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The cardiovascular–dialysis nexus: the transition to dialysis is a treacherous time for the heart

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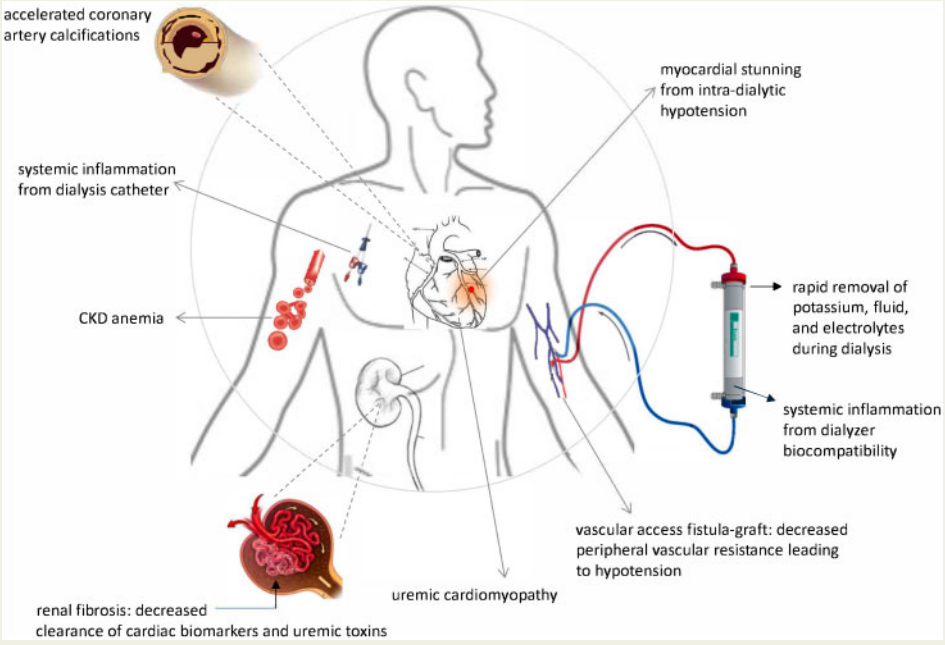
Chronic kidney disease (CKD) patients require dialysis to manage the progressive complications of uraemia. Yet, many physicians and patients do not recognize that dialysis initiation, although often necessary, subjects patients to substantial risk for cardiovascular (CV) death. While most recognize CV mortality risk approximately doubles with CKD the new data presented here show that this risk spikes to >20 times higher than the US population average at the initiation of chronic renal replacement therapy, and this elevated CV risk continues through the first 4 months of dialysis. Moreover, this peak reflects how dialysis itself changes the pathophysiology of CV disease and transforms its presentation, progression, and prognosis. This article reviews how dialysis initiation modifies the interpretation of circulating biomarkers, alters the accuracy of CV imaging, and worsens prognosis. We advocate a multidisciplinary approach and outline the issues practitioners should consider to optimize CV care for this unique and vulnerable population during a perilous passage.

Graphical Abstract



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Keywords End-stage renal disease • Sudden death • Haemodialysis initiation

The initiation of dialysis superimposes new CV challenges on the substrate of chronic kidney disease (CKD). These factors include increased myocardial oxygen demand, for example, due to access-associated increase in cardiac output, and hypotension due to volume shifts during dialysis. Intra-dialytic hypotension can also decrease oxygen supply to the myocardium, particularly a lower diastolic pressure head for coronary artery perfusion augmented by arteriosclerosis affecting both the intimal and medial layers of conduit arteries. Hypotension superimposed on macro- and micro-vascular disease can lead to the myocardial stunning documented during and immediately post-dialysis. In addition, dialysis involves inflammatory insults from innate immune activation due to contact with the dialysis membrane and catheters. Rapid fluid and electrolyte shifts during dialysis can predispose towards arrhythmia, contributing to the augmented sudden death that follows the initiation of dialysis. All of these new factors related to dialysis initiation superimpose upon the chronic anaemia, the uraemic cardiomyopathy, and uraemic toxins associated with CKD.

Introduction

Worldwide, more than 700 000 patients will start chronic dialysis this year, and this number is expected to double in the next 20 years.[1] Both the European Society of Cardiology and American Heart Association Guidelines recognize chronic kidney disease (CKD) as a marker of heart disease, but neither articulates that starting dialysis for end-stage kidney disease (ESKD) may be a period of high risk because the cardiovascular (CV) death rate unexpectedly surges in the first 4 months of dialysis therapy, as demonstrated by the new data presented here (*Figure 1*).[3–5]

Nephrologists only recently recognized this spike in CV mortality because traditional studies followed patients after Day 90 when patients become Medicare eligible. Other practitioners who co-manage these vulnerable patients may not share this awareness of 'the spike' mandating its broader recognition. Starting dialysis entails a major shift in the pathophysiology of disease that changes the clinical CV manifestations of heart disease that underlies this peak in CV mortality.[4,6]

This review article summarizes how this pathophysiological shift changes the presentation, diagnosis, and management of CV disease the moment CKD patients start dialysis.

We advocate a multi-disciplinary approach to mitigate the spike in CV mortality precipitated by starting chronic dialysis, concordant with a recent Kidney Disease Improving Global Outcomes (KDIGO) Controversies Conference.[7]

Epidemiology surrounding the start of dialysis

Almost 60% of the US population will develop CKD (*Table 1*) with consequently enhanced CV mortality.[8,9] The lifetime risk of ESKD is 3.6%, which is higher than death from suicide, automobile accidents, firearms, or cancer of either breast, colon, or prostate.[8,10,11]

CV mortality during the first 4 months following the start of chronic dialysis exceeds by 20-fold that of age-matched individuals in the general US population.[3,4,6,12,13] We present new data in *Figure 1* illustrating this critical spike in mortality when dialysis begins where the combined rate of CV death and sudden cardiac death (SCD) is 14 events per 100 patient-years during these first 4 months. CV/SCD mortality peaks during Month 2 of dialysis, yielding an annualized rate of 20.4 deaths per 100 patient-years, then subsequently plateaus to a steady state of 7 deaths per 100 patient-years at Month 8. The combined CV and SCD death risk in the first 4 months is remarkably 50% higher than Stage 5 CKD, an equally comorbid population who are not yet on dialysis but quickly approaching ESKD.

Dialysis initiation changes the causes of CV death. Ischaemic heart disease causes the majority of deaths in CKD. Once dialysis starts, SCD risk doubles and becomes the most common cause of death, suggesting a shift in mechanisms (*Figure 1*).[14] The rate of SCD exceeds by 3.5-fold that of pre-dialysis CKD 4 patients. Myocardial infarction (MI) also peaks during this period (*Figure 2*). The incidence of MI is 0.27 events per 100 patient-years in the general population, ranges from 1 to 2 events per 100 patient-years in mild CKD, increases to >3 events per 100 patient-years on dialysis, and 'spikes' to 34 events per 100 patient-years in the first month of chronic renal replacement therapy, which is >11 times higher than pre-dialysis CKD 4 patients (*Figure 2*).[15,16] Stroke rates parallel those of MI possibly from repeated cerebral hypoperfusion, anticoagulation, and inflammation from dialysis.[17] The incident stroke and transient ischaemic attack rate in the year before dialysis of 0.25 event per 100 patient-months increases 7-fold on dialysis initiation and then declines in the following month.[17]

Compared to the general population, both ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI) increase in CKD. While STEMI rates remain flat around 0.2 events per 100 patient-years for all levels of CKD, NSTEMI rates increase as glomerular filtration rate (GFR) decreases, suggesting that the presentation, mechanisms, and diagnosis of acute coronary syndrome (ACS) change during the progression of renal dysfunction.[18] Moreover, kidney disease impairs the clearance of biomarkers of cardiac injury e.g. troponin, perhaps heightening the detection of NSTEMI.[19]

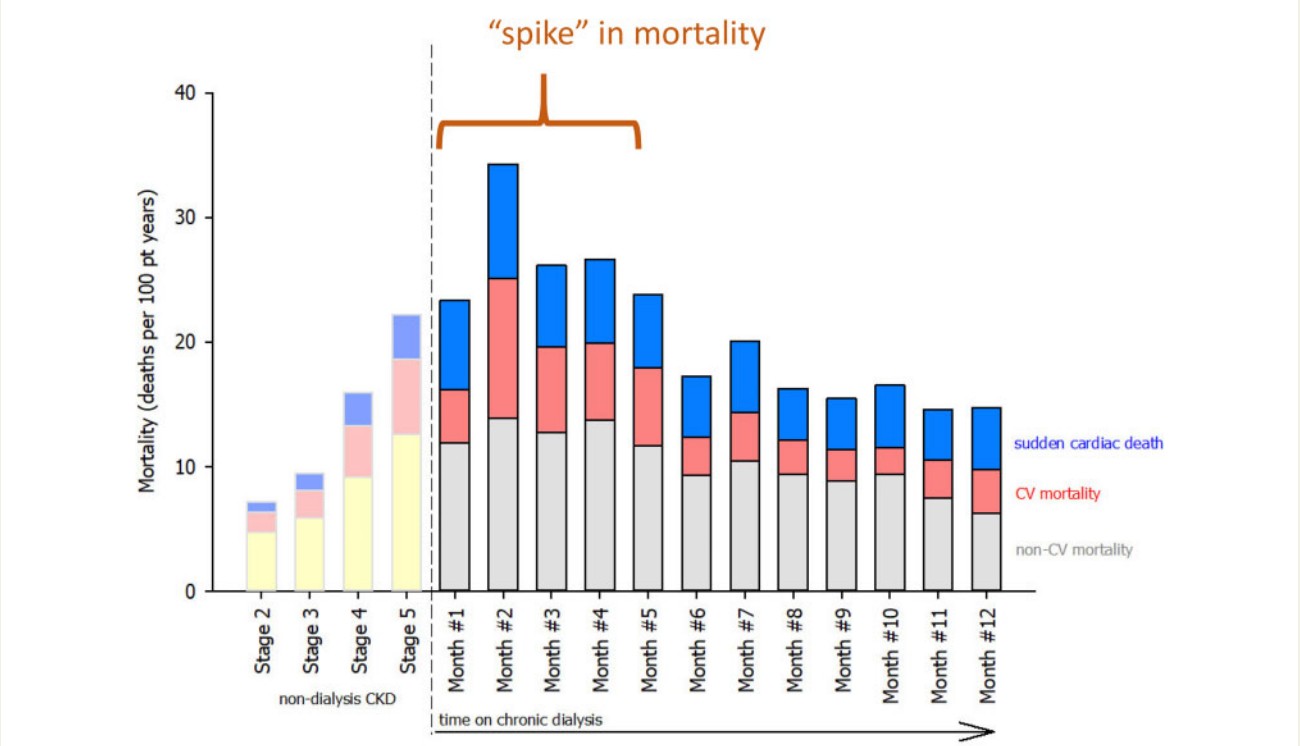

Figure 1 Standardized mortality rates in the chronic kidney disease and dialysis population, Medicare 5% CKD sample (2011–2014). Our analysis of a 5% random sample of Medicare claims highlights 'the spike' in cardiovascular mortality that occurs when dialysis starts that extends into the first 4 months of chronic dialysis. Direct standardized rates for age, gender, and race were calculated as per methods outlined by Ahmad *et al.*[2] See Supplementary material online for details regarding the generation of this figure.

Presentation: detection of cardiovascular disease in patients starting dialysis

ESKD complicates the presentation of heart disease for patients starting dialysis by impairing the performance of biomarker assays, decreasing the sensitivity of non-invasive testing, and increasing the risk of procedural complication. Dialysis patients with coronary artery disease (CAD) may not exhibit typical symptoms due to coexistent diabetes, uraemic neuropathy, and limited exercise capacity. Overall, these challenges may hinder accurate diagnoses, delay vital therapies, and complicate testing for these patients at the very time of greatest need for optimal CV care.

Imaging modalities

Over 50% of patients starting dialysis have angiographically obstructive CAD, with multi-vessel involvement in 25–40%.[20,21] Dobutamine stress ECHO (DSE) predicts severe CAD in dialysis patients (*Table 2*) even though ~50% of patients starting dialysis have left ventricular (LV) hypertrophy (LVH) that blunts the detection of wall-motion abnormalities.[22,23] Myocardial perfusion imaging (MPI) has lower sensitivity in dialysis patients than in the general population due to reduced coronary vasodilatory response and balanced ischaemia because of multi-vessel involvement (*Table 2*).[24–26] Frequent baseline electrocardiogram (ECG) abnormalities and inadequate functional capacity limit the predictive ability of exercise electrocardiography (sensitivity = 35%, specificity = 60%) in the dialysis population.[27] Only two small dialysis studies evaluate the performance of coronary artery calcification (CAC) scoring for detecting CAD: Rosario *et al.* reported a sensitivity = 0.64, specificity = 0.65.[24,28] Winther *et al.*[29] reported a sensitivity = 0.67, specificity = 0.77 (27) Similarly, data on coronary computed tomography angiography is sparse: 93% sensitivity and 63% specificity in 138 advanced CKD patients who underwent concurrent coronary arteriography.

DSE, MPI, or CAC testing in patients starting dialysis can effectively risk stratify subjects for future CAD events.[30] However, results from ISCHEMIA-CKD indicate that advanced CKD and dialysis patients with a positive non-invasive stress test do not benefit from angiography/revascularization additional to optimal medical therapy; moreover, angiography/revascularization causes harm where the risk of stroke was 3.76 higher than the medication alone group.[31] A surprising 31.1% of angiograms showed no obstructive lesions, suggesting that epicardial coronary artery stenoses alone do not account for excess mortality in end-stage renal disease. Thus, these invasive procedures generally should be reserved for severe cases where patients become refractory to maximal medical management, have

decompensated heart failure, with recent ACS, or have an LV ejection fraction < 35% who were excluded from the ISCHEMIA-CKD trial.

For severe and refractory symptomatic patients approaching dialysis [estimated GFR (eGFR) < 30 mL/min], a positive DSE or MPI can present a clinical dilemma. In the ISCHEMIA-CKD trial, angiogram +/- revascularization resulted in 7.9% risk for contrast nephropathy and 48% risk increase in death and dialysis initiation when compared to medical treatment alone. The risk of dialysis initiation after coronary artery bypass grafting (CABG) was 11–12.5%. Thus, invasive management can provoke contrast-induced nephropathy and CABG can hasten dialysis start and premature exposure to the CV spike. Risk-scoring tools for contrast-induced acute kidney injury and dialysis can inform decisions about the risk vs. benefit of invasive procedures (*Table 3*).[32]

Table 1 Chronic kidney disease classification and grade

CKD grade	Classification	Glomerular filtration rate (mL/min)
Stage 1–2	Mild	60–89
Stage 3	Moderate	30–59
Stage 4	Severe	15–29
Stage 5	Kidney failure	<15
Dialysis	End-stage renal failure	Dialysis

Circulating biomarkers

Troponin concentrations increase immediately after haemodialysis (HD), suggesting that the procedure itself can induce haemoconcentration and/or cardiac injury from rapid fluid removal and coronary hypoperfusion in a population with predisposing obstructive or microvascular CAD[33,34]; furthermore, both cardiac troponin T and cardiac troponin I fragments depend on renal clearance, which may contribute to raised serum troponin concentrations due to myocardial injury.[19] These mechanisms may also contribute to the 'spike' in MI, NSTEMI, and stroke following dialysis initiation (*Figure 2*).[17]

Newer fifth-generation troponin testing (hs-TNI) detects levels 100-fold lower than traditional assays, which complicates the diagnostic interpretation of a positive troponin for MI in dialysis patients.[35] Asymptomatic dialysis patients already have elevated hs-TNI (>99th percentile values) from increased ventricular pressure, coronary microvascular dysfunction, anaemia, hypotension, and myocardial uraemic toxicity with impaired renal hs-TNI clearance.[34,36] These mechanisms decrease the test specificity for ACS in this population.[37,38] (*Table 2*). As such, The 2018 Universal Definition of MI[39] requires a > 20% increase in serial hs-TNI values in symptomatic dialysis patients with EKG changes for ACS, although this strategy has not undergone rigorous testing in trials.[40–44]

Patients starting dialysis have high proBNP and B-type natriuretic peptide (BNP) levels due to reduced renal clearance, prevalent LVH, and fluid retention from advanced CKD. ProBNP (more than BNP) are cleared by the kidney and dialysis, further increasing inter- and intra-patient variability,[45,46] such that establishing cut-off values for

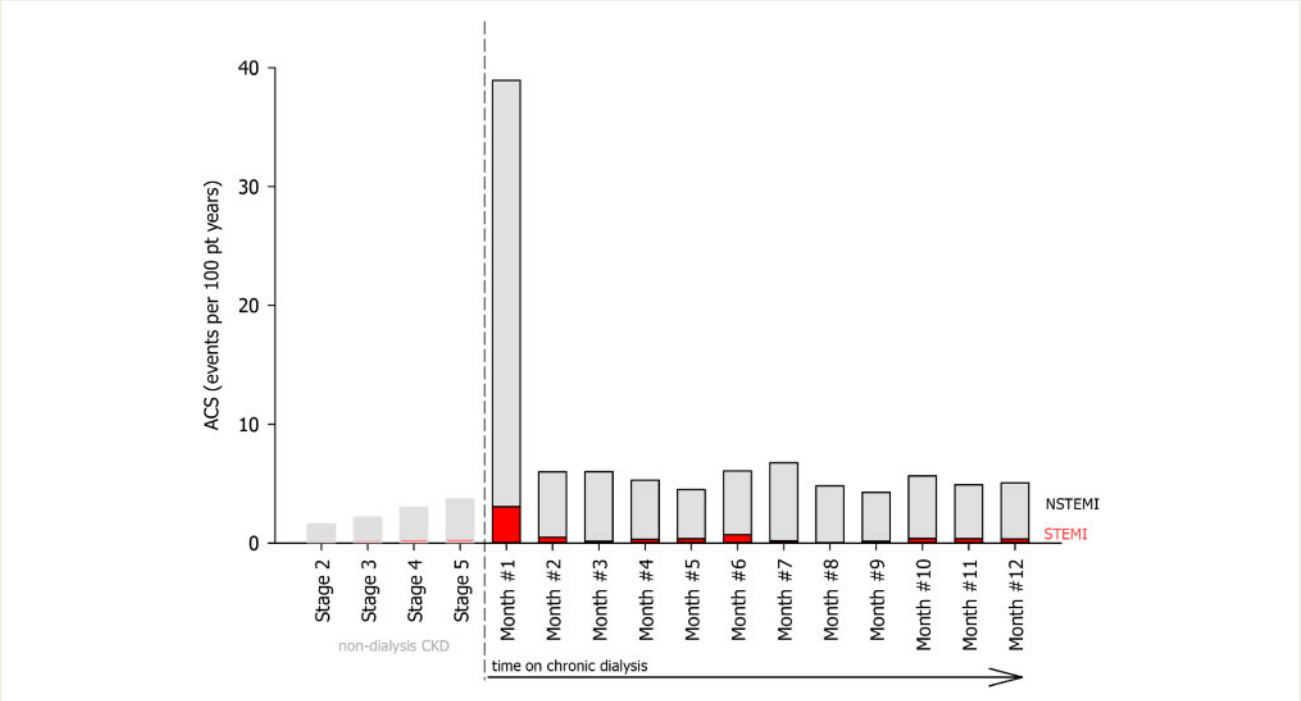

Figure 2 Standardized acute coronary syndrome rates in the chronic kidney disease and dialysis population, Medicare 5% CKD sample (2011–2014). Our analysis of a 5% random sample of Medicare claims shows the rate of myocardial infarction, while is already heightened in chronic kidney disease, and peaks right after dialysis starts. Direct standardized rates for age, gender, and race were calculated as per methods outlined by Ahmad *et al.*[2] See supplementary material for details regarding the generation of this figure.

Table 2 Performance characteristics of fifth-generation hs-TNI assay, dobutamine stress ECHO, and myocardial perfusion scintigraphy CAD in the dialysis and general population

	Sensitivity		specificity	
	Dialysis population	General population	Dialysis population	General population
Fifth-generation hs-TNI (27)	0.41	0.93	1.00	0.94
Dobutamine stress ECHO (35)	0.79	0.85	0.89	0.77
Myocardial perfusion scintigraphy (35)	0.74	0.87	0.70	0.64

these biomarkers remains difficult, limiting their clinical utility in dialysis patients.[47]

Pathophysiology: the mechanisms of cardiovascular disease shift when dialysis starts

Myocardial stunning

Haemodialysis is associated with intra-dialytic myocardial stunning.[48] In 70 HD patients, echocardiograms performed before, during, and after HD determined the direct effect of dialysis on cardiac function. Surprisingly, 64% of patients had new or worsening regional wall motion abnormalities (RWMA) during dialysis, indicating that the procedure can precipitate regional ischaemia. Furthermore, such RWMA associated with death or a major CV event 1 year later.[48] In a follow-up study, 12 patients underwent intradialytic cardiac magnetic resonance scanning, which showed immediate worsening of LV function (cardiac and stroke volume index), peak systolic circumferential/longitudinal strain, and decreasing myocardial perfusion during HD.[49] These studies link HD to cardiac dysfunction.

Other mechanisms also contribute to the excess CV death with dialysis initiation. HD rapidly removes fluid, potassium, calcium, bicarbonate, and magnesium from the intravascular space. Electrolyte shifts can trigger arrhythmias and drive excess SCD peri-dialysis. Excessive ultrafiltration decreases intravascular volume, reducing coronary perfusion, while the extracorporeal circuit subsumes approximately one unit of blood, reducing the already impaired oxygen-carrying capacity caused by the chronic anaemia commonly encountered in ESKD. Further, the creation of an arterio-venous shunt for dialysis access also reduces total peripheral resistance and diastolic pressure that drives coronary perfusion, and increases cardiac output, increasing myocardial oxygen demand.[50,51] The high prevalence of obstructive coronary plaques further impedes coronary blood flow.[52] In non-CKD patients, cardiac injury doubles and CV mortality increases 30% with a diastolic blood pressure (DBP) <60 mmHg relative to 80–89 mmHg.[53] Twenty percent of dialysis patients have a pre-dialysis DBP < 65 and an additional 17% of patients will become hypotensive during HD.[54,55] Indeed, low DBP or intra-dialytic hypotension are associated with increased CV mortality.[54–56] Thus, aggressive blood pressure (BP) targets (e.g. 120/70 mmHg) derived from landmark non-dialysis trials such as SPRINT may not apply during dialysis.[57] In fact, a dialysis randomized controlled trial (RCT) showed the opposite: lowering pre-dialysis BP to 143/74 increased CV events by 18% when compared to a pre-dialysis BP of 156/82 mmHg.[58] These data collectively suggest that BP targets differ in dialysis, and highlight the pitfalls of extrapolating results of general outcome trials to patients starting dialysis.

Inflammation

Systemic inflammation links strongly to atherosclerosis and subsequent CV events in both the general and dialysis population.[59,60] Thirty to sixty percent of US and European dialysis patients have C-reactive protein (CRP) levels > 3 mg/L, a level designated as high risk.[61,62] Exceeding this cut-off point is associated with a doubling of CV mortality risk in the general population.[63] Contact of blood with the dialysis membrane can trigger innate immune activation. A single HD session recirculates 100 litres of patient whole blood against 1.2 m^2 of polymer fibre membrane and 200 litres of pre-mixed dialysate. Indeed, *in vitro* and *in vivo* studies suggest the large interface of human blood against an engineered membrane incites an inflammatory reaction through immune cell stimulation, complement activation, and cytokine generation.[64–67] Similarly, peritoneal dialysis patients expose their abdominal cavity to 8–16 L of dialysate daily that contains plasticizers, which incite a direct inflammatory response.[68] Dialysate from poorly processed municipal water can contain bacterial products including endotoxins that can cross the dialysis membrane into the patient's bloodstream to activate monocytes that induce inflammation.[68] In addition, 80% of patients in the USA initiate chronic dialysis using a catheter as their vascular access.[69] Multiple studies show a statistically significant association between elevated CRP levels and catheter use in dialysis patients.[70] Both anti-inflammatory and LDL-lowering effects of statins might decrease the risk of coronary events in CKD patients, but we lack evidence of their efficacy once patients start dialysis. In the Study of Heart and Renal Protection (SHARP), simvastatin with ezetimibe decreased MIs, strokes, and arterial revascularization procedures in CKD, but not in dialysis patients.[71] Two separate dialysis trials also demonstrated the lack of improved CV and ACS outcomes with LDL lowering.[72–74] The failure of statins to improve outcomes in ESKD in SHARP and other trials may reflect the distinct pathophysiology of CV events and/or the advanced state of arterial disease in this population. While MIs account for many CKD deaths, statins do not directly prevent arrythmias, which cause much mortality in dialysis patients.[75]

Anti-inflammatory therapies to prevent CV complications in the dialysis population remains in its infancy. Moderate CKD patients randomized to an antibody that neutralizes the pro-inflammatory cytokine interleukin-1β, canakinumab, significantly reduced their risk of major adverse CV events by 18% compared to placebo.[76] The

Table 3 Risk prediction of contrast-induced nephropathy after percutaneous coronary intervention[32]

Risk factor	Scoring
Hypotension • Systolic pressure <80 mmHg for >1 h, AND • Patient requires inotropic support or an intra-aortic balloon pump within 24 h after the procedure	5 points
Use of intra-aortic balloon pump	5 points
Heart failure: • New York Heart Association class III or IV, OR • History of pulmonary oedema	5 points
Elderly: >75 years old	4 points
Anaemia: haematocrit <39% for men or <36% for women	3 points
Diabetes	3 points
Volume of contrast medium	1 point per 100 cc
Serum creatinine level >1.5 mg/dL (133 µmol/L) OR Estimated GFR <60 mL/min/1.73 m^2 body surface area	4 points 2 points for GFR = 40–60 mL/min 4 points for GFR = 20–39 mL/min 6 points for GFR < 20 mL/min

Total score	Risk of contrast-induced nephropathy[a]	Risk of dialysis
≤5	7.5%	0.04%
6–10	14%	0.12%
11–16	26.1%	1.09%
≥16	57.3%	12.6%

[a]>25% or >5 mg/dL (44 umol/L) increase in serum creatinine.

beneficial effect was most pronounced [hazard ratio (HR) = 0.68] in those whose hsCRP fell to <2 mg/L on canakinumab. These data support further trials of anti-inflammatory treatments in patients starting dialysis.

Vascular calcification

Coronary and other arterial calcification may contribute to CV disease and are highly prevalent in patients starting dialysis. While only 10.1% of the Multi-Ethnic Study of Atherosclerosis population has CAC, more than 70% of patients starting dialysis will have CAC.[77–79] In dialysis patients, CAC is associated with increased mortality and diastolic dysfunction by echocardiography.[80,81] Calciphylaxis occurs almost exclusively in the dialysis population when microvascular calcification of the dermo-hypodermic arterioles leads to necrotic skin lesion.[82] The 6-month survival of patients with calciphylaxis is ∼50%, mostly due to sepsis.[83]

The genesis of CAC may differ in dialysis patients. While autopsy studies show similar coronary plaque burden in dialysis and non-CKD patients who die of cardiac death, atheromata of dialysis patients harbour markedly more calcium.[84] The extensive arterial calcifications in ESKD extend to intra-myocardial arterioles.[85] Aortic calcification causes arterial stiffness that increases pulse pressure, reduces DBP, and thus decreases coronary perfusion.[86] Aortic stiffness also raises LV afterload, which can increase LV mass, an independent predictor of death, in > 70% of those starting dialysis.[87] These abnormalities may predispose to heart failure with preserved systolic function in patients with CKD and on dialysis.

The complex pathogenesis of uraemic vascular calcification includes systemic inflammation and disordered mineral metabolism.[88–90] Arterial smooth muscle cells can acquire osteoblastic functions that promote arterial calcification in CKD due to hyperphosphataemia, oxidative stress, and activity of the osteoblastic transcription factor RUNX2.[91,92] Furthermore, ESKD patients have low concentrations of calcification inhibitors such as fetuin-A and matrix gla-protein, favouring calcification.[93–95] FGF23, which increases markedly in patients undergoing dialysis, can induce LVH in uraemic rats.[96,97] For these reasons, normalizing calcium, phosphorus, PTH, and FGF23 merit consideration as interventions to limit CV events in those starting dialysis.

Impaired autonomic modulation

Finally, several heart rate variability studies provide evidence of impaired cardiac autonomic modulation in dialysis patients.[98] This autonomic imbalance may predispose to lethal arrythmias.[99]

Prevention: decreasing cardiovascular burden as dialysis starts

Reducing CV risk in patients starting dialysis merits a combined approach. Nephrologists optimize dialysate prescription, dialysis temperature, and ultrafiltration rate to remove excess fluid and normalize electrolytes while minimizing hypotension and coronary hypoperfusion during dialysis.[100,101] Peritoneal dialysis (PD) places fewer haemodynamic demands on the heart. According to observational studies, PD may mitigate the 'cardiovascular spike'; however, it remains inconclusive if HD vs. PD improves long-term survival.[102–104] The only attempted randomized controlled trial of HD vs. PD halted because of inadequate enrolment, as most patients clearly prefer one modality.[105] Frequent, shorter dialysis (6 times per week) can control BP, phosphorus, and improve LV function over conventional protocols (3 times per week)[106,107]; however, these RCTs lack adequate power for mortality and did not enrol patients just starting dialysis.

CV disease management during dialysis overlaps with outpatient care, mandating an integrated, multidisciplinary approach. Dialysis initiation should signal the care team to shift management targets strategies to align with the altered mechanisms of disease. As CV clinical trials typically exclude those with advanced CKD and dialysis, we lack conclusive data to inform diabetes, BP, cardiomyopathy, and arrhythmia management of dialysis.[108] We must therefore base practice on the pathophysiology of disease with extrapolation from small validation trials in dialysis patients or on trials done in the non-dialysis population. The safety of such extrapolation remains unproved, and all members of the care team should acknowledge these limitations.

Blood pressure management

During the first 4 months of dialysis, fluctuating BP presents a management challenge.[109] Sodium restriction and dialysis fluid removal offer first-line therapies for hypertension at this juncture.[110,111] Most patients have excess volume at dialysis initiation; however, ultrafiltration in the first months of dialysis will reduce BP and permit reduction of hypertensive medications. Nephrologists often advise omission of BP medication before a session to achieve a pre-dialysis BP = 150–159/80–99 that reduces intra-dialytic hypotension and vascular access thrombosis[58] although pre- and post-dialysis BP correlate minimally with CV mortality.[112] In contrast, a 20/10 mmHg increase in inter-dialytic BP taken at home or in the doctor's office is associated with a significant 50% increase in CV mortality.[113] A meta-analysis of dialysis subgroups from RCTs reports that a 4–5/2–3 mmHg lowering of BP with anti-hypertensive medication in dialysis patients reduces both CV events and mortality by 29%.[114] No dialysis RCTs have evaluated BP targets, but extrapolation from general population studies suggests that dialysis patients could target a home or outpatient-measured BP of 120–135/60–80 mmHg in between HD treatments.[115]

Anti-hypertenisve medications

Some, albeit limited, RCTs have evaluated classes of anti-hypertensive drugs in this context. Beta-blockers might seem a logical first choice, as arrhythmia may contribute to death in dialysis initiation. One trial randomized 200 hypertensive dialysis patients to atenolol vs. lisinopril and stopped early as the incidence of MI, stroke, chronic heart failure (CHF), and CV death increased two-fold in those allocated to lisinopril.[112] Even though a meta-analysis of five RCTs of angiotensin-converting enzyme inhibitor (ACEI)/angiotensin II receptor blocker (ARB) vs. placebo reported significant reductions in LV mass index, these findings have not consistently translated into improved outcomes.[116] Four small trials randomized dialysis patients to an ACEI/ARB or placebo. Two of these trials showed CV benefit with ACEI/ARB while two other trials did not, such that the efficacy of renin–angiotensin–aldosterone system (RAAS) inhibition remains unclear in ESKD.[110] Amlodipine (vs. placebo) in dialysis patients reduces mortality, non-fatal stroke, and coronary/peripheral revascularization by 47% when compared to placebo in one small trial ($n = 251$).[117] Finally, 253 non-heart failure dialysis patients randomly received 25 mg spironolactone or placebo. Those treated with spironolactone had 58% less cardiocerebrovascular death, sudden death, and cardiac arrest, but no statistically significant difference in the incidence of hyperkalaemia.[118] Another RCT found that spironolactone (25 mg/day) significantly decreased CV/cerebral hospitalization and death by 60% and all-cause mortality by 65% in HD when compared to placebo ($n = 157$), while serious hyperkalaemia occurred in only 1.9% of patients on the drug.[119] Given the small size of these trials and their inclusion of subjects without a history of hyperkalaemia, the use of spironolactone in those starting dialysis requires caution pending the results from two ongoing larger trials examining the safety and efficacy of mineralocorticoid antagonists in dialysis.[120,121]

In addition to class of drug, whether dialysis removes the prescribed drug requires consideration. A propensity-matched observational study reported 40% higher mortality in dialysis patients prescribed dialysable beta-blockers (atenolol, metoprolol) when compared to non-dialysable beta-blockers (propranolol, carvedilol).[122] ARBs are not cleared by the kidney or removed by dialysis and thus do not require dosing adjustments, which simplifies their prescribing in dialysis. The use of an ACEI can present more challenges, as each drug has a different renal and dialysis clearance properties (see *Table 4*). Dialysis does not remove amlodipine, diltiazem, or doxazocin. Dialysable medications should be avoided or taken after dialysis to avoid their removal from the bloodstream.

For dialysis patients with reduced ejection fraction (EF) heart failure, small ESKD trials validate RCT findings in the general population. Carvedilol (up to 25 mg BID) significantly improved LV EF by 27%, CV mortality by 78%, and survival by 49% when compared to placebo ($n = 114$) in dialysis patients with an EF < 35%.[129,130] Similarly, two small placebo-controlled spironolactone (25 mg/day) trials discussed above indicate promise for mineralocorticoid antagonism; however, we await confirmatory results from an ongoing larger trial[120] conducted in dialysis patients with an EF < 40%. While RAAS dialysis trials in the non-heart failure cohorts described above were inconclusive, ACEI/ARB therapy may have efficacy when dialysis patients have coexisting heart failure. In a double-blind trial of 332 HD patients with an EF < 40% on ACEI randomly receiving add-on telmisartan (40–80 mg/day) vs. placebo, the ARB significantly reduced CV mortality (HR = 0.42) and CHF hospitalization (HR = 0.38) without causing excess hyperkalaemia.[131]

Medication reconciliation

The start of dialysis should prompt a careful review of a patient's medications. Some CV medications depend on renal clearance,

necessitating dose reduction or discontinuation, as renal function is minimal at dialysis initiation. Additionally, dialysis clears some medications, which may require a supplementary dose given after dialysis to maintain therapeutic drug levels (see *Table 4*). The use of antiarrhythmic drugs proves challenging in this population, as these drugs are often dialysable and cleared by the kidney, which can lead to fluctuations in the drug levels. Additionally, many anti-arrhythmics have a narrow therapeutic window, and toxicity can precipitate lethal arrhythmias in a population that is already prone to SCD.[132] Dose reduction, plasma level testing and ECG monitoring may enhance the use of these drugs in dialysis patients.[132] Amiodarone merits consideration in these patients due to its predictable elimination/clearance unaffected by dialysis.[132] Forty percent of dialysis patients have a prolonged QTc interval, and QTc intervals increase after HD, likely from the rapid removal of potassium, magnesium, and calcium.[133] Clinicians should consider omitting QT-prolonging medications before patients initiate dialysis, especially if the baseline ECG shows a long QT interval.

Hyperkalaemia

Hyperkalaemia is prevalent in patients starting dialysis and is associated with increased risk of SCD.[134,135] Hyperkalaemia refractory to dietary restriction and dialysis removal can be treated with sodium polystyrene or newer agents that remove potassium by exchanging cations for potassium in the distal colon.[136]

Anticoagulation

The practice of anticoagulation in dialysis persists in a state of clinical equipoise. About 30% of HD patient have atrial fibrillation at the start of dialysis; yet, it remains unclear if the benefits of warfarin outweigh the risks of accelerating bleeding, CAC, and calciphylaxis in dialysis.[137] Direct oral anticoagulants do not aggravate arterial calcification, but these drugs depend on renal clearance to variable extents, such that drug accumulation can enhance bleeding risk.[138] The US FDA label does make pharmacokinetically-based dose recommendation for the use of rivaroxaban and apixaban in dialysis even though ESKD patients were excluded from all phase 3 clinical trials for atrial fibrillation and venous thromboembolism prophylaxis.[139,140] The risk of bleeding was 20% higher in apixaban vs. warfarin (statistically non-significant) in an RCT of dialysis patients with atrial fibrillation; however, the trial was underpowered and terminated early because of slow enrolment.[141]

Implantable cardioverter-defibrillator

Given the high risk of SCD and frequent cardiomyopathy, CV implantable cardioverter-defibrillator (ICD) use is prevalent (10%) in the dialysis population.[142] ICDs may have reduced efficacy in dialysis patients compared to non-dialysis patients.[143,144] More study is needed on the risk–benefit of ICD therapy once patients start dialysis. Concurrent comorbid conditions, the dialysis access, and repeated cannulation raise the risk of device infection.[145] Additionally, ICD infection-related mortality in dialysis remains significantly higher than in the general population even after prompt device extraction.[146–149]

Anaemia

Erythropoietin and IV iron can treat the anaemia of CKD to increase haemoglobin to 10-12 g/dL to attempt to limit cardiac complications and regress LV mass,[150] yet raising haemoglobin levels beyond 12 g/dL is associated with CV harm.[151] Ongoing trials for Hypoxia Inducible Factors (HIF) inhibitors may demonstrate that these drugs can raise haemoglobin without the CV risks seen with EPO.[152]

Diabetes management

Unfortunately, we lack trial evidence to inform diabetes management in patients starting dialysis, and the efficacy and safety of different antidiabetic agents. Because of this information gap, HD patients are typically switched to insulin, although some physicians will elect to use an oral agent. Among the sulphonylurea/meglitinide drugs, glipizide, and repaglinide depend least on renal clearance.[153,154] Metformin (lactic acidosis), thiazolidinediones (oedema and CHF), GLP-1 agonists, and SGLT2 inhibitors are all not recommended in dialysis. FDA labels do support DDP-4 inhibitor prescription in dialysis. A small dialysis trial ($n = 129$) showed that sitagliptin is equivalent to glipizide at lowering Hba1c with less severe hypoglycaemia, but larger studies are needed.[123] Given the reduction in CV events recently demonstrated with SGLT2 inhibitors and GLP-1 agonists, we urgently need more information about the utility and safety of these classes of agents in the dialysis setting.

Finally, providers should ensure that CKD patients have nephrology care by the time their eGFR falls below 30 mL/min for vascular access and pre-emptive transplantation planning.[124] The best outcome and quality of life for patients with progressive CKD is pre-emptive kidney transplantation, when clinical circumstances permit.[125] Fistula or graft vascular access should be placed for HD because it associated with better cardiac outcomes than those using a catheter.[6] There is evidence that brachial plexus block is superior to general and local anaesthesia in fistula placement because it improves haemodynamics and fistula maturation.[126] If urgent, new-generation multilaminated grafts can be placed that can be used 24–72 h after implantation.[127] Altered dialysis initiation practices to preserve residual renal function, such as peritoneal dialysis and starting with twice weekly dialysis, are under study.[128]

Conclusion

Dialysis initiation encompasses the period of highest CV risk in the spectrum of CKD, entailing a 20-fold mortality excess over age-matched controls. This ‘cardiovascular spike’ coincides with the start of dialysis, which shifts the mechanism of disease to alter the manifestations, response, and outcomes of CV disease in this vulnerable population. This critical period affords an opportunity for clinicians to heighten their vigilance for CV complications while ongoing research attempts to address the many gaps in our knowledge regarding optimum management of this perilous point in the patient’s journey with CKD. A cooperative approach between the nephrology and CV care teams assumes even greater importance during this critical passage.

Table 4 Cardiovascular medications dosing and clearance for patients starting dialysis[123–125]

Medication	Drug clearance		Comments
	Kidneys	Dialysis	
Anticoagulant and antiplatelet			
Enoxaparin	Yes	No	20–30 mg SQ for DVT prophylaxis likely acceptable; avoid otherwise
Apixaban	Yes	Negligible	PK modelled dose of 2.5 mg b.i.d.; but no data to support safety and efficacy of drug; prescribe drug at own discretion
Dabigatran	Yes	Yes	Contraindicated; drug bio-accumulation can cause bleeding
Edoxaban	Yes	Negligible	Not recommended; drug bio-accumulation can cause bleeding
Rivaroxaban	Yes	No	PK models suggest 15 mg qd; but no data to support safety and efficacy of drug; prescribe drug at own discretion
Fondaparinux	Yes	Unknown	Not indicated
Eptifibatide	Yes	Yes	Contraindicated; drug bio-accumulation can cause bleeding
Prasugrel	Yes	No	No dosage adjustment
Ticagrelor	No	No	No dosage adjustment
Dalteparin	Yes	No	5000 units prophylaxis ×7 days likely safe; monitor anti-Xa levels for treatment level dosing
Aspirin	Yes	Yes	Administer after HD on dialysis days
Clopidogrel	Yes	No	
Cangrelor	Yes	Unknown	No dose adjustment
Diabetic drugs			
Insulin	Yes	No	Decrease initial dose by 50%
Glipizide	No	Unknown	No dose reduction needed in dialysis
Repaglinide	No	unknown	No dose reduction needed in dialysis
Metformin	Yes	Yes	Contraindicated; causes lactic acidosis
Thiazolidinediones (rosiglitazone, pioglitazone)	No	No	Not recommended; risk of oedema and CHF in anuric dialysis patients
Diabetic drugs: GLP-1 inhibitors			
Exenatide	Yes	Unknown	Not recommended: severe GI side effects, many reports of AKI[126]
Liraglutide	No	No[127]	Not recommended; no safety and efficacy data
Dulaglitide	No	Unknown	Not recommended; no safety and efficacy data, increased risk AKI[128]
All SGLT2 inhibitors	Yes	Unknown	Contraindicated
Diabetic drugs: DPP-4 inhibitors			
Sitaglipin	Yes	Minimal	25 mg qd
Saxaglipin	Yes	Yes	2.5 mg qd, post-dialysis
Linagliptin	No	No	No dose adjustment
Aglopliptin	Yes	No	6.25 mg qd
B-blockers			
Atenolol	Yes	Yes	Administer after HD, reduce starting dose ∼50%
Metoprolol	No	Yes	Administer after HD
Carvdedilol,	No	No	
Labetalol	No	No	
Propranolol	No	No	No dose adjustment, but use with caution as weak active metabolite cleared by kidney
Bisoprolol	yes	no	Initial: 2.5 mg daily; increase cautiously
Other anti-hypertensive drugs			
ACEI	Yes/No	Yes/No	Renal and dialysis clearance vary by ACEI type; Use ARB instead as all ARB require no dose adjustment thus simpler to dose
ARB	No	No	
Amlodipine	No	No	
Clonidine	Yes	No	Decrease starting dose but no mcg recommendations provided
Doxazocin	No	No	
Isosorbide mononitrate	Yes	Yes	Dose after dialysis
Spironolactone	Yes	Unknown	25 mg qd

Continued

Table 4 *Continued*

Medication	Drug clearance		Comments
	Kidneys	Dialysis	
Anti-arrhythmic			
Procainamide (Ia)	Yes	Yes	Monitor procainamide/N-acetylprocainamide (NAPA) concentrations; supplementation may be necessary
Quinidine (Ia)	Yes	Yes	No dosage adjustment provided in manufacturer's labelling. Use with caution. Some clinicians advocate 75% normal dose after HD
Disopyramide (Ia)	Yes	No	Reduce dose; monitor drug levels and ECG; increased risk of torsades do pointes
Lidocaine (Ib)	No	No	
Mexiletine (Ib)	No	Yes	
Propafenone (Ic)	No	No	Accumulation of active metabolites in ESKD; no dose recommendation on label but some recommend 50% dose reduction
Flecainide (Ic)	Yes	No	Reduce dose 50%; plasma levels to guide dosing
Sotalol (III)	Yes	Yes	Contraindicated
Dofetilide (III)	Yes	No	Contraindicated
Amiodarone (III)	No	No	Safest anti-arrhythmic to use in ESKD
Digoxin	Yes	No	Keep serum level ≤1 if not avoid; rapid shifts in potassium during haemodialysis may precipitate arrhythmias through hypokalaemia[2]

Search strategy

Search strategy and selection criteria: Data for this seminar were identified from PubMed, MEDLINE, and references from relevant articles using the search terms 'incident dialysis', 'cardiovascular', 'dialysis initiation', and 'dialysis early mortality'. Only articles published in English after 1980 were included.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Data availability

Standard analytic file data provided by USRDS Data Coordinating Center.

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References

1. Wetmore JB, Collins AJ. Meeting the World's need for maintenance dialysis. *J Am Soc Nephrol* 2015;**26**:2601–2603.
2. Ahmad OB, Boschi-Pinto C, Lopez AD, Murray CJL, Lozano R, Inoue M. Age Standardization of Rates: a New WHO Standard (GPE Discussion Paper Series: No. 31). 2000, 1–14.
3. Goff DC, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, Greenland P, Lackland DT, Levy D, O'Donnell CJ, Robinson JG, Schwartz JS, Shero ST, Smith SC, Sorlie P, Stone NJ, Wilson PWF. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. *Circulation* 2014;**129**:S49–S73.
4. Chan KE, Maddux FW, Tolkoff-Rubin N, Karumanchi SA, Thadhani R, Hakim RM. Early outcomes among those initiating chronic dialysis in the United States. *Clin J Am Soc Nephrol* 2011;**6**:2642–2649.
5. Hazara AM, Bhandari S. Early mortality rates after commencement of maintenance hemodialysis: a systematic review and meta-analysis. *Ther Apher Dial* 2020; **24**:275–284.
6. Bradbury BD, Fissell RB, Albert JM, Anthony MS, Critchlow CW, Pisoni RL, Port FK, Gillespie BW. Predictors of early mortality among incident US hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Clin J Am Soc Nephrol* 2007;**2**:89–99.
7. Turakhia MP, Blankestijn PJ, Carrero J-J, Clase CM, Deo R, Herzog CA, Kasner SE, Passman RS, Pecoits-Filho R, Reinecke H, Shroff GR, Zareba W, Cheung M, Wheeler DC, Winkelmayer WC, Wanner C, Amann K, Banerjee D, Bansal N, Boriani G, Bunch J, Chan CT, Charytan DM, Conen D, Friedman AN, Genovesi S, Holden RM, House AA, Jadoul M, Jardine AG, Johnson DW, Jun M, Labriola L, Mark PB, McCullough PA, Nolin TD, Potpara TS, Pun PH, Ribeiro ALP, Rossignol P, Shen JI, Sood MM, Tsukamoto Y, Wang AY-M, Weir MR, Wetmore JB, Wranicz JK, Yamasaki H; Conference Participants. Chronic kidney disease and arrhythmias: conclusions from a Kidney Disease: improving Global Outcomes (KDIGO) Controversies Conference. *Eur Heart J* 2018;**39**: 2314–2317.
8. Grams ME, Chow EKH, Segev DL, Coresh J. Lifetime incidence of CKD stages 3-5 in the United States. *Am J Kidney Dis* 2013;**62**:245–252.
9. Bansal N, Katz R, Robinson-Cohen C, Odden MC, Dalrymple L, Shlipak MG, Sarnak MJ, Siscovick DS, Zelnick L, Psaty BM, Kestenbaum B, Correa A,

Afkarian M, Young B, de Boer IH. Absolute rates of heart failure, coronary heart disease, and stroke in chronic kidney disease: an analysis of 3 community-based cohort studies. *JAMA Cardiol* 2016;**98104**:1–5.
10. National Safety Council. Odds of dying. https://injuryfacts.nsc.org/all-injuries/preventable-death-overview/odds-of-dying/?gclid=EAIaIQobChMIpKWz8YCv3AIVhI2zCh2ASAZ2EAMYASAAEgKwZPD_BwEdata-details (22 November 2019).
11. National Cancer Society. Lifetime risk of developing or dying from cancer. https://www.cancer.org/cancer/cancer-basics/lifetime-probability-of-developing-or-dying-from-cancer.html (22 November 2019).
12. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney M-T, Corrà U, Cosyns B, Deaton C, Graham I, Hall MS, Hobbs FDR, Løchen M-L, Löllgen H, Marques-Vidal P, Perk J, Prescott E, Redon J, Richter DJ, Sattar N, Smulders Y, Tiberi M, van der Worp HB, van Dis I, Verschuren WMM, Binno S; ESC Scientific Document Group. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: the Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts): developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2016;**37**:2315–2381.
13. Centers for disease control and prevention: National Center for Health Statistics. https://www.cdc.gov/nchs/fastats/heart-disease.htm (22 November 2019).
14. Thompson S, James M, Wiebe N, Hemmelgarn B, Manns B, Klarenbach S, Tonelli M. Cause of death in patients with reduced kidney function. *J Am Soc Nephrol* 2015;**26**:2504–2511.
15. Trespalacios FC, Taylor AJ, Agodoa LY, Abbott KC. Incident acute coronary syndromes in chronic dialysis patients in the United States. *Kidney Int* 2002;**62**:1799–1805.
16. Yeh RW, Sidney S, Chandra M, Sorel M, Selby JV, Go AS. Population trends in the incidence and outcomes of acute myocardial infarction. *N Engl J Med* 2010;**362**:2155–2165.
17. Murray AM, Seliger S, Lakshminarayan K, Herzog CA, Solid CA. Incidence of stroke before and after dialysis initiation in older patients. *J Am Soc Nephrol* 2013;**24**:1166–1173.
18. Centers for Disease Control and Prevention. Acute coronary syndrome rates by eGFR category by CKD stage 2007. https://nccd.cdc.gov/ckd/detail.aspx?Qnum=Q628&Strat=CKD+Stage&Year=2007#refreshPosition (22 November 2019).
19. Diris JHC, Hackeng CM, Kooman JP, Pinto YM, Hermens WT, van Dieijen-Visser MP. Impaired renal clearance explains elevated troponin T fragments in hemodialysis patients. *Circulation* 2004;**109**:23–25.
20. Joki N, Hase H, Nakamura R, Yamaguchi T. Onset of coronary artery disease prior to initiation of haemodialysis in patients with end-stage renal disease. *Nephrol Dial Transplant* 1997;**12**:718–723.
21. Ohtake T, Kobayashi S, Moriya H, Negishi K, Okamoto K, Maesato K, Saito S. 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.
22. 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.
23. Stewart GA, Gansevoort RT, Mark PB, Rooney E, McDonagh TA, Dargie HJ, Stuart R, Rodger C, Jardine AG. Electrocardiographic abnormalities and uremic cardiomyopathy. *Kidney Int* 2005;**67**:217–226.
24. Wang LW, Fahim MA, Hayen A, Mitchell RL, Baines L, Lord S, Craig JC, Webster AC. Cardiac testing for coronary artery disease in potential kidney transplant recipients. *Cochrane Database Syst Rev* 2011;**12**:CD008691.
25. Ragosta M, Samady H, Isaacs RB, Gimple LW, Sarembock IJ, Powers ER. Coronary flow reserve abnormalities in patients with diabetes mellitus who have end-stage renal disease and normal epicardial coronary arteries. *Am Heart J* 2004;**147**:1017–1023.
26. Dilsizian V, Gewirtz H, Marwick TH, Kwong RY, Raggi P, Al-Mallah MH, Herzog CA. Cardiac imaging for coronary heart disease risk stratification in chronic kidney disease. *JACC Cardiovasc Imaging* 2020;S1936-878X(20)30531-3.
27. Sharma R, Pellerin D, Gaze DC, Gregson H, Streather CP, Collinson PO, Brecker SJD. Dobutamine stress echocardiography and the resting but not exercise electrocardiograph predict severe coronary artery disease in renal transplant candidates. *Nephrol Dial Transplant* 2005;**20**:2207–2214.
28. Rosário MA, de Lima JJ, Parga JR, Avila LF, Gowdak LH, Lemos PA, Rochitte CE. Coronary calcium score as predictor of stenosis and events in pretransplant renal chronic failure. *Arq Bras Cardiol* 2010;**94**:252–243. 252–**60**, 239–47.
29. Winther S, Svensson M, Jorgensen HS, Bouchelouche K, Gormsen LC, Pedersen BB, Holm NR, Botker HE, Ivarsen P, Bottcher M. Diagnostic performance of coronary CT angiography and myocardial perfusion imaging in kidney transplantation candidates. *JACC Cardiovasc Imaging* 2015;**8**:553–562.
30. Hakeem A, Bhatti S, Chang SM. Screening and risk stratification of coronary artery disease in end-stage renal disease. *JACC Cardiovasc Imaging* 2014;**7**:715–728.
31. Bangalore S, Maron DJ, O'Brien SM, Fleg JL, Kretov EI, Briguori C, Kaul U, Reynolds HR, Mazurek T, Sidhu MS, Berger JS, Mathew RO, Bockeria O, Broderick S, Pracon R, Herzog CA, Huang Z, Stone GW, Boden WE, Newman JD, Ali ZA, Mark DB, Spertus JA, Alexander KP, Chaitman BR, Chertow GM, Hochman JS. Management of coronary disease in patients with advanced kidney disease. *N Engl J Med* 2020;**382**:1608–1618.
32. Mehran R, Aymong ED, Nikolsky E, Lasic Z, Iakovou I, Fahy M, Mintz GS, Lansky AJ, Moses JW, Stone GW, Leon MB, Dangas G. A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. *J Am Coll Cardiol* 2004;**44**:1393–1399.
33. Wayand D, Baum HRG, SchäTzle G, SchäRf J, Neumeier D. Cardiac troponin T and I in end-stage renal failure. *Clin Chem* 2000;**46**:1345–1350.
34. van der Linden N, Cornelis T, Kimenai DM, Klinkenberg LJJ, Hilderink JM, Luck S, Litjens EJR, Peeters F, Streng AS, Breidthardt T, van Loon LJC, Bekers O, Kooman JP, Westermark PO, Mueller C, Meex SJR. Origin of cardiac troponin T elevations in chronic kidney disease. *Circulation* 2017;**136**:1073–1075.
35. Garg P, Morris P, Fazlanie AL, Vijayan S, Dancso B, Dastidar AG, Plein S, Mueller C, Haaf P. Cardiac biomarkers of acute coronary syndrome: from history to high-sensitivity cardiac troponin. *Intern Emerg Med* 2017;**12**:147–155.
36. Januzzi JL Jr, Filippatos G, Nieminen M, Gheorghiade M. Troponin elevation in patients with heart failure: on behalf of the third Universal Definition of Myocardial Infarction Global Task Force: Heart Failure Section. *Eur Heart J* 2012;**33**:2265–2271.
37. Parikh RH, Seliger SL, DeFilippi CR. Use and interpretation of high sensitivity cardiac troponins in patients with chronic kidney disease with and without acute myocardial infarction. *Clin Biochem* 2015;**48**:247–253.
38. Gunsolus I, Sandoval Y, Smith SW, Sexter A, Schulz K, Herzog CA, Apple FS. Renal dysfunction influences the diagnostic and prognostic performance of high-sensitivity cardiac troponin I. *J Am Soc Nephrol* 2018;**29**:636–643.
39. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD, Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD; ESC Scientific Document Group Fourth universal definition of myocardial infarction (2018). *Eur Heart J* 2019;**40**:237–269.
40. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction; Katus HA, Lindahl B, Morrow DA, Clemmensen PM, Johanson P, Hod H, Underwood R, Bax JJ, Bonow RO, Pinto F, Gibbons RJ, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW, Uretsky BF, Steg PG, Wijns W, Bassand JP, Menasche P, Ravkilde J, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Simoons ML, Januzzi JL, Nieminen MS, Gheorghiade M, Filippatos G, Luepker RV, Fortmann SP, Rosamond WD, Levy D, Wood D, Smith SC, Hu D, Lopez-Sendon JL, Robertson RM, Weaver D, Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ, Mendis S. Third universal definition of myocardial infarction. *Circulation* 2012;**126**:2020–2035.
41. Twerenbold R, Badertscher P, Boeddinghaus J, Nestelberger T, Wildi K, Puelacher C, Sabti Z, Rubini Gimenez M, Tschirky S, Du Fay de Lavallaz J, Kozhuharov N, Sazgary L, Mueller D, Breidthardt T, Strebel I, Flores Widmer D, Shrestha S, Miro O, Martin-Sanchez FJ, Morawiec B, Parenica J, Geigy N, Keller DI, Rentsch K, von Eckardstein A, Osswald S, Reichlin T, Mueller C. 0/1-Hour triage algorithm for myocardial infarction in patients with renal dysfunction. *Circulation* 2018;**137**:436–451.
42. Kraus D, von Jeinsen B, Tzikas S, Palapies L, Zeller T, Bickel C, Fette G, Lackner KJ, Drechsler C, Neumann JT, Baldus S, Blankenberg S, Munzel T, Wanner C, Zeiher AM, Keller T. Cardiac troponins for the diagnosis of acute myocardial infarction in chronic kidney disease. *J Am Heart Assoc* 2018;**7**:e008032.
43. Miller-Hodges E, Anand A, Shah ASV, Chapman AR, Gallacher P, Lee KK, Farrah T, Halbesma N, Blackmur JP, Newby DE, Mills NL, Dhaun N. High-sensitivity cardiac troponin and the risk stratification of patients with renal impairment presenting with suspected acute coronary syndrome. *Circulation* 2018;**137**:425–435.
44. deFilippi CR, Herzog CA. Interpreting cardiac biomarkers in the setting of chronic kidney disease. *Clin Chem* 2017;**63**:59–65.
45. Isakova T, Wahl P, Vargas 2GS, Gutirrez 2OM, Scialla 2J, Xie 2H, Appleby 2D, Nessel 2L, Bellovich K, Chen 2J, Hamm 2L, Gadegbeku 2C, Horwitz 2E, Townsend 2RR, Anderson 2CAM, Lash 2JP, Hsu 2C-Y, Leonard 2MB, Wolf M. Fibroblast growth factor 23 is elevated before parathyroid hormone and phosphate in chronic kidney disease. *Kidney Int* 2011;**79**:1370–1378.
46. Cataliotti A, Malatino LS, Jougasaki M, Zoccali C, Castellino P, Giacone G, Bellanuova I, Tripepi R, Seminara G, Parlongo S, Stancanelli B, Bonanno G, Fatuzzo P, Rapisarda F, Belluardo P, Signorelli SS, Heublein DM, Lainchbury JG, Leskinen HK, Bailey KR, Redfield MM, Burnett JC. Circulating natriuretic peptide

concentrations in patients with end-stage renal disease: role of brain natriuretic peptide as a biomarker for ventricular remodeling. *Mayo Clin Proc* 2001;**76**: 1111–1119.
47. Mueller C, Laule-Kilian K, Scholer A, Nusbaumer C, Zeller T, Staub D, Perruchoud AP. B-type natriuretic peptide for acute dyspnea in patients with kidney disease: insights from a randomized comparison. *Kidney Int* 2005;**67**: 278–284.
48. Burton JO, Jefferies HJ, Selby NM, McIntyre CW. Hemodialysis-induced cardiac injury: determinants and associated outcomes. *Clin J Am Soc Nephrol* 2009;**4**: 914–920.
49. Buchanan C, Mohammed A, Cox E, Köhler K, Canaud B, Taal MW, Selby NM, Francis S, McIntyre CW. Intradialytic cardiac magnetic resonance imaging to assess cardiovascular responses in a short-term trial of hemodiafiltration and hemodialysis. *J Am Soc Nephrol* 2017;**28**:1269–1277.
50. Coskun I, Colkesen Y, Altay H, Ozkan U, Demirturk OS, Gulcan O, Guvener M. Hemodynamic effects of left upper extremity arteriovenous fistula on ipsilateral internal mammary coronary artery bypass graft. *Thorac Cardiovasc Surg* 2013;**61**:663–667.
51. MacRae JM, Levin A, Belenkie I. Editorials: the cardiovascular effects of arteriovenous fistulas in chronic kidney disease: a cause for concern? *Semin Dial* 2006; **19**:349–352.
52. Ramanathan T, Skinner H. Coronary blood flow. *Continuing Educ Anaesth Crit Care Pain* 2005;**5**:61–64.
53. McEvoy JW, Chen Y, Rawlings A, Hoogeveen RC, Ballantyne CM, Blumenthal RS, Coresh J, Selvin E. Diastolic blood pressure, subclinical myocardial damage, and cardiac eventsimplications for blood pressure control. *J Am Coll Cardiol* 2016;**68**:1713–1722.
54. Sands JJ, Usvyat LA, Sullivan T, Segal JH, Zabetakis P, Kotanko P, Maddux FW, Diaz-Buxo JA. Intradialytic hypotension: frequency, sources of variation and correlation with clinical outcome. *Hemodial Int* 2014;**18**:415–422.
55. Foley RN, Herzog CA, Collins AJ. Blood pressure and long-term mortality in United States hemodialysis patients: USRDS Waves 3 and 4 Study. *Kidney Int* 2002;**62**:1784–1790.
56. Iseki K, Miyasato F, Tokuyama K, Nishime K, Uehara H, Shiohira Y, Sunagawa H, Yoshihara K, Yoshi S, Toma S, Kowatari T, Wake T, Oura T, Fukiyama K. Low diastolic blood pressure, hypoalbuminemia, and risk of death in a cohort of chronic hemodialysis patients. *Kidney Int* 1997;**51**:1212–1217.
57. , Wright JT Jr, Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, Reboussin DM, Rahman M, Oparil S, Lewis CE, Kimmel PL, Johnson KC, Goff DC Jr, Fine LJ, Cutler JA, Cushman WC, Cheung AK, Ambrosius WT; Sprint Research Group. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 2015;**373**:2103–2116.
58. Miskulin DC, Gassman J, Schrader R, Gul A, Jhamb M, Ploth DW, Negrea L, Kwong RY, Levey AS, Singh AK, Harford A, Paine S, Kendrick C, Rahman M, Zager P. BP in dialysis: results of a pilot study. *J Am Soc Nephrol* 2018;**29**: 307–316.
59. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO 3rd, Criqui M, Fadl YY, Fortmann SP, Hong Y, Myers GL, Rifai N, Smith SC Jr, Taubert K, Tracy RP, Vinicor F. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation* 2003;**107**:499–511.
60. Wanner C, Zimmermann J, Schwedler S, Metzger T. Inflammation and cardiovascular risk in dialysis patients. *Kidney Int Suppl* 2002;**61**:S99–S102.
61. Yeun JY, Levine RA, Mantadilok V, Kaysen GA. C-Reactive protein predicts all-cause and cardiovascular mortality in hemodialysis patients. *Am J Kidney Dis* 2000;**35**:469–476.
62. Owen WF, Lowrie EG. C-reactive protein as an outcome predictor for maintenance hemodialysis patients. *Kidney Int* 1998;**54**:627–636.
63. Menon V, Greene T, Wang X, Pereira AA, Marcovina SM, Beck GJ, Kusek JW, Collins AJ, Levey AS, Sarnak MJ. C-reactive protein and albumin as predictors of all-cause and cardiovascular mortality in chronic kidney disease. *Kidney Int* 2005;**68**:766–772.
64. Honkanen E, Gronhagen-Riska C, Teppo AM, Maury CP, Meri S. Acute-phase proteins during hemodialysis: correlations with serum interleukin-1 beta levels and different dialysis membranes. *Nephron* 1991;**57**:283–287.
65. Bingel M, Lonnemann G, Koch KM, Dinarello CA, Shaldon S. Plasma interleukin-1 activity during hemodialysis: the influence of dialysis membranes. *Nephron* 1988;**50**:273–276.
66. Pertosa G, Tarantino EA, Gesualdo L, Montinaro V, Schena FP. C5b-9 generation and cytokine production in hemodialyzed patients. *Kidney Int Suppl* 1993; **41**:S221–S225.
67. Canivet E, Lavaud S, Wong T, Guenounou M, Willemin JC, Potron G, Chanard J. Cuprophane but not synthetic membrane induces increases in serum tumor necrosis factor-alpha levels during hemodialysis. *Am J Kidney Dis* 1994;**23**:41–46.
68. Ga KAYSEN. The microinflammatory state in uremia: causes and potential consequences. *J Am Soc Nephrol* 2001;**12**:1549–1557.
69. System USRD. *2018 USRDS Annual Data Report: Epidemiology of Kidney Disease in the United States. In*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2018.
70. Goldstein SL, Ikizler TA, Zappitelli M, Silverstein DM, Ayus JC. Non-infected hemodialysis catheters are associated with increased inflammation compared to arteriovenous fistulas. *Kidney Int* 2009;**76**:1063–1069.
71. Baigent C, Landry M. Study of heart and renal protection (SHARP). *Kidney Int Suppl* 2003;**63**:S207–S210.
72. Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, Wanner C, Krane V, Cass A, Craig J, Neal B, Jiang L, Hooi LS, Levin A, Agodoa L, Gaziano M, Kasiske B, Walker R, Massy ZA, Feldt-Rasmussen B, Krairittichai U, Ophascharoensuk V, Fellstrom B, Holdaas H, Tesar V, Wiecek A, Grobbee D, de Zeeuw D, Gronhagen-Riska C, Dasgupta T, Lewis D, Herrington W, Mafham M, Majoni W, Wallendszus K, Grimm R, Pedersen T, Tobert J, Armitage J, Baxter A, Bray C, Chen Y, Chen Z, Hill M, Knott C, Parish S, Simpson D, Sleight P, Young A, Collins R. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet* 2011;**377**:2181–2192.
73. Fellstrom BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J, Chae DW, Chevaile A, Cobbe SM, Gronhagen-Riska C, De Lima JJ, Lins R, Mayer G, McMahon AW, Parving HH, Remuzzi G, Samuelsson O, Sonkodi S, Sci D, Suleymanlar G, Tsakiris D, Tesar V, Todorov V, Wiecek A, Wuthrich RP, Gottlow M, Johnsson E, Zannad F. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. *N Engl J Med* 2009;**360**:1395–1407.
74. Wanner C, Krane V, März W, Olschewski M, Mann JFE, Ruf G, Ritz E. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med* 2005;**353**:238–248.
75. Strippoli GFM, Craig JC. Sunset for statins after AURORA? *N Engl J Med* 2009; **360**:1455–1457.
76. Ridker PM, MacFadyen JG, Glynn RJ, Koenig W, Libby P, Everett BM, Lefkowitz M, Thuren T, Cornel JH. Inhibition of interleukin-1beta by Canakinumab and cardiovascular outcomes in patients with chronic kidney disease. *J Am Coll Cardiol* 2018;**71**:2405–2414.
77. Okwuosa TM, Greenland P, Ning H, Liu K, Bild DE, Burke GL, Eng J, Lloyd-Jones DM. Distribution of coronary artery calcium scores by framingham 10-year risk strata in the MESA (multi-ethnic study of atherosclerosis): potential implications for coronary risk assessment. *J Am Coll Cardiol* 2011;**57**:1838–1845.
78. Braun J, Oldendorf M, Moshage W, Heidler R, Zeitler E, Luft FC. Electron beam computed tomography in the evaluation of cardiac calcification in chronic dialysis patients. *Am J Kidney Dis* 1996;**27**:394–401.
79. Chertow GM, Burke SK, Raggi PA. Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. *Kidney Int* 2002;**62**: 245–252.
80. Raggi P, Cooil B, Callister TQ. Use of electron beam tomography data to develop models for prediction of hard coronary events. *Am Heart J* 2001;**141**: 375–382.
81. Anaya P, Blomquist G, Davenport D, Monier-Faugere M-C, Sorrell V, Malluche H. Coronary artery calcification in CKD-5D patients is tied to adverse cardiac function and increased mortality. *Clin Nephrol* 2016;**86**:291–302.
82. Nigwekar SU, Thadhani R, Brandenburg VM. Calciphylaxis. *N Engl J Med* 2018; **378**:1704–1714.
83. McCarthy JT, El-Azhary RA, Patzelt MT, Weaver AL, Albright RC, Bridges AD, Claus PL, Davis MD, Dillon JJ, El-Zoghby ZM, Hickson LJ, Kumar R, McBane RD, McCarthy-Fruin KA, McEvoy MT, Pittelkow MR, Wetter DA, Williams AW. Survival, risk factors, and effect of treatment in 101 patients with calciphylaxis. *Mayo Clin Proc* 2016;**91**:1384–1394.
84. Schwarz U, Buzello M, Ritz E, Stein G, Raabe G, Wiest G, Mall G, Amann K. Morphology of coronary atherosclerotic lesions in patients with end-stage renal failure. *Nephrol Dial Transplant* 2000;**15**:218–223.
85. Moe SM. Calcium as a cardiovascular toxin in CKD-MBD. *Bone* 2017;**100**: 94–99.
86. Goodman WG, London G, Amann K, Block GA, Giachelli C, Hruska KA, Ketteler M, Levin A, Massy Z, McCarron DA, Raggi P, Shanahan CM, Yorioka N. Vascular calcification in chronic kidney disease. *Am J Kidney Dis* 2004;**43**: 572–579.
87. Foley RN, Parfrey PS, Harnett JD, Kent GM, Martin CJ, Murray DC, Barre PE. Clinical and echocardiographic disease in patients starting end-stage renal disease therapy. *Kidney Int* 1995;**47**:186–192.
88. Yung L-M, Sánchez-Duffhues G, ten Dijke P, Yu PB. Bone morphogenetic protein 6 and oxidized low-density lipoprotein synergistically recruit osteogenic differentiation in endothelial cells. *Cardiovasc Res* 2015;**108**:278–287.

89. Speer MY, Li X, Hiremath PG, Giachelli CM. Runx2/Cbfa1, but not loss of myocardin, is required for smooth muscle cell lineage reprogramming toward osteochondrogenesis. *J Cell Biochem* 2010;**110**:935–947.
90. Heine GH, Nangaku M, Fliser D. Calcium and phosphate impact cardiovascular risk. *Eur Heart J* 2013;**34**:1112–1121.
91. Moe SM, Chen NX. Mechanisms of vascular calcification in chronic kidney disease. *J Am Soc Nephrol* 2008;**19**:213–216.
92. Ketteler M. Fetuin-A and extraosseous calcification in uremia. *Curr Opin Nephrol Hypertens* 2005;**14**:337–342.
93. Hermans MMH, Brandenburg V, Ketteler M, Kooman JP, van der Sande FM, Boeschoten EW, Leunissen KML, Krediet RT, Dekker FWa. Association of serum fetuin-A levels with mortality in dialysis patients. *Kidney Int* 2007;**72**:202–207.
94. Faul C, Amaral AP, Oskouei B, Hu M-C, Sloan A, Isakova T, Gutiérrez OM, Aguillon-Prada R, Lincoln J, Hare JM, Mundel P, Morales A, Scialla J, Fischer M, Soliman EZ, Chen J, Go AS, Rosas SE, Nessel L, Townsend RR, Feldman HI, St. John Sutton M, Ojo A, Gadegbeku C, Di Marco GS, Reuter S, Kentrup D, Tiemann K, Brand M, Hill JA, Moe OW, Kuro-O M, Kusek JW, Keane MG, Wolf M. FGF23 induces left ventricular hypertrophy. *J Clin Invest* 2011;**121**:4393–4408.
95. Aoun M, Makki M, Azar H, Matta H, Chelala DN. High dephosphorylated-uncarboxylated MGP in hemodialysis patients: risk factors and response to vitamin K2, A pre-post intervention clinical trial. *BMC Nephrol* 2017;**18**:191.
96. Gutiérrez OM, Mannstadt M, Isakova T, Rauh-Hain JA, Tamez H, Shah A, Smith K, Lee H, Thadhani R, Jüppner H, Wolf M. Fibroblast growth factor 23 and mortality among patients undergoing hemodialysis. *N Engl J Med* 2008;**359**:584–592.
97. Moe SM, Chertow GM, Parfrey PS, Kubo Y, Block GA, Correa-Rotter R, Drüeke TB, Herzog CA, London GM, Mahaffey KW, Wheeler DC, Stolina M, Dehmel B, Goodman WG, Floege J. Cinacalcet, fibroblast growth factor-23, and cardiovascular disease in hemodialysis: the evaluation of cinacalcet HCl therapy to lower cardiovascular events (EVOLVE) trial. *Circulation* 2015;**132**:27–39.
98. Poulikakos D, Banerjee D, Malik M. Risk of sudden cardiac death in chronic kidney disease. *J Cardiovasc Electrophysiol* 2014;**25**:222–231.
99. Poulikakos D, Hnatkova K, Skampardoni S, Green D, Kalra P, Malik M. Sudden cardiac death in dialysis: arrhythmic mechanisms and the value of non-invasive electrophysiology. *Front Physiol* 2019;**10**:144.
100. Eldehni MT, Odudu A, McIntyre CW. Randomized clinical trial of dialysate cooling and effects on brain white matter. *J Am Soc Nephrol* 2015;**26**:957–965.
101. Flythe JE, Kimmel SE, Brunelli SM. Rapid fluid removal during dialysis is associated with cardiovascular morbidity and mortality. *Kidney Int* 2011;**79**:250–257.
102. Inrig JK, Toto RD. Differential outcomes between dialysis modalities: purely a reflection of selection bias? *J Am Soc Nephrol* 2011;**22**:989–990.
103. Liu X, Huang R, Wu H, Wu J, Wang J, Yu X, Yang X. Patient characteristics and risk factors of early and late death in incident peritoneal dialysis patients. *Sci Rep* 2016;**6**:1–8.
104. Jung HY, Choi H, Choi JY, Cho JH, Park SH, Kim CD, Ryu DR, Kim YL; ESRD Registry Committee of the Korean Society of Nephrology. Dialysis modality-related disparities in sudden cardiac death: hemodialysis versus peritoneal dialysis. *Kidney Res Clin Pract* 2019;**38**:490–498.
105. Korevaar JC, Feith GW, Dekker FWa. Effect of starting with hemodialysis compared with peritoneal dialysis in patients new on dialysis treatment: a randomized controlled trial. *Kidney Int* 2003;**64**:2222–2228.
106. Culleton BF, Walsh M, Klarenbach SW, Mortis G, Scott-Douglas N, Quinn RR, Tonelli M, Donnelly S, Friedrich MG, Kumar A, Mahallati H, Hemmelgarn BR, Manns BJ. Effect of frequent nocturnal hemodialysis vs conventional hemodialysis. *J Am Med Assoc* 2007;**298**:1291–1299.
107. Chertow GM, Levin NW, Beck GJ, Depner TA, Eggers PW, Gassman JJ, Gorodetskaya I, Greene T, James S, Larive B, Lindsay RM, Mehta RL, Miller B, Ornt DB, Rajagopalan S, Rastogi A, Rocco MV, Schiller B, Sergeyeva O, Schulman G, Ting GO, Unruh ML, Star RA, Kliger AS; FHN Trial Group. In-center hemodialysis six times per week versus three times per week. *N Engl J Med* 2010;**363**:2287–2300.
108. Rossignol P, Agarwal R, Canaud B, Charney A, Chatellier G, Craig JC, Cushman WC, Gansevoort RT, Fellström B, Garza D, Guzman N, Holtkamp FA, London GM, Massy ZA, Mebazaa A, Mol PGM, Pfeffer MA, Rosenberg Y, Ruilope LM, Seltzer J, Shah AM, Shah S, Singh B, Stefánsson BV, Stockbridge N, Stough WG, Thygesen K, Walsh M, Wanner C, Warnock DG, Wilcox CS, Wittes J, Pitt B, Thompson A, Zannad F. Cardiovascular outcome trials in patients with chronic kidney disease: challenges associated with selection of patients and endpoints. *Eur Heart J* 2019;**40**:880–886.
109. Rohrscheib MR, Myers OB, Servilla KS, Adams CD, Miskulin D, Bedrick EJ, Hunt WC, Lindsey DE, Gabaldon D, Zager PG. Age-related blood pressure patterns and blood pressure variability among hemodialysis patients. *Clin J Am Soc Nephrol* 2008;**3**:1407–1414.
110. Georgianos PI, Agarwal R. Pharmacotherapy of hypertension in chronic dialysis patients. *Clin J Am Soc Nephrol* 2016;**11**:2062–2075.
111. Agarwal R, Alborzi P, Satyan S, Light RP. Dry-weight reduction in hypertensive hemodialysis patients (DRIP): a randomized, controlled trial. *Hypertension* 2009;**53**:500–507.
112. Agarwal R, Sinha AD, Pappas MK, Abraham TN, Tegegne GG. Hypertension in hemodialysis patients treated with atenolol or lisinopril: a randomized controlled trial. *Nephrol Dial Transplant* 2014;**29**:1–10.
113. Alborzi P, Patel N, Agarwal R. Home blood pressures are of greater prognostic value than hemodialysis unit recordings. *Clin J Am Soc Nephrol* 2007;**2**:1228–1234.
114. Heerspink H, Ninomiya T, Zoungas S, de Zeeuw D, Grobbee DE, Jardine MJ, Gallagher M, Roberts MA, Cass A, Neal B, Perkovic V. Effect of lowering blood pressure on cardiovascular events and mortality in patients on dialysis: a systematic review and meta-analysis of randomised controlled trials. *Lancet* 2009;**373**:1009–1015.
115. Turner JM, Peixoto AJ. Blood pressure targets for hemodialysis patients. *Kidney Int* 2017;**92**:816–823.
116. Tai DJ, Lim TW, James MT, Manns BJ, Tonelli M, Hemmelgarn BR; for the Alberta Kidney Disease Network. Cardiovascular effects of angiotensin converting enzyme inhibition or angiotensin receptor blockade in hemodialysis: a meta-analysis. *Clin J Am Soc Nephrol* 2010;**5**:623–630.
117. Tepel M, Hopfenmueller W, Scholze A, Maier A, Zidek W. Effect of amlodipine on cardiovascular events in hypertensive haemodialysis patients. *Nephrol Dial Transplant* 2008;**23**:3605–3612.
118. Lin C, Zhang Q, Zhang H, Lin A. Long-term effects of low-dose spironolactone on chronic dialysis patients: a randomized placebo-controlled study. *J Clin Hypertens* 2016;**18**:121–128.
119. Matsumoto Y, Mori Y, Kageyama S, Arihara K, Sugiyama T, Ohmura H, Yakushigawa T, Sugiyama H, Shimada Y, Nojima Y, Shio N. Spironolactone reduces cardiovascular and cerebrovascular morbidity and mortality in hemodialysis patients. *J Am Coll Cardiol* 2014;**63**:528–536.
120. Rossingol P. ALdosterone Antagonist Chronic HEModialysis Interventional Survival Trial (ALCHEMIST). 2013. https://clinicaltrials.gov/ct2/show/NCT01848639 (22 November 2019).
121. Wilkinson J, Pohl K. Aldosterone bloCkade for Health Improvement EValuation in End-stage Renal Disease (ACHIEVE). 2017. https://clinicaltrials.gov/ct2/show/NCT03020303 (22 November 2019).
122. Weir MA, Dixon SN, Fleet JL, Roberts MA, Hackam DG, Oliver MJ, Suri RS, Quinn RR, Ozair S, Beyea MM, Kitchlu A, Garg AX. Blocker dialyzability and mortality in older patients receiving hemodialysis. *J Am Soc Nephrol* 2015;**26**:987–996.
123. Arjona Ferreira JC, Corry D, Mogensen CE, Sloan L, Xu L, Golm GT, Gonzalez EJ, Davies MJ, Kaufman KD, Goldstein BJ. Efficacy and safety of sitagliptin in patients with type 2 diabetes and ESRD receiving dialysis: a 54-week randomized trial. *Am J Kidney Dis* 2013;**61**:579–587.
124. Stevens PE, Levin A. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. *Ann Intern Med* 2013;**158**:825–830.
125. Sayin B, Colak T, Tutal E, Sezer S. Comparison of preemptive kidney transplant recipients with nonpreemptive kidney recipients in single center: 5 years of follow-up. *Int J Nephrol Renovasc Dis* 2013;**6**:95–99.
126. Gao C, Weng C, He C, Xu J, Yu L. Comparison of regional and local anesthesia for arteriovenous fistula creation in end-stage renal disease: a systematic review and meta-analysis. *BMC Anesthesiol* 2020;**20**:219.
127. Lawson JH, Niklason LE, Roy-Chaudhury P. Challenges and novel therapies for vascular access in haemodialysis. *Nat Rev Nephrol* 2020;**16**:586–602.
128. Deira J, Suárez MA, López F, García-Cabrera E, Gascón A, Torregrosa E, García GE, Huertas J, de la Flor JC, Puello S, Gómez-Raja J, Grande J, Lerma JL, Corradino C, Musso C, Ramos M, Martín J, Basile C, Casino FG. IHDIP: a controlled randomized trial to assess the security and effectiveness of the incremental hemodialysis in incident patients. *BMC Nephrol* 2019;**20**:8.
129. Cice G, Ferrara L, Di Benedetto A, Russo PE, Marinelli G, Pavese F, Iacono A. Dilated cardiomyopathy in dialysis patients–beneficial effects of carvedilol: a double-blind, placebo-controlled trial. *J Am Coll Cardiol* 2001;**37**:407–411.
130. Cice G, Ferrara L, D'Andrea A, D'Isa S, Di Benedetto A, Cittadini A, Russo PE, Golino P, Calabrò R. Carvedilol increases two-year survivalin dialysis patients with dilated cardiomyopathy: a prospective, placebo-controlled trial. *J Am Coll Cardiol* 2003;**41**:1438–1444.
131. Cice G, Di Benedetto A, D'Isa S, D'Andrea A, Marcelli D, Gatti E, Calabrò R. 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.
132. Chow T, Galvin J, McGovern B. Antiarrhythmic drug therapy in patients with renal failure, liver failure, and congestive heart failure. *Heart Dis* 1999;**1**:98–107.

133. Covic A, Diaconita M, Gusbeth-Tatomir P, Covic M, Botezan A, Ungureanu G, Goldsmith DJ. Haemodialysis increases QT c interval but not QT c dispersion in ESRD patients without manifest cardiac disease. *Nephrol Dial Transplant* 2002; **17**:2170–2177.
134. Huang CW, Lee MJ, Lee PT, Hsu CY, Huang WC, Chen CL, Chou KJ, Fang HC. Low potassium dialysate as a protective factor of sudden cardiac death in hemodialysis patients with hyperkalemia. *PLoS One* 2015;**10**:e0139886.
135. Kovesdy CP, Matsushita K, Sang Y, Brunskill NJ, Carrero JJ, Chodick G, Hasegawa T, Heerspink HL, Hirayama A, Landman GWD, Levin A, Nitsch D, Wheeler DC, Coresh J, Hallan SI, Shalev V, Grams ME; CKD Prognosis Consortium. Serum potassium and adverse outcomes across the range of kidney function: a CKD Prognosis Consortium meta-analysis. *Eur Heart J* 2018;**39**: 1535–1542.
136. Pitt B, Bakris GL. New potassium binders for the treatment of hyperkalemia: current data and opportunities for the future. *Hypertension* 2015;**66**:731–738.
137. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CWA. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *Circulation* 2014;**130**:2071–2104.
138. Chan KE, Giugliano RP, Patel MR, Abramson S, Jardine M, Zhao S, Perkovic V, Maddux FW, Piccini JP. Nonvitamin K anticoagulant agents in patients with advanced chronic kidney disease or on dialysis with AF. *J Am Coll Cardiol* 2016; **67**:2888–2899.
139. US Food and Drug Administration. XARELTO (rivaroxaban) tablets, for oral use: initial U.S. Approval: 2011. In: Pharmaceuticals J (ed). Belgium; 2016. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/202439s017lbl.pdf.
140. US Food and Drug Administration. ELIQUIS (apixaban) tablets for oral use Initial U.S. Approval: 2012. In: Squibb B-M, (ed). New York; 2014. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202155s000lbl.pdf.
141. Pokorney SD. RENal hemodialysis patients ALlocated apixaban versus warfarin in Atrial Fibrillation (RENAL-AF)—Presentation Slides. In: *AHA 2019 Annual Scientific Sessions*. 2019.
142. Nakhoul GN, Schold JD, Arrigain S, Harb SC, Jolly S, Wilkoff BL, Nally JV, Navaneethan SD. Implantable cardioverter-defibrillators in patients with CKD: a propensity-matched mortality analysis. *Clin J Am Soc Nephrol* 2015;**10**: 1119–1127.
143. Pun PH, Hellkamp AS, Sanders GD, Middleton JP, Hammill SC, Al-Khalidi HR, Curtis LH, Fonarow GC, Al-Khatib SM. Primary prevention implantable cardioverter defibrillators in end-stage kidney disease patients on dialysis: a matched cohort study. *Nephrol Dial Transplant* 2015;**30**:829–835.
144. Khattak A, Charytan DM. Shades of Grey: the conundrum of implantable defibrillators in individuals with advanced CKD. *Clin J Am Soc Nephrol* 2015;**10**: 1107–1109.
145. Saad TF, Ahmed W, Davis K, Jurkovitz C. Cardiovascular implantable electronic devices in hemodialysis patients: prevalence and implications for arteriovenous hemodialysis access interventions. *Semin Dial* 2015;**28**:94–100.
146. Guha A, Maddox WR, Colombo R, Nahman NS, Kintziger KW, Waller JL, Diamond M, Murphy M, Kheda M, Litwin SE, Sorrentino RA. Cardiac implantable electronic device infection in patients with end-stage renal disease. *Heart Rhythm* 2015;**12**:2395–2401.
147. Opelami O, Sakhuja A, Liu X, Tang WHW, Schold JD, Navaneethan SD. Outcomes of infected cardiovascular implantable devices in dialysis patients. *Am J Nephrol* 2014;**40**:280–287.
148. Lin Y-S, Chen T-H, Lin M-S, Chen DY, Mao C-T, Hsu J-T, Chen H-C, Chen M-C. Impact of chronic kidney disease on short-term cardiac implantable electronic device related infection: a nationwide population-based cohort study. *Medicine* 2016;**95**:e2587.
149. Hickson LJ, Gooden JY, Le KY, Baddour LM, Friedman PA, Hayes DL, Wilson WR, Steckelberg JM, Sohail MR. Clinical presentation and outcomes of cardiovascular implantable electronic device infections in hemodialysis patients. *Am J Kidney Dis* 2014;**64**:104–110.
150. Parfrey PS, Lauve M, Latremouille-Viau D, Lefebvre P. Erythropoietin therapy and left ventricular mass index in CKD and ESRD patients: a meta-analysis. *Clin J Am Soc Nephrol* 2009;**4**:755–762.
151. Pfeffer MA, Burdmann EA, Chen C-Y, Cooper ME, de Zeeuw D, Eckardt K-U, Feyzi JM, Ivanovich P, Kewalramani R, Levey AS, Lewis EF, McGill JB, McMurray JJV, Parfrey P, Parving H-h, Remuzzi G, Singh AK, Solomon SD, Toto R. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. *N Engl J Med* 2009;**361**:2019–2032.
152. Besarab A, Chernyavskaya E, Motylev I, Shutov E, Kumbar LM, Gurevich K, Chan DTM, Leong R, Poole L, Zhong M, Saikali KG, Franco M, Hemmerich S, Yu KHP, Neff TB. Roxadustat (FG-4592): correction of anemia in incident dialysis patients. *J Am Soc Nephrol* 2016;**27**:1225–1233.
153. Daugirdas JT, Ing TS, Blake PG. *Handbook of Dialysis*. Philadelphia, PA: Wolters Kluwer Health, 2015.
154. K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. *Am J Kidney Dis* 2005;**45**:S1–153.