robert G. Hart[5], Kai-Uwe Eckardt[6], Bertram L. Kasiske[1,2], Peter A. McCullough[7], Rod S. Passman[8], Stephanie S. DeLoach[9], Patrick H. Pun[10] and Eberhard Ritz[11]

[1]Hennepin County Medical Center, Minneapolis, Minnesota, USA; [2]University of Minnesota, Minneapolis, Minnesota, USA; [3]Brigham and Women's Hospital, Boston, Massachusetts, USA; [4]University of Navarra, Pamplona, Spain; [5]Population Health Research Institute/ McMaster University, Hamilton, Ontario, Canada; [6]University of Erlangen-Nuremberg, Erlangen, Germany; [7]St John Providence Health System, Novi, Michigan, USA; [8]Northwestern University, Chicago, Illinois, USA; [9]Jefferson Medical College, Philadelphia, Pennsylvania, USA; [10]Duke University, Durham, North Carolina, USA and [11]University of Heidelberg, Heidelberg, Germany

Cardiovascular morbidity and mortality in patients with chronic kidney disease (CKD) is high, and the presence of CKD worsens outcomes of cardiovascular disease (CVD). CKD is associated with specific risk factors. Emerging evidence indicates that the pathology and manifestation of CVD differ in the presence of CKD. During a clinical update conference convened by the Kidney Disease: Improving Global Outcomes (KDIGO), an international group of experts defined the current state of knowledge and the implications for patient care in important topic areas, including coronary artery disease and myocardial infarction, congestive heart failure, cerebrovascular disease, atrial fibrillation, peripheral arterial disease, and sudden cardiac death. Although optimal strategies for prevention, diagnosis, and management of these complications likely should be modified in the presence of CKD, the evidence base for decision making is limited. Trials targeting CVD in patients with CKD have a large potential to improve outcomes.

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Correspondence: *Charles A. Herzog, Chronic Disease Research Group, Minneapolis Medical Research Foundation, 914 South 8th Street, Suite S-406, Minneapolis, Minnesota 55404, USA. E-mail: cherzog@cdrg.org*

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In October 2010, the KDIGO (Kidney Disease: Improving Global Outcomes) convened a Clinical Update Conference in London, United Kingdom, titled 'Cardiovascular Disease in CKD: What is it and what can we do about it?' The objective was to define the current state of knowledge about cardiovascular disease (CVD) in patients with chronic kidney disease (CKD) stages 1–5 (see Table 1 for terminology). Topics included epidemiology, pathophysiology, diagnosis, prevention, and treatment, focusing on areas of clinical relevance: (1) coronary artery disease (CAD) and myocardial infarction (MI); (2) congestive heart failure (CHF); (3) cerebrovascular disease, stroke, atrial fibrillation, peripheral arterial disease (PAD); and (4) sudden cardiac death (SCD). A total of 80 international experts in these areas attended, including nephrologists, cardiologists, neurologists, and representatives of other disciplines. This is a report on conference proceedings and recommendations; it is not intended as a critical review of available literature. Conference details are posted on the KDIGO website, http://www.kdigo.org/meetings_events/Cardiovascular_Disease_in_Chronic_Kidney_Disease.php. Growing evidence suggests that CKD is an important, independent risk factor for CVD. Many patients with CKD die prematurely before or after beginning dialysis. Reasons for these adverse associations are not well understood and are thus the subject of controversy. Whether CVD events differ in patients with and without CKD is poorly defined. Similarly, whether differences in CVD in CKD patients suggest preventative or therapeutic strategies unique to this population is unclear.

CAD AND MI

Epidemiology and pathophysiology

The incidence and severity of obstructive CAD increases as glomerular filtration rate (GFR) declines.[1,2] CAD shows a pattern of diffuse multi-vessel involvement with coronary calcification;[2,3] small angiographic studies suggest that this

Table 1 | Glossary of KGIDO chronic kidney disease (CKD) abbreviations

Abbreviation	Definition
CKD	All stages of CKD, including dialysis
CKD 1, 2, 3, or 4	Specific stages of CKD
CKD 5	Dialysis- and non-dialysis-dependent CKD stage 5
CKD ND	Non-dialysis-dependent CKD
CKD 5D	Dialysis-dependent CKD stage 5, including hemodialysis and peritoneal dialysis; equivalent to end-stage renal disease
CKD 5HD	Hemodialysis
CKD 5PD	Peritoneal dialysis

incidence exceeds 50% in unselected CKD 5D patients.[4–7] Among patients with CAD, concomitant CKD portends a worse prognosis. Cardiovascular morbidity and mortality are inversely and independently associated with kidney function, particularly at estimated GFR <15 ml/min per 1.73 m^2.[8–15] Although the absolute incidence and mortality rate of MI is clearly elevated in advanced CKD,[16] standard cardiovascular risk factors are common in the setting of CKD, and the degree to which CKD is independently associated with the risk of initial MI is not well defined. Standard cardiovascular risk factors are common in CKD, but do not fully explain the high incidence of cardiovascular events or increased mortality rates;[17–19] their association with cardiovascular outcomes is attenuated or even reversed at the most advanced CKD stages.[20] Inflammation and oxidative stress have been linked to the pathogenesis of plaque formation and plaque rupture;[21] both are associated with worse cardiovascular outcomes.[7,22–24] The role of mineralocorticoid excess in the development of cardiovascular complications is increasingly recognized.[25] Recent studies have implicated disordered mineral and bone metabolism in the pathogenesis of coronary disease and CVD in CKD patients.[26–28]

Diagnosis

Although early detection of coronary plaque may permit risk factor modification and pharmacological intervention, the increased prevalence of CAD among CKD patients diminishes the negative predictive value of diagnostic studies in this population. CKD patients are underrepresented in cohort studies evaluating the diagnostic sensitivities and specificities of non-invasive tests. Exercise electrocardiography is limited by lack of specificity of the ST-segment response and by inability of many CKD patients to exercise to a diagnostic workload.[29,30] The risks of contrast agents limit the use of perfusion magnetic resonance imaging and computed tomography coronary angiography, and the latter is compromised by a high prevalence of coronary calcification among CKD patients.[31] Radionuclide perfusion imaging is more sensitive but less specific than stress echocardiography,[32] but may be problematic in the setting of elevated left-ventricular (LV) mass index and frank LV hypertrophy (LVH) because limited spatial resolution and disturbed coronary flow reserve may lead to false results.[30] The accuracy of exercise and of pharmacological myocardial perfusion imaging is reduced in CKD patients compared with the general population, and sensitivities and specificities $<80\%$ have been reported.[4,29,33] Conversely, stress echocardiography may be compromised by small LV cavity size in patients with elevated LV mass index.[34,35] Sensitivity and specificity for pharmacological stress echocardiography is 69–95% and 76–94%, respectively.[36,37]

Diagnosis of acute coronary syndrome may also be problematic in CKD. The classic triad of ischemic symptoms, elevated cardiac biomarkers, and electrocardiographic changes is frequently absent in CKD patients,[38,39] who are more likely to present with systolic or diastolic dysfunction causing heart failure symptoms, or with syncope.[39] LVH with a strain pattern may mask diagnostic ST depression. Conversely, creatine kinase MB isoform and cardiac troponins (cTns) may be elevated in the absence of true myocardial necrosis, possibly because of myocardial apoptosis or small vessel disease.[40] This mandates careful attention to trends over time and reduces the value of single tests, a problem that may be exacerbated by increased sensitivity of next-generation troponin assays.

Prevention

The altered relationship of typical risk factors with cardiovascular outcomes[41–43] and the routine exclusion of patients with advanced CKD from most clinical trials testing CVD therapies[44,45] engender doubt about the relevance of existing standards of care to these patients. Evidence of the efficacy of glycemic or blood pressure (BP) control or lifestyle modification to reduce cardiovascular events in patients with advanced CKD remains limited. Strict glycemic control may not benefit CKD 5D patients.[46,47] Randomized data on the efficacy of specific BP goals in CKD 5D patients are lacking. The labile nature of BP and the absence of clear associations between hypertension and adverse cardiovascular outcomes in CKD 5D[48] preclude definitive recommendations about BP control.[49] Lifestyle modifications have not been widely studied in CKD patients; in a small trial, multifactorial intervention that included smoking cessation was not associated with significant cardiovascular benefits.[50] Nevertheless, smoking cessation, exercise, dietary salt reduction, and weight loss are reasonable interventions at all CKD stages, and control of hypertension to usual goals or lower is indicated to slow CKD progression in patients with predialysis CKD.

Data are sparse regarding efficacy of prophylactic aspirin in advanced CKD. Subgroup analyses of randomized trials have demonstrated convincing cardiovascular risk reduction from daily aspirin in individuals with estimated GFR <45 ml/min per 1.73 m^2, including CKD 5D patients, despite higher incidence of bleeding in CKD patients.[51,52]

With release of initial results from the SHARP (Study of Heart and Renal Protection) trial, statins may now be the best-studied medical therapy in the context of advanced

CKD. Nevertheless, debate continues regarding their appropriate role. A subgroup analysis of several randomized clinical trials suggests benefit in patients with moderate CKD.[53] Conversely, two large trials comparing statins with placebo in hemodialysis patients did not demonstrate benefit.[54,55] More recently, in the SHARP trial, the combination of simvastatin and ezetimibe in CKD patients (including CKD 5D) reduced major atherosclerotic events by 17%, but did not appear to reduce overall mortality.[56] As no significant harm from statin use was demonstrated in any of the trials, this reduction in non-fatal events provides a rationale for the use of statins in CKD patients despite the apparent lack of efficacy in reducing the risk of death.

Treatment

Randomized data on treatment of acute MI in CKD patients are sparse, but treatment approaches using aspirin, clopidogrel, β-blockers, and angiotensin-converting enzyme inhibitors (ACEIs)/ARBs (angiotensin receptor blockers) seem to have similar benefits in CKD and non-CKD patients.[57,58] Several antiplatelet and anticoagulant agents are metabolized through the kidneys and warrant dose adjustment in CKD patients, and low-molecular weight heparins and eptifibatide may not be safe in CKD 5D patients.[59]

There is little reason to believe that kidney impairment diminishes the benefits of immediate reperfusion therapy in acute ST-elevation MI, but there are no randomized trials of reperfusion therapy in CKD. A recent analysis suggests that, when immediately available, primary percutaneous coronary intervention (PCI) should be the treatment of choice irrespective of CKD status.[60]

Among patients with non-ST elevation acute coronary syndrome (unstable angina and non-ST-elevation MI), the primary decision is between immediate angiography and a conservative approach. In the general population, an early invasive strategy reduces post-acute coronary syndrome morbidity and mortality by 20–30%,[61] and guidelines recommend early angiography in high-risk patients.[62] A recent meta-analysis suggested similar benefits in CKD 3–4 patients,[63] but CKD 4 was underrepresented ($n<300$) and CKD 5D patients were not included. Conversely, a recent retrospective analysis of all non-ST-elevation MI patients in Sweden suggested that an early invasive strategy was harmful for CKD 5 patients.[64]

There is a paucity of data regarding revascularization in CKD patients with stable angina. Surgical coronary revascularization is generally recommended for non-CKD patients with high-risk features such as left-main CAD, and PCI is typically recommended for symptomatic single- or two-vessel CAD or when a significant amount of myocardium is at risk.[65,66] No randomized clinical trials compare coronary revascularization strategies in advanced CKD patients. A subgroup analysis of the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial did not find a benefit from PCI compared with medical therapy in ~320 patients with CKD 3–4 and predominantly anatomically low-risk, multivessel disease.[67] The ARTS-1 (Arterial Revascularization Therapies Study) trial found no significant difference in the primary end point (death, MI, stroke) between PCI and coronary artery bypass graft (CABG) surgery in 290 patients with creatinine clearance <60 ml/min.[68] However, the revascularization rate was markedly lower in the CABG arm.

Observational data consistently show increased risk of serious operative complications in CKD patients.[66–74] Incidence of operative death after CABG is 9–12.2% for CKD 5D patients, and 3- to 7-fold higher in CKD 4–5ND patients than in non-CKD patients.[69–71] PCI may be an alternative, but may pose the added risk of contrast-induced nephropathy. In a study of CKD 5D patients undergoing first revascularization, in-hospital mortality was lower with PCI (4.1 vs 8.6%), but 2-year survival was better with CABG (56.4 vs 48.4%).[72] Similarly, a more recent retrospective study demonstrated that in CKD 5D, CABG was associated with a 71% reduction in the risk of death compared with PCI.[73] Available studies thus provide conflicting evidence on the relative merits of PCI and CABG in CKD patients. These studies may also be biased by differential referral of CKD patients to CABG or PCI. Studies in the drug-eluting stent era provide conflicting evidence on their benefit in CKD patients.[74,75]

Table 2 lists knowledge gaps and research needs.

CONGESTIVE HEART FAILURE

Epidemiology

CKD is associated with increased prevalence of concomitant CHF, ischemic heart disease, cardiac arrhythmias (most commonly atrial fibrillation), and valvular calcification.[76–78] In observational studies, CHF prevalence increases with declining kidney function.[79] CHF is the leading cardiovascular condition in CKD patients,[80] with mortality slightly higher for diastolic than for systolic CHF.[81] Terminal events in CHF are pump failure and sudden arrhythmic death.

Pathophysiology

CKD exposes the heart to three major mechanisms that facilitate the development of cardiomyopathy and induce LV failure: pressure overload, volume overload, and CKD-associated non-hemodynamic factors that alter the myocardium (Figure 1). Pressure overload is largely the result of long-standing hypertension and vascular stiffness. Increased LV wall stress (from pressure and volume overload) fuels changes in the composition and function of the myocardium, and this process is accentuated by CKD-associated abnormalities. CKD progression is accompanied by progressive LVH and diastolic dysfunction.[82] Arterial stiffening may be a key etiological aspect in CKD leading to CVD.[83,84]

Beyond hemodynamic factors, inappropriate activation of the renin–angiotensin system, catalytic iron-dependent oxidative stress, inflammation, and stimulation of pro-hypertrophic and profibrogenic factors (cardiotrophin-1, galectin-3, transforming growth factor-β, fibroblast growth

Table 2 | Future directions for cardiovascular disease in chronic kidney disease

Condition	Knowledge gaps	Research needs
CAD, MI	Screening may be beneficial, but data are insufficient to advocate screening asymptomatic patients. Evidence lacking regarding primary and secondary treatment of CAD. Cardiovascular trials have frequently excluded CKD patients from enrollment.	Clarify the interdependence of CKD with MI, and its relation to demographic characteristics such as gender. Clarify the pathophysiological relationship between development of plaque and subsequent rupture of selected plaques. Clarify roles of novel risk factors that are potential therapeutic targets. Broad-based validation of current stress and imaging modalities using coronary angiography with fractional flow reserve. Adequately powered CKD-specific clinical trials of aspirin, statins, novel anti-lipidemic agents, ACEIs, and ARBs. Define the ideal LDL cholesterol level and the role of newer antiplatelet and anticoagulant therapies. Randomized clinical trials comparing early invasive with conservative therapy post-ACS, and PCI with CABG.
CHF	Understanding development and prevention of LVH, fibrosis, and LV dysfunction (systolic and diastolic). Benefits of prolonged or quotidian dialysis. Absence of CKD-specific data on CHF treatment. Impact of sodium balance (intake, dialysate sodium concentration).	Evaluate asymptomatic LV dysfunction, examine changes in the kidney and cardiac function over time, and incorporate kidney- and cardiac-specific biomarkers. Clinical studies to investigate innovative monitoring and management techniques (serial biomarkers, bioimpedance, chronic *in vivo* monitoring.[212] Evaluate effects of CHF-specific risk-modifying and cardio-protective therapies (ACEIs, ARBs, renin and mineralocorticoid hormone inhibitors. Investigate speculative treatments (vitamin D analogs/calcimimetics, cytokine-modulating drugs, iron-related treatments, endothelin receptor blockers, regenerative therapies).
Stroke	High-quality observational data on risk factors, precipitants, etiological subtypes, causes of death, and underlying arteropathies. Risk of carotid artery stenting is undefined. Few data on treatment of acute stroke.	Randomized clinical trials testing interventions for secondary prevention of stroke. Determine safety of intravenous thrombolysis of CKD 5D patients with acute ischemic stroke.
Atrial fibrillation	Risks/benefits of anticoagulation with warfarin for stroke prevention. Efficacy, safety of dabigatran in stage 4 CKD. Uncertainty regarding validity of the 2005 KDOQI guidelines regarding anticoagulation in dialysis patients with atrial fibrillation.	Randomized clinical trials of warfarin and novel anticoagulants for stroke prevention in CKD 4–5D patients with atrial fibrillation. Interventions to prevent atrial fibrillation: radio frequency ablation, percutaneous closure of the left-atrial appendage, surgery.
PAD	Few high-quality observational data on risk factors. Role of ankle-brachial index vs other diagnostic techniques. Prospective data on non-surgical therapies. Data regarding percutaneous vs surgical revascularization.	Determine prevalence of preventive foot care. Assess regional differences in practice patterns. Generate management guidelines. Assess amputation frequency in programs that do and do not perform preventive foot care. Study bacteriology of diabetic patient feet.
SCD	Standard risk factors derived from the general population may not apply. Few autopsy data. Dialysis patients excluded from primary and secondary prevention trials.	Disease-specific, large-scale prospective cohort studies for risk stratification. Study heterogeneous CKD populations at all stages using all available risk-stratification techniques. Remove barriers preventing data linkage to allow for population-wide cohort and case–control studies. Randomized trials assessing the spectrum of interventions: β-blockers (such as carvedilol), ICDs, sympathetic ablation. Incorporate SCD as specific outcome in registry and clinical trial data. Investigate the potential role of sleep apnea in SCD.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; ICD, implantable cardioverter-defibrillator; KDOQI, Kidney Disease Outcomes Quality Initiative; LDL, low-density lipoprotein; LV, left ventricular; LVH, LV hypertrophy; MI, myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; SCD, sudden cardiac death.

factor-23) may be relevant.[85] The bufadienolides (steroid hormones circulating in the blood and excreted in urine) are elevated in CKD. They inhibit preferentially the α_1 isoform of Na^+-K^+-ATPase, resulting in volume expansion and hypertension.[86] Histopathological studies indicate that capillary density is reduced in the hypertrophied myocardium, and pronounced interstitial fibrosis is a dominant feature of CKD-associated structural myocardial remodeling.

LV diastolic dysfunction is frequent among CKD patients and is associated with the risk of CHF and increased mortality; impaired diastolic function may occur early in CKD, even without LVH.[85] Myocardial fibrosis results from an imbalance between exaggerated collagen synthesis and unchanged or depressed collagen degradation. In CKD patients, it is a major determinant of LV stiffness, increased LV filling pressure, and disturbances in diastolic filling, predisposing to development of diastolic dysfunction/failure.[87]

In CKD patients, resting LV systolic function is usually normal or even hyperdynamic, at least in the absence of

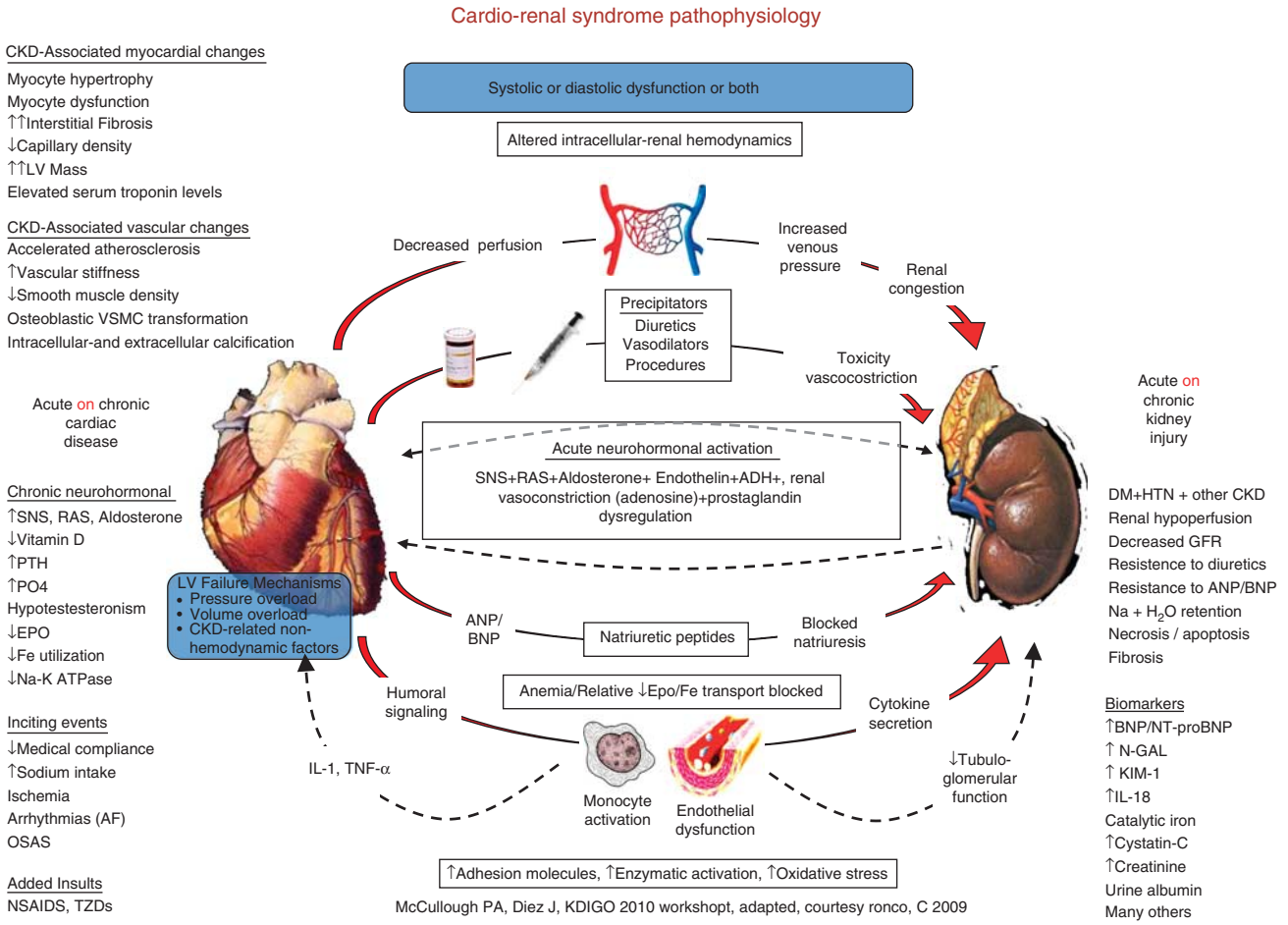

Figure 1 | Cardio–renal syndrome pathophysiology. ADH, antidiuretic hormone; ANP, atrial natriuretic peptide; BNP, B-type natriuretic peptide; CKD, chronic kidney disease; DM, diabetes mellitus; EPO, erythropoietin; HTN, hypertension; IL-1, interleukin-1; KIM-1, kidney injury molecule-1; LV, left ventricular; N-GAL, neutrophil gelatinase-associated lipocalin; NSAID, non-steroidal anti-inflammatory drug; OSAS, obstructive sleep apnea syndrome; PTH, parathyroid hormone; SNS, sympathetic nervous system; TNF-α, tumor necrosis factor-α; TZD, thiazolidinediones; VSMC, vascular smooth muscle cell.

ischemic heart disease or severe hemodynamic stress.[88] Hemodialysis is associated with repetitive hemodynamic instability and subsequent myocardial ischemia (perhaps due to microvascular dysfunction), resulting in prolonged LV systolic dysfunction ('myocardial stunning') and adverse outcome.[89]

Diagnosis

The clinical syndrome of CHF in CKD, heralded by effort intolerance, fatigue, and edema, is difficult to distinguish from volume overload. Echocardiography (including tissue Doppler imaging) has a key role in diagnosing LVH, diastolic and systolic LV dysfunction, and global assessment of cardiovascular prognosis. Despite issues of cost and availability, performing an echocardiogram is reasonable in each CKD patient with cardiac symptoms, new clinical events, or treatments likely to affect LV function.[90] 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 in subsequent 3-year intervals, regardless of symptoms.[91] Follow-up with serial examinations at closer intervals of 12–18 months may increase prognostic value.[92,93] Less clear is the usefulness of B-type natriuretic peptides (BNP and NT-proBNP) in the diagnosis and management of CHF; the concentration of these peptides is influenced by kidney function and by CHF severity.[94,95]

The cTns T and I, biomarkers of cardiomyocyte damage, accumulate in CHF. Although the clinical significance of increased cTn concentrations in CKD patients with CHF is unclear,[94] they are strong predictors of all-cause mortality in CKD 5D, and the US FDA (Food and Drug Administration) approved cTnT for risk stratification in CKD 5D patients.[96,97]

Novel cardiac and renal biomarkers include neutrophil gelatinase-associated lipocalin, kidney injury molecule 1, interleukin-18, galectin-3, mid-regional pro-adrenomedullin, catalytic iron, and markers of oxidative stress.[94] For all these markers, the critical issue is independence of GFR. A recent review scaled the following in order of decreasing effect size: tumor necrosis factor-α, hematocrit, interleukin-6, cTn T,

Kt/V(urea), prealbumin, urea reduction ratio, serum albumin, and C-reactive protein.[98] Only troponin T has strong biological plausibility for a link to myocardial disease; the others appear to represent chronic illness, inflammation, and malnutrition.

Prevention and treatment

Prevention relies on BP and volume control and modification of usual risk factors for CHF and CKD progression. Treatment of CHF in CKD patients using the European Society of Cardiology Guidelines is reasonable;[99] however, these therapeutic strategies are not based on strong evidence, as CKD patients are not adequately represented in randomized controlled trials in CHF.

Dietary salt restriction should be a mainstay of clinical counseling. With regard to pharmacological treatment, several considerations are appropriate.[100] CHF patients with kidney dysfunction often retain excessive salt and water and require more intensive diuretic treatment than do CHF patients with normal kidney function. Aldosterone antagonists should be used with caution as they may cause significant hyperkalemia. Despite strong evidence from randomized clinical trials that suggests that treatment with ACEIs and ARBs reduces cardiovascular morbidity and mortality in CHF, there is little equivalent evidence for CKD patients. Randomized clinical trials of CHF management with ACEIs, ARBs, new direct renin inhibitors, and mineralocorticoid receptor blockers (with or without potassium-binding resins) are required for CKD patients. Specialist supervision is recommended for patients with GFR levels below $\sim$30 ml/min per 1.73 m^2. One small randomized trial supports the combined use of ACEI + ARBs in the treatment of CHF in CKD 5D patients.[101] Recent data strongly support the use of bisoprolol[102] or carvedilol[103] in CKD patients with CHF.

Other potentially useful management strategies include correcting anemia and minimizing vascular calcification.[100] Anemia correction, aiming for hemoglobin levels $>$10 g/dl, has been shown to reduce LVH in CKD patients,[104] but total correction does not further improve LV geometry or cardiovascular outcome.[105,106] Erythropoiesis-stimulating agents and/or intravenous iron[107] may improve exercise tolerance but are without survival benefit.[108,109] Control of calcium and phosphate concentrations is instrumental in minimizing vessel calcification. Concern about calcification due to calcium-containing phosphate binders is increasing.[110,111] Therefore, the use of non-calcium-containing phosphate binders may be advantageous,[112] although data are insufficient to establish the comparative superiority of these agents over calcium-containing phosphate binders for cardiovascular end points in CKD.[113] Achieving adequate vitamin D status and avoiding excessively high or low parathyroid hormone concentrations (oversuppression) are reasonable treatment goals, although their efficacy has not been demonstrated.

For CKD 5D patients with CHF, adequate ultrafiltration should be coupled with dietary sodium restriction and lower dialysate sodium concentrations; more frequent or longer dialysis sessions may be beneficial.[114,115] High-flow fistulae or grafts may cause high cardiac output states.[116]

Evidence for management of acute CHF in CKD is limited. Inotropic therapy (dobutamine, milrinone, levosimendan) may be considered in patients with worsening renal function secondary to the fall in cardiac output; however, routine use of inotropes or other adrenergic-stimulating agents for acute decompensated CHF is not indicated in CKD patients.[117] Ultrafiltration may be useful in refractory congestion.

Table 2 lists knowledge gaps and research needs.

CVD AND STROKE, ATRIAL FIBRILLATION, PERIPHERAL ARTERIAL DISEASE

Stroke

CKD 3–4 is an independent risk factor for ischemic and hemorrhagic stroke, with a relative risk of $\sim$1.4 (ref. 118). The relative risk of stroke in CKD 5D patients was estimated to be 5–10 times that of the age-matched general population[119] with an overall stroke rate of $\sim$4% per year.

Ischemic stroke is caused by several distinct arteriopathies; few studies using modern imaging techniques and classification paradigms have assessed etiological subtypes in CKD patients. The best recent descriptive data in CKD 5D patients come from the prospective CHOICE (Choices for Healthy Outcomes in Caring for ESRD) study, involving 1041 incident US CKD 5D patients (74% receiving hemodialysis).[120] The observed stroke rate was $\sim$4.2% per year. Most (87%) strokes were ischemic, and the distribution of etiological subtypes was similar to the distribution in registries of CKD ND patients. Independent predictors of higher risk were age and diabetes. African-American race was associated with lower risk. About one-third of strokes occurred during or shortly after hemodialysis treatment.[120,121] The stroke mortality rate was nearly three times higher (35%) than that for non-end-stage renal disease patients. High mortality rates were also reported in three randomized trials in which 43,[55] 38,[54] and 36%[122] of all strokes were fatal, apparently reflecting ischemic stroke. The high fatality rate could reflect systematic underdetection of minor strokes in CKD 5D patients or withdrawal of dialysis when stroke occurs. Less is known about stroke rates and stroke subtypes in end-stage renal disease patients undergoing peritoneal dialysis, but available data support similar rates.[120,123] CKD 4 seems to be an independent risk factor for fatal stroke.[124]

Evidence-based secondary prevention of non-cardioembolic ischemic stroke includes BP lowering, antiplatelet agents, statin therapy, and, in the presence of ipsilateral high-grade carotid stenosis, carotid endarterectomy. BP lowering with ACEIs and thiazide diuretic reduced stroke recurrence in patients with CKD 3–4.[125] Optimal BP management in CKD 5HD patients with prior stroke has not been defined. Exploratory analyses of randomized trials show that low-dose aspirin for primary prevention of stroke in hypertensive CKD 3–4 patients[51] and antiplatelet therapy for prevention of major vascular events are effective in CKD 5HD.[52] Efficacy of antiplatelet prophylaxis likely extends to secondary stroke prevention in CKD patients, but no randomized trial data are available. Statin therapy was not efficacious for

stroke prevention in CKD 5D patients,[54,55] but results of the SHARP trial indicate efficacy of statins for prevention of atherosclerotic events (including ischemic stroke) in CKD patients.[56]

A subgroup analysis of the NASCET (North American Symptomatic Carotid Endarterectomy) trial demonstrated absolute benefit of carotid endarterectomy for CKD 3 patients with recent cerebral ischemia and high-grade ipsilateral carotid stenosis.[126] Carotid artery stenting is more frequently performed recently, and the benefits and risks of carotid artery endarterectomy have been defined by large randomized trials.[127,128] Although results have engendered controversy, the trials are generally interpreted as favoring endarterectomy except in special circumstances.[128] Because CKD, particularly CKD 5D, patients' carotid arteries are unduly calcified and stiff, complications of stenting may be increased. The risk of perioperative complications of carotid endarterectomy also seems to be higher for CKD patients.[129,130] Both procedures require administration of substantial amounts of iodinated contrast for cerebral arteriography (although many surgeons perform endarterectomy based on non-invasive imaging). The benefit vs risk of these procedures compared with medical therapy has not been defined for CKD 5D patients.

Intravenous thrombolysis with tissue plasminogen activator is of net benefit for patients with ischemic stroke when given within 4.5 h of symptom onset, with intracranial bleeding as the major complication. In small studies, intracranial hemorrhage was not increased in patients with CKD stages 3–4 (refs. 131,132). However, CKD may be an independent predictor of poor neurological outcome.[131] Many acute strokes occur in CKD 5D patients. The 2005 KDOQI guidelines on CVD in dialysis patients recommend considering thrombolysis on an individual basis.[91] The safety of intravenous thrombolysis has not been defined in CKD 5HD patients with acute ischemic stroke. Heparin administered during dialysis is often problematic in this situation because recent heparin use with prolonged activated partial thromboplastin time is generally considered a contraindication to intravenous tissue plasminogen activator.

The 2005 KDOQI guidelines state that all CKD 5D patients should follow the AHA (American Heart Association) guidelines for prevention, screening, evaluation, and treatment of stroke, with minor caveats.[91] The paucity of new data precludes modification of most previous KDOQI recommendations.

Atrial fibrillation

Atrial fibrillation is the most common cardiac rhythm disturbance in CKD patients; prevalence among dialysis patients is 15–20%, and it is associated with increased incidence of stroke.[133–135] The mechanism of stroke associated with atrial fibrillation is embolization of left atrial appendage thrombus. Multiple randomized clinical trials of anticoagulation with the vitamin K antagonist warfarin in the general population have shown a marked reduction in stroke with warfarin compared with placebo or aspirin.[136] Thus, the American College of Cardiology/AHA/European Society of Cardiology guidelines recommend anticoagulation with warfarin for primary and secondary prevention of stroke in patients with atrial fibrillation.[137] Extrapolating these data to CKD 5D patients, the 2005 KDOQI guidelines recommend anticoagulation in non-valvular atrial fibrillation with careful monitoring due to increased risk for bleeding.[91] However, randomized controlled trials of antithrombotic therapy for stroke in atrial fibrillation patients excluded CKD 5D patients.

The clinical conundrum balances reduced risk of stroke with warfarin with increased risk of anticoagulant-associated bleeding, vascular calcification, and calciphylaxis.[138] Multivariate analyses of placebo- and aspirin-assigned patients from randomized clinical trials identified several risk factors that have been incorporated into stroke risk-stratification schemes. The most common is the CHADS2 risk score,[139] which assigns one point each for CHF (moderate to severe decreased LV systolic performance), hypertension, age older than 75 years, and diabetes, and two points for previous stroke. Patients with a CHADS2 score greater than one are generally considered to be at sufficient risk for stroke to warrant warfarin treatment (target international normalized ratio range of 2–3). Because CKD 5D patients were not included in randomized controlled trials of warfarin, they were also not included in derivation of this or of most other stroke risk-stratification schemes. One large retrospective study of hemodialysis patients with atrial fibrillation found that increasing age, CHF, and systolic BP correlated with stroke risk.[140] Multivariate analysis of another study reported that previous stroke, diabetes, and advancing age independently predicted hospitalization for stroke, but hypertension and CHF did not.[134] These and a third study reported that the CHADS2 scheme successfully stratified stroke risk in CKD 5D patients with atrial fibrillation, but the contribution of each component appeared to differ.[134,140,141] How reliably the CHADS2 and other stroke risk-stratification schemes apply to CKD 5D patients with atrial fibrillation remains unclear.

It is uncertain how schemes designed to estimate bleeding risk during warfarin anticoagulation apply to CKD patients, and particularly to hemodialysis patients.[142]

Risk stratification for hemorrhage has also been proposed; two schemes were derived from databases that included atrial fibrillation patients with CKD.[143,144] Both identified CKD as a risk factor, but how many CKD 5D patients were included is unclear. CKD 5HD patients have abnormal platelet function and are subjected to therapeutic heparin three times a week during dialysis. Excessive bleeding has been noted in patients administered warfarin in therapeutic doses.[145] The clinical dilemma is that stroke risk increases with declining kidney function,[135] but bleeding risk increases during warfarin anticoagulation.

Retrospective analyses of large dialysis databases raise concerns regarding the efficacy of warfarin anticoagulation in CKD 5HD patients with atrial fibrillation.[134,140,146] Studies

from a national network of incident dialysis patients identified warfarin use with increased risk of stroke and overall mortality.[140,146] The increased risk of stroke showed a 'dose effect,' with higher international normalized ratios associated with increased, not decreased, risk.[140] Another study from the DOPPS (Dialysis Outcomes and Practice Patterns Study) database reported increased stroke hazard ratios for patients receiving warfarin,[134] and that warfarin use in patients aged older than 75 years was associated with higher stroke risk (perhaps due to hemorrhagic stroke, but this could not be determined). These observations prompted reconsideration of the value of warfarin for stroke prevention in CKD 5D patients with atrial fibrillation. Weighing the available evidence, the benefit of warfarin anticoagulation for primary prevention of stroke in CKD 5D patients is questionable.

The number of patients with atrial fibrillation is projected to double by the middle of this century,[147] stimulating development of new oral anticoagulants and non-pharmacological methods to prevent stroke in atrial fibrillation.[148,149] Recently, the US FDA approved the oral direct thrombin inhibitor dabigatran (150 mg twice daily) for stroke prevention in atrial fibrillation, including CKD 3 patients.[150] Dabigatran trough levels correlate with efficacy for stroke prevention and are altered in CKD patients because 80–85% of dabigatran is excreted unchanged by the kidney. The superior efficacy and comparable safety of dabigatran compared with warfarin was demonstrated in a subgroup of 3505 participants with estimated creatinine clearance $\geqslant 30$ to $\leqslant 50$ ml/min per 1.73 m^2 in the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial.[151,152] The 2.8% per year stroke rate among patients assigned to warfarin was reduced to 1.5% per year ($P<0.01$) with dabigatran 150 mg twice daily in CKD 3 patients. The FDA also approved a reduced dose of dabigatran (75 mg twice daily) for CKD 4 patients based on pharmacokinetic and pharmacodynamic studies.[153]

Therefore, until new data become available, and in contrast to the previous KDOQI recommendation 9.1,[91] routine anticoagulation of CKD 5D patients with atrial fibrillation for primary prevention of stroke is not indicated, whereas previous KDOQI recommendations for secondary prevention and careful monitoring[154] of all dialysis patients receiving anticoagulation remain valid.

Peripheral arterial disease

PAD is common in CKD patients. Among adults aged >40 years with estimated GFR <60 ml/min per 1.73 m^2, National Health and Nutrition Examination Survey data from 1999 to 2000 report prevalence of 24%.[155] The Chronic Renal Insufficiency Cohort study data show PAD in 7% of adult CKD ND patients;[156] prevalence in CKD 5D patients is 17–48%.[157,158] CKD is an independent risk factor for PAD events.[159]

Higher rates of PAD among CKD patients are attributed to greater prevalence of traditional risk factors, such as diabetes, hypertension, dyslipidemia, advanced age, and 'renal-specific factors.' A cross-sectional analysis of the USRDS (United States Renal Data System) data identified traditional (such as age, male sex, diabetes, smoking) and kidney-specific risk factors (dialysis duration, low Kt/V, hypoalbuminemia, low parathyroid hormone) as associated with PAD.[160] Hyperphosphatemia, inflammation, and malnutrition have been associated with PAD in CKD 5D.[161–163]

Screening for PAD is recommended for adults in the general population based on age and number of risk factors.[137] For CKD 5D patients, the 2005 KDOQI guidelines recommend screening (including physical examination with assessment of arterial pulse and skin integrity) at the time of dialysis initiation. However, screening guidelines are problematic for clinicians because of the lack of clarity regarding diagnostic testing and optimal therapies for PAD in CKD.

The ankle–brachial index is widely considered the standard diagnostic tool for PAD, with <0.9 generally considered the diagnostic value. Greater prevalence of calcified vessels in CKD patients raises concerns regarding the utility of this test in these patients and suggests consideration of alternate tests, such as toe–brachial index and pulse volume recording. Limited data on these measurements in CKD 5D patients demonstrate an association with future cardiovascular events and amputations.[164]

Evidence-based medical therapies for PAD in CKD patients are lacking. Smoking cessation is mandatory. Aspirin may be beneficial for prevention of cardiovascular events. Clopidogrel has not been studied in CKD patients with PAD. Antiplatelet agents carry the risk of bleeding, which is of particular concern because CKD patients have inherently higher risks of bleeding associated with renal disease and heparin use with hemodialysis. Prospective studies regarding other medical therapies, such as statins, renin–angiotensin aldosterone system blockade, and exercise therapy, are required. Cilostazol, a phosphodiesterase inhibitor that blocks platelet aggregation and functions as a vasodilator, is also commonly used in PAD. It is approved for symptomatic management of claudication. A retrospective analysis of its impact in reducing restenosis among CKD 5HD patients with PAD who underwent percutaneous transluminal angioplasty found an association between cilostazol use and 5-year event-free survival.[165]

For patients with advanced PAD, particularly those with critical limb ischemia, revascularization or amputation is often required. Critical limb ischemia is defined by lower-extremity ischemic rest pain, ulceration, or gangrene. No randomized studies evaluating percutaneous vs surgical revascularization techniques have been conducted in CKD patients with PAD. Percutaneous methods are preferred, but outcomes are worse among patients with higher rates of repeat percutaneous angioplasty, subsequent surgical revascularization, or limb loss and death.[166] In another retrospective analysis, CKD 5D patients who underwent percutaneous compared with surgical revascularization experienced higher limb salvage rates.[167] Perioperative morbidity and mortality are high among CKD patients undergoing these

procedures. Surgical revascularization is often complicated by perioperative mortality, prolonged hospitalization, and limb loss in dialysis patients.[167–169] Diabetes, advanced age, and African-American or American-Indian race/ethnicity are also associated with greater risk for amputation in this population.[170,171] Optimal management of CKD patients with critical limb ischemia is unclear. Rates of complications, including subsequent amputation and perioperative and 1-year mortality, are higher for PAD therapies in CKD patients.[167,172,173]

Preventive strategies may be key for reducing PAD-associated morbidity, particularly for decreasing amputation rates. Diabetes is the leading cause of CKD in the United States. Diabetic foot ulcers and neuropathy increase the risk of amputations. Small, single-center studies have shown preventive foot care to be beneficial in reducing amputation rates in CKD 5D patients with diabetes.[174]

Table 2 lists knowledge gaps and research needs.

SUDDEN CARDIAC DEATH

Epidemiology

SCD is generally defined as sudden, unexpected death within an hour of symptom onset, or unwitnessed, unexpected death without obvious non-cardiac cause in patients known to be well within the past 24 h.[175,176] In CKD 5D patients, this definition is problematic. Determining the unexpectedness of death is vexing in patients with a high burden of comorbidity who spend a disproportionate amount of time in health-care facilities. CKD 5D patient deaths are frequently unobserved, and the exact timing is unknown. Many possible non-cardiac causes (for example cerebrovascular) may contribute to sudden death in CKD 5D patients, and their relative contribution is unknown. However, commonly accepted definitions of SCD should be adopted to facilitate communication between disciplines and interpretation of pre-existing literature. Some circumstances unique to CKD 5D patients may require special consideration. For instance, sudden death occurring in the setting of missed hemodialysis treatment should not be considered SCD.

SCD accounts for about one-fourth of dialysis patient deaths, with an annual rate of 5.5%.[177–179] Survival of CKD 5D patients after sudden cardiac arrest is universally poor, with a 6-month survival of 3–11%.[180–183] The cause of death derived from registry data may be prone to misclassification because of the lack of a precise SCD definition; however, findings from randomized clinical trials (HEMO, 4D) and prospective CKD 5HD (CHOICE) and CKD 5PD cohorts are remarkably consistent regarding the relative contribution of SCD to all-cause mortality (22–26%) in dialysis patients.[54,184–187] Further studies in two areas are warranted. First, little is known about regional differences in SCD epidemiology. Preliminary evidence suggests that SCD rates may vary in different populations; for example, reported rates are substantially lower in Japanese patients. Second, although available data do not suggest a significant difference between hemodialysis and peritoneal dialysis patients, less is known about comparative SCD rates in patients using non-conventional hemodialytic techniques such as frequent and nocturnal hemodialysis.

The relationship between less severe CKD stages and SCD risk has recently been explored. Secondary analyses of patients with moderate CKD enrolled in the MADIT-II (Second Multicenter Automated Defibrillator Implantation) and the COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure) trials have found an incremental risk of SCD with decreasing baseline GFR.[188,189] Inverse linear relationships between kidney function and SCD risk have been observed in a large cohort with CKD and significant CAD,[190] postmenopausal women with CAD,[191] and elderly individuals without clinically significant cardiac disease.[192] In one observational study of 19,440 patients, estimated GFR was independently associated with sudden death (hazard ratio 1.11 per 10 ml/min decline in estimated GFR).[190] In these studies, the increased risk of SCD associated with CKD could not be accounted for by the degree of measured cardiac or other comorbidities.

Pathophysiology

The association between CKD 5D and SCD is multifactorial and complex, likely involving vulnerable myocardial substrate and superimposed transient triggers. Both are abundant in the dialysis population. For example, CAD is prevalent among CKD patients, producing structural heart disease (ischemic cardiomyopathy with decreased systolic function) and a source of triggering events (acute myocardial ischemia) from which terminal arrhythmias arise.[193] CAD is the underlying substrate in most SCD in non-CKD patients,[193] and recognized risk factors for CAD identified in the general population are prevalent among CKD patients.

However, the pathophysiology of CAD as the main determinant of SCD risk is problematic among CKD patients. Evidence suggests that CAD-related risks are insufficient to explain the markedly increased risk of SCD among CKD patients. In CKD ND patients, SCD risk associated with diminished GFR cannot be accounted for by severity of CAD, CHF, diabetes, or decreased use of cardiovascular medications.[190] In clinical trials, only 9% of deaths were directly attributable to CAD, whereas SCD accounted for 26%.[54] Recognized risk factors such as LV systolic dysfunction are present in only a minority of CKD 5D patients, but LVH is endemic.[194,195] The degree to which unique dialysis-specific complications (such as hyperkalemia) and other non-cardiac mechanisms contribute to the overall sudden death rate is unknown, and few autopsy data are available. A small autopsy series of Japanese CKD 5D patients found stroke to be the most frequent cause of sudden death (26%), followed by cardiac disease (19%) and infectious disease (17%).[196] Obtaining autopsy data is difficult, but additional studies using postmortem information would be illuminating.

A related issue is characterizing the primary arrhythmias responsible for sudden death in CKD patients. In the general population, SCD may be due to several catastrophic events and sustained ventricular tachycardia and ventricular

fibrillation constitute about half the cases.[197] Whether the same pattern holds true among CKD 5D patients is unclear, given the differences in underlying cardiac disease patterns. Small retrospective studies of presenting arrhythmias in CKD 5D patients with SCD report a wide range of ventricular arrhythmias (19–72%).[181,197–199] Unique metabolic derangements and other non-cardiac events may cause terminal arrhythmias beyond ventricular tachycardia and ventricular fibrillation. Characterizing SCD arrhythmias in CKD 5D patients is important, because non-ventricular arrhythmias would not be expected to respond to traditional resuscitative measures involving defibrillation.[200] Implantable loop recorders used to identify terminal arrhythmias could prove useful, but a coordinated effort would be necessary given low enrollment rates anticipated in such studies.

Prevention

Preventive strategies for SCD in CKD 5D patients should be a major public health concern. Attempts to evaluate the efficacy of preventive strategies in CKD patients rely on reasonable risk-stratification data. This is extremely challenging, as SCD is a generic term encompassing widely disparate events, the risk factors of which likely also vary widely. Diminished GFR by itself should be considered a significant SCD risk factor.[188] CKD 5D confers additional risk; one study suggested that SCD risk doubles in CKD 5 patients with dialysis initiation.[190] Most studies of SCD risk factors in dialysis patients focus on retrospective and small observational prospective cohorts, and are limited by small sample size, inherent limitations in the adjudication of end points, and failure to examine a wide range of candidate variables.

An important and consistent observation is increased SCD occurrence in CKD 5HD patients on the first hemodialysis day following the long intradialytic period, suggesting that fluid and electrolyte accumulation and rapid shifts during hemodialysis may be important triggering factors.[198,201] Exposure to low-potassium and calcium dialysate, volume removal on dialysis, and pre-dialysis hyperkalemia and hypokalemia have been consistently associated with increased risk of intradialytic SCD.[181,186,202] Obstructive sleep apnea has been associated with arrhythmias in the general population, and disordered nocturnal breathing is highly prevalent among CKD 5D patients.[203] Although evidence of a direct link to SCD is lacking, nocturnal hypoxemia in CKD 5D patients has been associated with increased cardiovascular events.[204] Measures of structural heart disease have been variably associated with increased SCD risk; one small study suggested that change in the LV mass index is the most potent predictor of SCD, and another found no association between LVH and SCD risk.[186,205] The high prevalence of LVH in CKD 5D patients limits its utility in SCD risk stratification. Ejection fraction $\leqslant$35%, regardless of etiology, identifies a subgroup of CHF patients with high risk of sudden death due to arrhythmia, and even milder degrees of LV dysfunction may be associated with increased event rates in peritoneal dialysis patients.[187]

Other non-invasive cardiac markers, including ambient ventricular ectopy, heart rate variability, QT dispersion, baroreflex sensitivity, and T-wave alternans, have been insufficiently studied in this population to be of clinical utility. Serum biomarkers, particularly cTnT, have been associated with all-cause mortality and SCD and may serve as markers for cardiac apoptosis and CHF. Other biomarkers associated with SCD among CKD 5D patients include markers of inflammation (interleukin-6,[186] C-reactive protein,[186] and adiponectin[206]) and nutrition (serum albumin,[186] pre-dialysis serum creatinine[202]), but these have not been validated across cohorts. Multinational observational cohorts including diverse populations of CKD ND and CKD 5D patients and examining a broad spectrum of potential risk factors and risk-stratification techniques are desirable.

The major question facing risk-stratification studies is what to do with results. Avoiding rapid fluid and electrolyte shifts and low-potassium dialysate in hemodialysis is supported by observational data, but controlled trials should be performed to determine the potential benefit of intensive dialytic management with dialysate and ultrafiltration profiling to improve tolerance of the hemodialysis procedure. Whether frequent or long, slow hemodialysis or other modifications can improve tolerance and help prevent SCD remains to be seen. Otherwise, few effective therapies are available to prevent SCD in CKD 5D patients. β-Adrenergic blockers improved survival and decreased SCD risk in a study of CKD 5D patients with dilated cardiomyopathy, but more work in this promising area is required.[103] There are no data on the prevention of SCD using anti-arrhythmic therapy, and such an approach is unlikely to prove beneficial in CKD 5D patients. A recent study reported that use of digoxin was associated with increased mortality in CKD 5HD patients.[207] Implantable cardioverter-defibrillators (ICDs), a highly effective but expensive technology with a proven track record in CHF patients, have been inadequately studied. Although 4% of all ICD implants in the United States are in CKD 5D patients, no prospective trial data assess their utility. The USRDS reports median survival of only 18 months in CKD 5D patients receiving ICDs for primary prevention indications, well below survival in non-dialysis ICD recipients.[179] Observational data suggest modestly improved survival of CKD 5D cardiac arrest survivors receiving ICDs for secondary prevention indications.[208,209] Complications following device implantation increase fivefold in CKD 5D patients and short-term post-implant mortality fourfold.[210,211] Whether wearable defibrillators or leadless subcutaneous devices can impact survival while reducing complication rates is unknown.

Table 2 lists knowledge gaps and research needs.

CONCLUSIONS

Data that have become available in recent years generally reinforce the importance of CVD in determining quality of life and prognosis of CKD patients. Increasing evidence demonstrates that pathology, manifestations, and complications of CVD differ in the presence of CKD. Thus, the risk–benefit

relationship of management strategies evaluated in the general population may differ significantly in patients with CKD. The number of trials that specifically address CVD in CKD patients, or that enroll CKD patients, remains small; however, increasing awareness may stimulate future trials. When results of needed studies of atrial fibrillation, coronary revascularization, SCD, and other relevant topics become available, KDIGO will consider developing a clinical practice guidelines based on a systematic evidence review.

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REFERENCES

1. Nakano T, Ninomiya T, Sumiyoshi S *et al.* Association of kidney function with coronary atherosclerosis and calcification in autopsy samples from Japanese elders: the Hisayama study. *Am J Kidney Dis* 2010; **55**: 21–30.
2. Chonchol M, Whittle J, Desbien A *et al.* Chronic kidney disease is associated with angiographic coronary artery disease. *Am J Nephrol* 2008; **28**: 354–360.
3. Ix JH, Shlipak MG, Liu HH *et al.* Association between renal insufficiency and inducible ischemia in patients with coronary artery disease: the heart and soul study. *J Am Soc Nephrol* 2003; **14**: 3233–3238.
4. Marwick TH, Steinmuller DR, Underwood DA *et al.* Ineffectiveness of dipyridamole SPECT thallium imaging as a screening technique for coronary artery disease in patients with end-stage renal failure. *Transplantation* 1990; **49**: 100–103.
5. Joki N, Hase H, Nakamura R *et al.* Onset of coronary artery disease prior to initiation of haemodialysis in patients with end-stage renal disease. *Nephrol Dial Transplant* 1997; **12**: 718–723.
6. Ohtake T, Kobayashi S, Moriya H *et al.* High prevalence of occult coronary artery stenosis in patients with chronic kidney disease at the initiation of renal replacement therapy: an angiographic examination. *J Am Soc Nephrol* 2005; **16**: 1141–1148.
7. deFilippi C, Wasserman S, Rosanio S *et al.* Cardiac troponin T and C-reactive protein for predicting prognosis, coronary atherosclerosis, and cardiomyopathy in patients undergoing long-term hemodialysis. *JAMA* 2003; **290**: 353–359.
8. Gibson CM, Pinto DS, Murphy SA *et al.* Association of creatinine and creatinine clearance on presentation in acute myocardial infarction with subsequent mortality. *J Am Coll Cardiol* 2003; **42**: 1535–1543.
9. Shlipak MG, Heidenreich PA, Noguchi H *et al.* Association of renal insufficiency with treatment and outcomes after myocardial infarction in elderly patients. *Ann Intern Med* 2002; **137**: 555–562.
10. Wright RS, Reeder GS, Herzog CA *et al.* Acute myocardial infarction and renal dysfunction: a high-risk combination. *Ann Intern Med* 2002; **137**: 563–570.
11. Al SJ, Reddan DN, Williams K *et al.* Prognostic implications of abnormalities in renal function in patients with acute coronary syndromes. *Circulaton* 2002; **106**: 974–980.
12. Anavekar NS, McMurray JJ, Velazquez EJ *et al.* Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. *N Engl J Med* 2004; **351**: 1285–1295.
13. Go AS, Chertow GM, Fan D *et al.* Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004; **351**: 1296–1305.
14. Matsushita K, van d V, Astor BC *et al.* Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet* 2010; **375**: 2073–2081.
15. Herzog CA, Ma JZ, Collins AJ. Poor long-term survival after acute myocardial infarction among patients on long-term dialysis. *N Engl J Med* 1998; **339**: 799–805.
16. US Renal Data System. *USRDS 2008 Annual Data Report: Atlas of Chronic Kidney Disease & End-Stage Renal Disease in the United States*. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases: Bethesda, MD, 2008.
17. Longenecker JC, Coresh J, Powe NR *et al.* Traditional cardiovascular disease risk factors in dialysis patients compared with the general population: the CHOICE Study. *J Am Soc Nephrol* 2002; **13**: 1918–1927.
18. Weiner DE, Tighiouart H, Elsayed EF *et al.* The Framingham predictive instrument in chronic kidney disease. *J Am Coll Cardiol* 2007; **50**: 217–224.
19. Fleischmann EH, Bower JD, Salahudeen AK. Are conventional cardiovascular risk factors predictive of two-year mortality in hemodialysis patients? *Clin Nephrol* 2001; **56**: 221–230.
20. Kalantar-Zadeh K, Block G, Humphreys MH *et al.* Reverse epidemiology of cardiovascular risk factors in maintenance dialysis patients. *Kidney Int* 2003; **63**: 793–808.
21. Bhatt DL. Anti-inflammatory agents and antioxidants as a possible 'third great wave' in cardiovascular secondary prevention. *Am J Cardiol* 2008; **101**: 4D–13D.
22. Weiner DE, Tighiouart H, Elsayed EF *et al.* Inflammation and cardiovascular events in individuals with and without chronic kidney disease. *Kidney Int* 2008; **73**: 1406–1412.
23. Menon V, Greene T, Wang X *et al.* C-reactive protein and albumin as predictors of all-cause and cardiovascular mortality in chronic kidney disease. *Kidney Int* 2005; **68**: 766–772.
24. Bayes B, Pastor MC, Bonal J *et al.* Homocysteine, C-reactive protein, lipid peroxidation and mortality in haemodialysis patients. *Nephrol Dial Transplant* 2003; **18**: 106–112.
25. Briet M, Schiffrin EL. Aldosterone: effects on the kidney and cardiovascular system. *Nat Rev Nephrol* 2010; **6**: 261–273.
26. Giovannucci E, Liu Y, Hollis BW *et al.* 25-Hydroxyvitamin D and risk of myocardial infarction in men: a prospective study. *Arch Intern Med* 2008; **168**: 1174–1180.
27. Kovesdy CP, Ahmadzadeh S, Anderson JE *et al.* Association of activated vitamin D treatment and mortality in chronic kidney disease. *Arch Intern Med* 2008; **168**: 397–403.
28. Gutierrez OM, Mannstadt M, Isakova T *et al.* Fibroblast growth factor 23 and mortality among patients undergoing hemodialysis. *N Engl J Med* 2008; **359**: 584–592.
29. Schmidt A, Stefenelli T, Schuster E *et al.* Informational contribution of noninvasive screening tests for coronary artery disease in patients on chronic renal replacement therapy. *Am J Kidney Dis* 2001; **37**: 56–63.
30. Karthikeyan V, Ananthasubramaniam K. Coronary risk assessment and management options in chronic kidney disease patients prior to kidney transplantation. *Curr Cardiol Rev* 2009; **5**: 177–186.
31. Taylor AJ, Cerqueira M, Hodgson JM *et al.* ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR 2010 Appropriate use Criteria for Cardiac Computed Tomography: a Report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the Society of Cardiovascular Computed Tomography, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the American Society of Nuclear Cardiology, the North American Society for Cardiovascular Imaging, the Society for Cardiovascular Angiography and Interventions, and the Society for Cardiovascular Magnetic Resonance. *Circulation* 2010; **122**: e525–e555.
32. Hendel RC, Berman DS, Di Carli MF *et al.* ACCF/ASNC/ACR/AHA/ASE/SCCT/SCMR/SNM 2009 Appropriate Use Criteria for Cardiac Radionuclide Imaging: a Report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the American Society of Nuclear

Cardiology, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the Society of Cardiovascular Computed Tomography, the Society for Cardiovascular Magnetic Resonance, and the Society of Nuclear Medicine. *Circulation* 2009; **119**: e561–e587.
33. Vandenberg BF, Rossen JD, Grover-McKay M *et al.* Evaluation of diabetic patients for renal and pancreas transplantation: noninvasive screening for coronary artery disease using radionuclide methods. *Transplantation* 1996; **62**: 1230–1235.
34. Bangalore S, Yao SS, Chaudhry FA. Usefulness of stress echocardiography for risk stratification and prognosis of patients with left ventricular hypertrophy. *Am J Cardiol* 2007; **100**: 536–543.
35. Yuda S, Khoury V, Marwick TH. Influence of wall stress and left ventricular geometry on the accuracy of dobutamine stress echocardiography. *J Am Coll Cardiol* 2002; **40**: 1311–1319.
36. Herzog CA, Marwick TH, Pheley AM *et al.* Dobutamine stress echocardiography for the detection of significant coronary artery disease in renal transplant candidates. *Am J Kidney Dis* 1999; **33**: 1080–1090.
37. Sharma R, Mehta RL, Brecker SJ *et al.* The diagnostic and prognostic value of tissue Doppler imaging during dobutamine stress echocardiography in end-stage renal disease. *Coron Artery Dis* 2009; **20**: 230–237.
38. Herzog CA, Littrell K, Arko C *et al.* Clinical characteristics of dialysis patients with acute myocardial infarction in the United States: a collaborative project of the United States Renal Data System and the National Registry of Myocardial Infarction. *Circulation* 2007; **116**: 1465–1472.
39. Sosnov J, Lessard D, Goldberg RJ *et al.* Differential symptoms of acute myocardial infarction in patients with kidney disease: a community-wide perspective. *Am J Kidney Dis* 2006; **47**: 378–384.
40. Freda BJ, Tang WH, Van LF *et al.* Cardiac troponins in renal insufficiency: review and clinical implications. *J Am Coll Cardiol* 2002; **40**: 2065–2071.
41. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis* 1998; **32**: S112–S119.
42. Kovesdy CP, Anderson JE. Reverse epidemiology in patients with chronic kidney disease who are not yet on dialysis. *Semin Dial* 2007; **20**: 566–569.
43. Kalantar-Zadeh K, Kilpatrick RD, McAllister CJ *et al.* Reverse epidemiology of hypertension and cardiovascular death in the hemodialysis population: the 58th annual fall conference and scientific sessions. *Hypertension* 2005; **45**: 811–817.
44. Charytan D, Kuntz RE. The exclusion of patients with chronic kidney disease from clinical trials in coronary artery disease. *Kidney Int* 2006; **70**: 2021–2030.
45. Coca SG, Krumholz HM, Garg AX *et al.* Underrepresentation of renal disease in randomized controlled trials of cardiovascular disease. *JAMA* 2006; **296**: 1377–1384.
46. Williams ME, Lacson Jr E, Wang W *et al.* Glycemic control and extended hemodialysis survival in patients with diabetes mellitus: comparative results of traditional and time-dependent Cox model analyses. *Clin J Am Soc Nephrol* 2010; **5**: 1595–1601.
47. Shurraw S, Majumdar SR, Thadhani R *et al.* Glycemic control and the risk of death in 1,484 patients receiving maintenance hemodialysis. *Am J Kidney Dis* 2010; **55**: 875–884.
48. Zager PG, Nikolic J, Brown RH *et al.* 'U' curve association of blood pressure and mortality in hemodialysis patients. *Kidney Int* 1998; **54**: 561–569.
49. Agarwal R. Blood pressure and mortality among hemodialysis patients. *Hypertension* 2010; **55**: 762–768.
50. Isbel NM, Haluska B, Johnson DW *et al.* Increased targeting of cardiovascular risk factors in patients with chronic kidney disease does not improve atheroma burden or cardiovascular function. *Am Heart J* 2006; **151**: 745–753.
51. Jardine MJ, Ninomiya T, Perkovic V *et al.* Aspirin is beneficial in hypertensive patients with chronic kidney disease: a post-hoc subgroup analysis of a randomized controlled trial. *J Am Coll Cardiol* 2010; **56**: 956–965.
52. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002; **324**: 71–86.
53. Tonelli M, Isles C, Curhan GC *et al.* Effect of pravastatin on cardiovascular events in people with chronic kidney disease. *Circulation* 2004; **110**: 1557–1563.
54. Wanner C, Krane V, Marz W *et al.* Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med* 2005; **353**: 238–248.
55. Fellstrom BC, Jardine AG, Schmieder RE *et al.* Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. *N Engl J Med* 2009; **360**: 1395–1407.
56. The SHARP Collaborative Group. *Should We Reduce LDL Cholesterol in Patients with Chronic Kidney Disease? The Results of the Study of Heart and Renal Protection (SHARP)*. American Society of Nephrology Renal Week 2010: Denver CO.
57. Keltai M, Tonelli M, Mann JF *et al.* Renal function and outcomes in acute coronary syndrome: impact of clopidogrel. *Eur J Cardiovasc Prev Rehabil* 2007; **14**: 312–318.
58. Berger AK, Duval S, Krumholz HM. Aspirin, beta-blocker, and angiotensin-converting enzyme inhibitor therapy in patients with end-stage renal disease and an acute myocardial infarction. *J Am Coll Cardiol* 2003; **42**: 201–208.
59. Tsai TT, Maddox TM, Roe MT *et al.* Contraindicated medication use in dialysis patients undergoing percutaneous coronary intervention. *JAMA* 2009; **302**: 2458–2464.
60. Chan MY, Becker RC, Sim LL *et al.* Reperfusion strategy and mortality in ST-elevation myocardial infarction among patients with and without impaired renal function. *Ann Acad Med Singapore* 2010; **39**: 179–184.
61. Bavry AA, Kumbhani DJ, Rassi AN *et al.* Benefit of early invasive therapy in acute coronary syndromes: a meta-analysis of contemporary randomized clinical trials. *J Am Coll Cardiol* 2006; **48**: 1319–1325.
62. Anderson JL, Adams CD, Antman EM *et al.* ACC/AHA 2007 guidelines for the management of patients with unstable angina/non ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2007; **116**: e148–e304.
63. Charytan DM, Wallentin L, Lagerqvist B *et al.* Early angiography in patients with chronic kidney disease: a collaborative systematic review. *Clin J Am Soc Nephrol* 2009; **4**: 1032–1043.
64. Szummer K, Lundman P, Jacobson SH *et al.* Influence of renal function on the effects of early revascularization in non-ST-elevation myocardial infarction: data from the Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART). *Circulation* 2009; **120**: 851–858.
65. Fraker Jr TD, Fihn SD, Gibbons RJ *et al.* 2007 chronic angina focused update of the ACC/AHA 2002 guidelines for the management of patients with chronic stable angina: a Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines Writing Group to develop the focused update of the 2002 guidelines for the management of patients with chronic stable angina. *Circulation* 2007; **116**: 2762–2772.
66. King III SB, Smith Jr SC, Hirshfeld Jr JW *et al.* 2007 focused update of the ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines: 2007 Writing Group to Review New Evidence and Update the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention, Writing on Behalf of the 2005 Writing Committee. *Circulation* 2008; **117**: 261–295.
67. Sedlis SP, Jurkovitz CT, Hartigan PM *et al.* Optimal medical therapy with or without percutaneous coronary intervention for patients with stable coronary artery disease and chronic kidney disease. *Am J Cardiol* 2009; **104**: 1647–1653.
68. Ix JH, Mercado N, Shlipak MG *et al.* Association of chronic kidney disease with clinical outcomes after coronary revascularization: the Arterial Revascularization Therapies Study (ARTS). *Am Heart J* 2005; **149**: 512–519.
69. Liu JY, Birkmeyer NJ, Sanders JH *et al.* Risks of morbidity and mortality in dialysis patients undergoing coronary artery bypass surgery. *Circulation* 2000; **102**: 2973–2977.
70. Charytan DM, Kuntz RE. Risks of coronary artery bypass surgery in dialysis-dependent patients—analysis of the 2001 National Inpatient Sample. *Nephrol Dial Transplant* 2007; **22**: 1665–1671.
71. Cooper WA, O'Brien SM, Thourani VH *et al.* Impact of renal dysfunction on outcomes of coronary artery bypass surgery: results from the Society of Thoracic Surgeons National Adult Cardiac Database. *Circulation* 2006; **113**: 1063–1070.
72. Herzog CA, Ma JZ, Collins AJ. Comparative survival of dialysis patients in the United States after coronary angioplasty, coronary artery stenting, and coronary artery bypass surgery and impact of diabetes. *Circulation* 2002; **106**: 2207–2211.

73. Szczech LA, Reddan DN, Owen WF *et al.* Differential survival after coronary revascularization procedures among patients with renal insufficiency. *Kidney Int* 2001; **60**: 292–299.
74. Wang ZJ, Zhou YJ, Liu YY *et al.* Comparison of drug-eluting stents and coronary artery bypass grafting for the treatment of multivessel coronary artery disease in patients with chronic kidney disease. *Circ J* 2009; **73**: 1228–1234.
75. Herzog CA, Solid CA. Long-term survival and repeat revascularization in U.S. dialysis patients after surgical versus percutaneous coronary intervention. [abstract]. *J Am Soc Nephrol* 2009; **20**: 41A.
76. Ronco C, McCullough P, Anker SD *et al.* Cardio-renal syndromes: report from the consensus conference of the acute dialysis quality initiative. *Eur Heart J* 2010; **31**: 703–711.
77. Schrier RW. Cardiorenal versus renocardiac syndrome: is there a difference? *Nat Clin Pract Nephrol* 2007; **3**: 637.
78. Das M, Aronow WS, McClung JA *et al.* Increased prevalence of coronary artery disease, silent myocardial ischemia, complex ventricular arrhythmias, atrial fibrillation, left ventricular hypertrophy, mitral annular calcium, and aortic valve calcium in patients with chronic renal insufficiency. *Cardiol Rev* 2006; **14**: 14–17.
79. Bagshaw SM, Cruz DN, Aspromonte N *et al.* Epidemiology of cardio-renal syndromes: workgroup statements from the 7th ADQI Consensus Conference. *Nephrol Dial Transplant* 2010; **25**: 1406–1416.
80. US Renal Data System. *USRDS 2004 Annual Data Report*. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases: Bethesda, MD, 2004.
81. Ahmed A, Rich MW, Sanders PW *et al.* Chronic kidney disease associated mortality in diastolic versus systolic heart failure: a propensity matched study. *Am J Cardiol* 2007; **99**: 393–398.
82. McCullough PA. Cardiovascular disease in chronic kidney disease from a cardiologist's perspective. *Curr Opin Nephrol Hypertens* 2004; **13**: 591–600.
83. Guerin AP, Pannier B, Marchais SJ *et al.* Arterial structure and function in end-stage renal disease. *Curr Hypertens Rep* 2008; **10**: 107–111.
84. Redheuil A, Yu WC, Wu CO *et al.* Reduced ascending aortic strain and distensibility: earliest manifestations of vascular aging in humans. *Hypertension* 2010; **55**: 319–326.
85. Cerasola G, Nardi E, Palermo A *et al.* Epidemiology and pathophysiology of left ventricular abnormalities in chronic kidney disease: a review. *J Nephrol* 2011; **24**: 1–10.
86. Puschett JB, Agunanne E, Uddin MN. Emerging role of the bufadienolides in cardiovascular and kidney diseases. *Am J Kidney Dis* 2010; **56**: 359–370.
87. Lopez B, Gonzalez A, Hermida N *et al.* Myocardial fibrosis in chronic kidney disease: potential benefits of torasemide. *Kidney Int Suppl* 2008; **74**: S19–S23.
88. Curtis BM, Parfrey PS. Congestive heart failure in chronic kidney disease: disease-specific mechanisms of systolic and diastolic heart failure and management. *Cardiol Clin* 2005; **23**: 275–284.
89. McIntyre CW. Haemodialysis-induced myocardial stunning in chronic kidney disease—a new aspect of cardiovascular disease. *Blood Purif* 2010; **29**: 105–110.
90. Pecoits-Filho R, Barberato SH. Echocardiography in chronic kidney disease: diagnostic and prognostic implications. *Nephron Clin Pract* 2010; **114**: c242–c247.
91. National Kidney Foundation. K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. *Am J Kidney Dis* 2005; **45**: S1–S153.
92. Foley RN, Parfrey PS, Kent GM *et al.* Serial change in echocardiographic parameters and cardiac failure in end-stage renal disease. *J Am Soc Nephrol* 2000; **11**: 912–916.
93. Zoccali C, Benedetto FA, Mallamaci F *et al.* Left ventricular mass monitoring in the follow-up of dialysis patients: prognostic value of left ventricular hypertrophy progression. *Kidney Int* 2004; **65**: 1492–1498.
94. Iwanaga Y, Miyazaki S. Heart failure, chronic kidney disease, and biomarkers—an integrated viewpoint. *Circ J* 2010; **74**: 1274–1282.
95. Wu AH, Jaffe AS, Apple FS *et al.* National academy of clinical biochemistry laboratory medicine practice guidelines: use of cardiac troponin and B-type natriuretic peptide or N-terminal proB-type natriuretic peptide for etiologies other than acute coronary syndromes and heart failure. *Clin Chem* 2007; **53**: 2086–2096.
96. Roberts MA, Hare DL, Macmillan N *et al.* Serial increased cardiac troponin T predicts mortality in asymptomatic patients treated with chronic haemodialysis. *Ann Clin Biochem* 2009; **46**: 291–295.
97. Apple FS, Murakami MM, Pearce LA *et al.* Predictive value of cardiac troponin I and T for subsequent death in end-stage renal disease. *Circulation* 2002; **106**: 2941–2945.
98. Desai AA, Nissenson A, Chertow GM *et al.* The relationship between laboratory-based outcome measures and mortality in end-stage renal disease: a systematic review. *Hemodial Int* 2009; **13**: 347–359.
99. Dickstein K, Cohen-Solal A, Filippatos G *et al.* ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur Heart J* 2008; **29**: 2388–2442.
100. Davenport A, Anker SD, Mebazaa A *et al.* ADQI 7: the clinical management of the Cardio-Renal syndromes: work group statements from the 7th ADQI consensus conference. *Nephrol Dial Transplant* 2010; **25**: 2077–2089.
101. Cice G, Di BA, D'Isa S *et al.* Effects of telmisartan added to angiotensin-converting enzyme inhibitors on mortality and morbidity in hemodialysis patients with chronic heart failure a double-blind, placebo-controlled trial. *J Am Coll Cardiol* 2010; **56**: 1701–1708.
102. Erdmann E, Lechat P, Verkenne P *et al.* Results from post-hoc analyses of the CIBIS II trial: effect of bisoprolol in high-risk patient groups with chronic heart failure. *Eur J Heart Fail* 2001; **3**: 469–479.
103. Cice G, Ferrara L, D'Andrea A *et al.* Carvedilol increases two-year survival in dialysis patients with dilated cardiomyopathy: a prospective, placebo-controlled trial. *J Am Coll Cardiol* 2003; **41**: 1438–1444.
104. Sikole A, Polenakovic M, Spirovska V *et al.* Analysis of heart morphology and function following erythropoietin treatment of anemic dialysis patients. *Artif Organs* 1993; **17**: 977–984.
105. Parfrey PS, Foley RN, Wittreich BH *et al.* Double-blind comparison of full and partial anemia correction in incident hemodialysis patients without symptomatic heart disease. *J Am Soc Nephrol* 2005; **16**: 2180–2189.
106. Eckardt KU, Scherhag A, Macdougall IC *et al.* Left ventricular geometry predicts cardiovascular outcomes associated with anemia correction in CKD. *J Am Soc Nephrol* 2009; **20**: 2651–2660.
107. Anker SD, Comin CJ, Filippatos G *et al.* Ferric carboxymaltose in patients with heart failure and iron deficiency. *N Engl J Med* 2009; **361**: 2436–2448.
108. Singh AK, Szczech L, Tang KL *et al.* Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med* 2006; **355**: 2085–2098.
109. Pfeffer MA, Burdmann EA, Chen CY *et al.* A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. *N Engl J Med* 2009; **361**: 2019–2032.
110. Chertow GM, Burke SK, Raggi P. Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. *Kidney Int* 2002; **62**: 245–252.
111. Russo D, Miranda I, Ruocco C *et al.* The progression of coronary artery calcification in predialysis patients on calcium carbonate or sevelamer. *Kidney Int* 2007; **72**: 1255–1261.
112. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *Kidney Int Suppl* 2009; **76**: S1–S130.
113. Navaneethan SD, Palmer SC, Vecchio M *et al.* Phosphate binders for preventing and treating bone disease in chronic kidney disease patients. *Cochrane Database Systematic Review* 2011; **2**: CD006023.
114. Davenport A, Cox C, Thuraisingham R. The importance of dialysate sodium concentration in determining interdialytic weight gains in chronic hemodialysis patients: the PanThames Renal Audit. *Int J Artif Organs* 2008; **31**: 411–417.
115. Asci G, Ozkahya M, Duman S *et al.* Volume control associated with better cardiac function in long-term peritoneal dialysis patients. *Perit Dial Int* 2006; **26**: 85–88.
116. Basile C, Lomonte C, Vernaglione L *et al.* The relationship between the flow of arteriovenous fistula and cardiac output in haemodialysis patients. *Nephrol Dial Transplant* 2008; **23**: 282–287.
117. Bock JS, Gottlieb SS. Cardiorenal syndrome: new perspectives. *Circulation* 2010; **121**: 2592–2600.
118. Lee M, Saver JL, Chang KH *et al.* Low glomerular filtration rate and risk of stroke: meta-analysis. *BMJ* 2010; **341**: c4249.
119. Seliger SL, Gillen DL, Longstreth Jr WT *et al.* Elevated risk of stroke among patients with end-stage renal disease. *Kidney Int* 2003; **64**: 603–609.

120. Sozio SM, Armstrong PA, Coresh J *et al.* Cerebrovascular disease incidence, characteristics, and outcomes in patients initiating dialysis: the choices for healthy outcomes in caring for ESRD (CHOICE) study. *Am J Kidney Dis* 2009; **54**: 468–477.
121. Toyoda K, Fujii K, Fujimi S *et al.* Stroke in patients on maintenance hemodialysis: a 22-year single-center study. *Am J Kidney Dis* 2005; **45**: 1058–1066.
122. Boaz M, Smetana S, Weinstein T *et al.* Secondary prevention with antioxidants of cardiovascular disease in endstage renal disease (SPACE): randomised placebo-controlled trial. *Lancet* 2000; **356**: 1213–1218.
123. Toyoda K, Fujii K, Ando T *et al.* Incidence, etiology, and outcome of stroke in patients on continuous ambulatory peritoneal dialysis. *Cerebrovasc Dis* 2004; **17**: 98–105.
124. Yahalom G, Schwartz R, Schwammenthal Y *et al.* Chronic kidney disease and clinical outcome in patients with acute stroke. *Stroke* 2009; **40**: 1296–1303.
125. Ninomiya T, Perkovic V, Gallagher M *et al.* Lower blood pressure and risk of recurrent stroke in patients with chronic kidney disease: PROGRESS trial. *Kidney Int* 2008; **73**: 963–970.
126. Mathew A, Eliasziw M, Devereaux PJ *et al.* Carotid endarterectomy benefits patients with CKD and symptomatic high-grade stenosis. *J Am Soc Nephrol* 2010; **21**: 145–152.
127. Brott TG, Hobson RW, Howard G *et al.* Stenting versus endarterectomy for treatment of carotid-artery stenosis. *N Engl J Med* 2010; **363**: 11–23.
128. Bonati LH, Dobson J, Algra A *et al.* Short-term outcome after stenting versus endarterectomy for symptomatic carotid stenosis: a preplanned meta-analysis of individual patient data. *Lancet* 2010; **376**: 1062–1073.
129. Stoner MC, Abbott WM, Wong DR *et al.* Defining the high-risk patient for carotid endarterectomy: an analysis of the prospective National Surgical Quality Improvement Program database. *J Vasc Surg* 2006; **43**: 285–295.
130. Debing E, Van den Brande P. Chronic renal insufficiency and risk of early mortality in patients undergoing carotid endarterectomy. *Ann Vasc Surg* 2006; **20**: 609–613.
131. Agrawal V, Rai B, Fellows J *et al.* In-hospital outcomes with thrombolytic therapy in patients with renal dysfunction presenting with acute ischaemic stroke. *Nephrol Dial Transplant* 2010; **25**: 1150–1157.
132. Marti-Fabregas J, Bravo Y, Cocho D *et al.* Frequency and predictors of symptomatic intracerebral hemorrhage in patients with ischemic stroke treated with recombinant tissue plasminogen activator outside clinical trials. *Cerebrovasc Dis* 2007; **23**: 85–90.
133. Kannel WB, Abbott RD, Savage DD *et al.* Epidemiologic features of chronic atrial fibrillation: the Framingham study. *N Engl J Med* 1982; **306**: 1018–1022.
134. Wizemann V, Tong L, Satayathum S *et al.* Atrial fibrillation in hemodialysis patients: clinical features and associations with anticoagulant therapy. *Kidney Int* 2010; **77**: 1098–1106.
135. Go AS, Fang MC, Udaltsova N *et al.* Impact of proteinuria and glomerular filtration rate on risk of thromboembolism in atrial fibrillation: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study. *Circulation* 2009; **119**: 1363–1369.
136. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007; **146**: 857–867.
137. Fuster V, Ryden LE, Cannom DS *et al.* ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation* 2006; **114**: e257–e354.
138. Wilmer WA, Magro CM. Calciphylaxis: emerging concepts in prevention, diagnosis, and treatment. *Semin Dial* 2002; **15**: 172–186.
139. Gage BF, Waterman AD, Shannon W *et al.* Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA* 2001; **285**: 2864–2870.
140. Chan KE, Lazarus JM, Thadhani R *et al.* Warfarin use associates with increased risk for stroke in hemodialysis patients with atrial fibrillation. *J Am Soc Nephrol* 2009; **20**: 2223–2233.
141. Chou CY, Kuo HL, Wang SM *et al.* Outcome of atrial fibrillation among patients with end-stage renal disease. *Nephrol Dial Transplant* 2010; **25**: 1225–1230.
142. Yang F, Chou D, Schweitzer P *et al.* Warfarin in haemodialysis patients with atrial fibrillation: what benefit? *Europace* 2010; **12**: 1666–1672.
143. Pisters R, Lane DA, Nieuwlaat R *et al.* A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest* 2010; **138**: 1093–1100.
144. Gage BF, Yan Y, Milligan PE *et al.* Clinical classification schemes for predicting hemorrhage: results from the National Registry of Atrial Fibrillation (NRAF). *Am Heart J* 2006; **151**: 713–719.
145. Elliott MJ, Zimmerman D, Holden RM. Warfarin anticoagulation in hemodialysis patients: a systematic review of bleeding rates. *Am J Kidney Dis* 2007; **50**: 433–440.
146. Chan KE, Lazarus JM, Thadhani R *et al.* Anticoagulant and antiplatelet usage associates with mortality among hemodialysis patients. *J Am Soc Nephrol* 2009; **20**: 872–881.
147. Go AS, Hylek EM, Phillips KA *et al.* Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA* 2001; **285**: 2370–2375.
148. Eikelboom JW, Weitz JI. New anticoagulants. *Circulation* 2010; **121**: 1523–1532.
149. Maisel WH. Left atrial appendage occlusion—closure or just the beginning? *N Engl J Med* 2009; **360**: 2601–2603.
150. Boehringer Ingelheim Pharmaceuticals I. Paradaxa (package insert). Ridgefield, CT, USA, 2010.
151. Connolly SJ, Ezekowitz MD, Yusuf S *et al.* Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009; **361**: 1139–1151.
152. Boehringer Ingelheim Pharmaceuticals I. Advisory Committee Briefing Document: Dabigatran Etexilate (DE). 2010. Available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM226009.pdf. Accessed 25 February 2011.
153. Stangier J, Rathgen K, Stahle H *et al.* Influence of renal impairment on the pharmacokinetics and pharmacodynamics of oral dabigatran etexilate: an open-label, parallel-group, single-centre study. *Clin Pharmacokinet* 2010; **49**: 259–268.
154. Marinigh R, Lane DA, Lip GY. Severe renal impairment and stroke prevention in atrial fibrillation: implications for thromboprophylaxis and bleeding risk. *J Am Coll Cardiol* 2011; **57**: 1339–1348.
155. O'Hare AM, Glidden DV, Fox CS *et al.* High prevalence of peripheral arterial disease in persons with renal insufficiency: results from the National Health and Nutrition Examination Survey 1999–2000. *Circulation* 2004; **109**: 320–323.
156. Lash JP, Go AS, Appel LJ *et al.* Chronic Renal Insufficiency Cohort (CRIC) Study: baseline characteristics and associations with kidney function. *Clin J Am Soc Nephrol* 2009; **4**: 1302–1311.
157. O'Hare A, Johansen K. Lower-extremity peripheral arterial disease among patients with end-stage renal disease. *J Am Soc Nephrol* 2001; **12**: 2838–2847.
158. Miskulin D, Bragg-Gresham J, Gillespie BW *et al.* Key comorbid conditions that are predictive of survival among hemodialysis patients. *Clin J Am Soc Nephrol* 2009; **4**: 1818–1826.
159. O'Hare AM, Vittinghoff E, Hsia J *et al.* Renal insufficiency and the risk of lower extremity peripheral arterial disease: results from the Heart and Estrogen/Progestin Replacement Study (HERS). *J Am Soc Nephrol* 2004; **15**: 1046–1051.
160. O'Hare AM, Hsu CY, Bacchetti P *et al.* Peripheral vascular disease risk factors among patients undergoing hemodialysis. *J Am Soc Nephrol* 2002; **13**: 497–503.
161. Boaz M, Weinstein T, Matas Z *et al.* Peripheral vascular disease and serum phosphorus in hemodialysis: a nested case-control study. *Clin Nephrol* 2005; **63**: 98–105.
162. Cooper BA, Penne EL, Bartlett LH *et al.* Protein malnutrition and hypoalbuminemia as predictors of vascular events and mortality in ESRD. *Am J Kidney Dis* 2004; **43**: 61–66.
163. Manns BJ, Burgess ED, Hyndman ME *et al.* Hyperhomocyst(e)inemia and the prevalence of atherosclerotic vascular disease in patients with end-stage renal disease. *Am J Kidney Dis* 1999; **34**: 669–677.
164. Makisalo H, Lepantalo M, Halme L *et al.* Peripheral arterial disease as a predictor of outcome after renal transplantation. *Transpl Int* 1998; **11**(Suppl 1): S140–S143.
165. Ishii H, Kumada Y, Toriyama T *et al.* Cilostazol improves long-term patency after percutaneous transluminal angioplasty in hemodialysis patients with peripheral artery disease. *Clin J Am Soc Nephrol* 2008; **3**: 1034–1040.

166. Abbas AE, Goodman LM, Timmis R *et al.* Predictors of poor outcome in female patients undergoing endovascular intervention. *J Interv Cardiol* 2010; **23**: 401–410.
167. Jaar BG, Astor BC, Berns JS *et al.* Predictors of amputation and survival following lower extremity revascularization in hemodialysis patients. *Kidney Int* 2004; **65**: 613–620.
168. Zannetti S, L'Italien GJ, Cambria RP. Functional outcome after surgical treatment for intermittent claudication. *J Vasc Surg* 1996; **24**: 65–73.
169. Reddan DN, Marcus RJ, Owen Jr WF *et al.* Long-term outcomes of revascularization for peripheral vascular disease in end-stage renal disease patients. *Am J Kidney Dis* 2001; **38**: 57–63.
170. Eggers PW, Gohdes D, Pugh J. Nontraumatic lower extremity amputations in the Medicare end-stage renal disease population. *Kidney Int* 1999; **56**: 1524–1533.
171. Speckman RA, Frankenfield DL, Roman SH *et al.* Diabetes is the strongest risk factor for lower-extremity amputation in new hemodialysis patients. *Diabetes Care* 2004; **27**: 2198–2203.
172. O'Hare AM, Feinglass J, Sidawy AN *et al.* Impact of renal insufficiency on short-term morbidity and mortality after lower extremity revascularization: data from the Department of Veterans Affairs' National Surgical Quality Improvement Program. *J Am Soc Nephrol* 2003; **14**: 1287–1295.
173. Ramdev P, Rayan SS, Sheahan M *et al.* A decade experience with infrainguinal revascularization in a dialysis-dependent patient population. *J Vasc Surg* 2002; **36**: 969–974.
174. Rith-Najarian S, Gohdes D. Preventing amputations among patients with diabetes on dialysis. *Diabetes Care* 2000; **23**: 1445–1446.
175. Myerburg RJ. Cardiac arrest and sudden cardiac death. In: Douglas P. Zipes, Peter Libby, Robert O. Bonow, Eugene Braunwald (eds). *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*. Elsevier Saunders: Philadelphia, PA, 2005.
176. Pratt CM, Greenway PS, Schoenfeld MH *et al.* Exploration of the precision of classifying sudden cardiac death. Implications for the interpretation of clinical trials. *Circulation* 1996; **93**: 519–524.
177. US Renal Data System. *USRDS 2005 Annual Data Report: Atlas of End-Stage Renal Disease in the United States*. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases: Bethesda, MD, 2005: 140–143.
178. Herzog CA. Can we prevent sudden cardiac death in dialysis patients? *Clin J Am Soc Nephrol* 2007; **2**: 410–412.
179. US Renal Data System. *USRDS 2010 Annual Data Report: Atlas of Chronic Kidney Disease & End-Stage Renal Disease in the United States*. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases: Bethesda, MD, 2010.
180. Pun PH, Lehrich RW, Smith SR *et al.* Predictors of survival after cardiac arrest in outpatient hemodialysis clinics. *Clin J Am Soc Nephrol* 2007; **2**: 491–500.
181. Karnik JA, Young BS, Lew NL *et al.* Cardiac arrest and sudden death in dialysis units. *Kidney Int* 2001; **60**: 350–357.
182. Lai M, Hung K, Huang J *et al.* Clinical findings and outcomes of intra-hemodialysis cardiopulmonary resuscitation. *Am J Nephrol* 1999; **19**: 468–473.
183. Moss AH, Holley JL, Upton MB. Outcomes of cardiopulmonary resuscitation in dialysis patients. *J Am Soc Nephrol* 1992; **3**: 1238–1243.
184. Eknoyan G, Beck GJ, Cheung AK *et al.* Effect of dialysis dose and membrane flux in maintenance hemodialysis. *N Engl J Med* 2002; **347**: 2010–2019.
185. Wanner C, Krane V, Marz W *et al.* Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med* 2005; **353**: 238–248.
186. Parekh RS, Plantinga LC, Kao WH *et al.* The association of sudden cardiac death with inflammation and other traditional risk factors. *Kidney Int* 2008; **74**: 1335–1342.
187. Wang AY, Lam CW, Chan IH *et al.* Sudden cardiac death in end-stage renal disease patients: a 5-year prospective analysis. *Hypertension* 2010; **56**: 210–216.
188. Goldenberg I, Moss AJ, McNitt S *et al.* Relations among renal function, risk of sudden cardiac death, and benefit of the implanted cardiac defibrillator in patients with ischemic left ventricular dysfunction. *Am J Cardiol* 2006; **98**: 485–490.
189. Saxon LA, Bristow MR, Boehmer J *et al.* Predictors of sudden cardiac death and appropriate shock in the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Trial. *Circulation* 2006; **114**: 2766–2772.
190. Pun PH, Smarz TR, Honeycutt EF *et al.* Chronic kidney disease is associated with increased risk of sudden cardiac death among patients with coronary artery disease. *Kidney Int* 2009; **76**: 652–658.
191. Deo R, Lin F, Vittinghoff E *et al.* Kidney dysfunction and sudden cardiac death among women with coronary heart disease. *Hypertension* 2008; **51**: 1578–1582.
192. Deo R, Sotoodehnia N, Katz R *et al.* Cystatin C and sudden cardiac death risk in the elderly. *Circ Cardiovasc Qual Outcomes* 2010; **3**: 159–164.
193. Rosenstock L, Olsen J. Firefighting and death from cardiovascular causes. *N Engl J Med* 2007; **356**: 1261–1263.
194. Herzog CA, Mangrum JM, Passman R. Sudden cardiac death and dialysis patients. *Semin Dialysis* 2008; **21**: 300–307.
195. Parfrey PS, Foley RN. The clinical epidemiology of cardiac disease in chronic renal failure. *J Am Soc Nephrol* 1999; **10**: 1606–1615.
196. Takeda K, Harada A, Okuda S *et al.* Sudden death in chronic dialysis patients. *Nephrol Dial Transplant* 1997; **12**: 952–955.
197. Huikuri HV, Castellanos A, Myerburg RJ. Sudden death due to cardiac arrhythmias. *N Engl J Med* 2001; **345**: 1473–1482.
198. Bleyer AJ, Hartman J, Brannon PC *et al.* Characteristics of sudden death in hemodialysis patients. *Kidney Int* 2006; **69**: 2268–2273.
199. Davis TR, Young BA, Eisenberg MS *et al.* Outcome of cardiac arrests attended by emergency medical services staff at community outpatient dialysis centers. *Kidney Int* 2008; **73**: 933–939.
200. Lafrance JP, Nolin L, Senecal L *et al.* Predictors and outcome of cardiopulmonary resuscitation (CPR) calls in a large haemodialysis unit over a seven-year period. *Nephrol Dial Transplant* 2006; **21**: 1006–1012.
201. Bleyer AJ, Russell GB, Satko SG. Sudden and cardiac death rates in hemodialysis patients. *Kidney Int* 1999; **55**: 1553–1559.
202. Pun PH, Lehrich RW, Honeycutt EF *et al.* Modifiable risk factors associated with sudden cardiac arrest within hemodialysis clinics. *Kidney Int* 2011; **79**: 218–227.
203. Kimmel PL, Miller G, Mendelson WB. Sleep apnea syndrome in chronic renal disease. *Am J Med* 1989; **86**: 308–314.
204. Zoccali C, Mallamaci F, Tripepi G. Nocturnal hypoxemia predicts incident cardiovascular complications in dialysis patients. *J Am Soc Nephrol* 2002; **13**: 729–733.
205. Paoletti E, Specchia C, Di MG *et al.* The worsening of left ventricular hypertrophy is the strongest predictor of sudden cardiac death in haemodialysis patients: a 10 year survey. *Nephrol Dial Transplant* 2004; **19**: 1829–1834.
206. Drechsler C, Krane V, Winkler K *et al.* Changes in adiponectin and the risk of sudden death, stroke, myocardial infarction, and mortality in hemodialysis patients. *Kidney Int* 2009; **76**: 567–575.
207. Chan KE, Lazarus JM, Hakim RM. Digoxin associates with mortality in ESRD. *J Am Soc Nephrol* 2010; **21**: 1550–1559.
208. Herzog CA, Li S, Weinhandl ED *et al.* Survival of dialysis patients after cardiac arrest and the impact of implantable cardioverter defibrillators. *Kidney Int* 2005; **68**: 818–825.
209. Charytan DM, Patrick AR, Liu J *et al.* Trends in the use and outcomes of implantable cardioverter defibrillators in patients undergoing dialysis in the United States. *Am J Kidney Dis* 2011. doi:10.1053/j.ajkd.2011.03.026 (e-pub ahead of print).
210. Dasgupta A, Montalvo J, Medendorp S *et al.* Increased complication rates of cardiac rhythm management devices in ESRD patients. *Am J Kidney Dis* 2007; **49**: 656–663.
211. Aggarwal A, Wang Y, Rumsfeld JS *et al.* Clinical characteristics and in-hospital outcome of patients with end-stage renal disease on dialysis referred for implantable cardioverter-defibrillator implantation. *Heart Rhythm* 2009; **6**: 1565–1571.
212. Abraham WT, Adamson PB, Bourge RC *et al.* Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. *Lancet* 2011; **377**: 658–666.