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Review

Management of Cardiovascular Diseases in Chronic Hemodialysis Patients

Zhen Zhang[1,2,3,4], Yaqiong Wang[1,2,3,4,*]

[1]Department of Nephrology, Zhongshan Hospital, Fudan University, 200032 Shanghai, China
[2]Shanghai Medical Center for Kidney Disease, Shanghai Municipal Health Commission, 200032 Shanghai, China
[3]Shanghai Institute of Kidney and Dialysis, 200032 Shanghai, China
[4]Hemodialysis Quality Control Center of Shanghai, Shanghai Medical Quality Control Management Center, 200032 Shanghai, China
*Correspondence: wang.yaqiong@zs-hospital.sh.cn (Yaqiong Wang)
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Abstract

Hemodialysis (HD) is the main treatment modality for patients with end-stage kidney disease. Cardiovascular diseases (CVD) are highly prevalent in HD patients and are the leading cause of death in this population, with the mortality from CVD approximately 20 times higher than that of the general population. Traditional and non-traditional cardiovascular risk factors accelerate progression of CVD and exacerbate the prognosis in HD patients. This review provides a brief overview of the characteristics of CVD in HD patients, and a description of advances in its management.

Keywords: hemodialysis; end-stage kidney disease; cardiovascular disease

1. Epidemiology of Cardiovascular Diseases (CVD) in Hemodialysis (HD) Patients

CVD is the leading cause of death in patients undergoing HD. Although patients with end-stage kidney disease (ESKD) tend to have hypertension and diabetes mellitus (DM), which are major risk factors for the progression of CVD, studies have shown that ESKD is still an independent risk factor for CVD, distinct from hypertension and DM [1,2]. CVD in HD patients is mainly manifested as left ventricular hypertrophy (LVH), coronary artery disease (CAD), heart failure (HF), arrhythmias, and sudden death. More than 50% of HD patients are reported to have CVD, and the relative risk of death from CVD events in HD patients is 20 times higher than that in the general population.

Globally, 70–90% of HD patients have hypertension [3] and 60–80% develop LVH [4,5], mostly due to eccentric ventricular remodeling induced by increased volume overload (VO) and concentric remodeling induced by increased afterload (high peripheral resistance). Other factors include high cardiac output induced by anemia and arteriovenous fistula, altered central arterial compliance, and dysregulation of neurohormonal systems such as the Renin-Angiotensin-Aldosterone System (RAAS) [6]. Studies have shown that LVH is strongly associated with cardiovascular mortality in patients with chronic kidney disease (CKD) and that the incidence and severity of LVH progressively increase with the progression of CKD [7].

The European Society of Cardiology (ESC) Guidelines for the diagnosis and treatment of acute and chronic HF classify heart failure into HF with reduced ejection fraction (HFrEF) (LVEF $\leq$40%), HF with preserved ejection fraction (HFpEF) (LVEF $\geq$50%), and HF with mid-range ejection fraction (LVEF 41–49%) [8]. It is reported that about 44% of HD patients have HF, 10% have HFpEF, and 13% have HFrEF [9].

CAD is common in patients with CKD, especially in those on HD. The United States Renal Data System (USRDS) report showed that the annual incidence of myocardial infarction and/or angina pectoris in dialysis patients is about 10%. Charytan *et al*. [10] found that in HD patients without angina pectoris, around 40% (28 of 67) had $\geq$50% stenosis in at least one major coronary artery, and 19 patients had severe coronary stenosis. Mortality rates are high in HD patients who develop a myocardial infarction. According to the USRDS data, after an acute myocardial infarction (AMI), the in-hospital mortality rate was 18.8%, and the unadjusted 2-year cumulative probability of death after AMI admission was 71.5% [11].

It is currently estimated that 25% of all-cause deaths among dialysis patients are caused by sudden cardiac death (SCD) [12]. Arrhythmias and sudden cardiac arrest (SCA) are important causes of SCD. The incidence of SCA in dialysis is 4.5–7.0/100,000 dialysis sessions [13,14]. Despite the low incidence, the outcome of SCA in dialysis is poor. Karnik *et al*. [13] observed that only 40% of patients with SCA were successfully resuscitated and remained alive after 2 days, 60% died within 48 hours after the cardiac arrest, and 13% died in the HD unit. In ambulatory patients, the most frequent cause of SCD is ventricular tachyarrhythmias, with ventricular fibrillation (VF) being the most frequent ventricular tachyarrhythmia [15]. By monitoring 75 HD patients using a wearable cardioverter-defibrillator, it

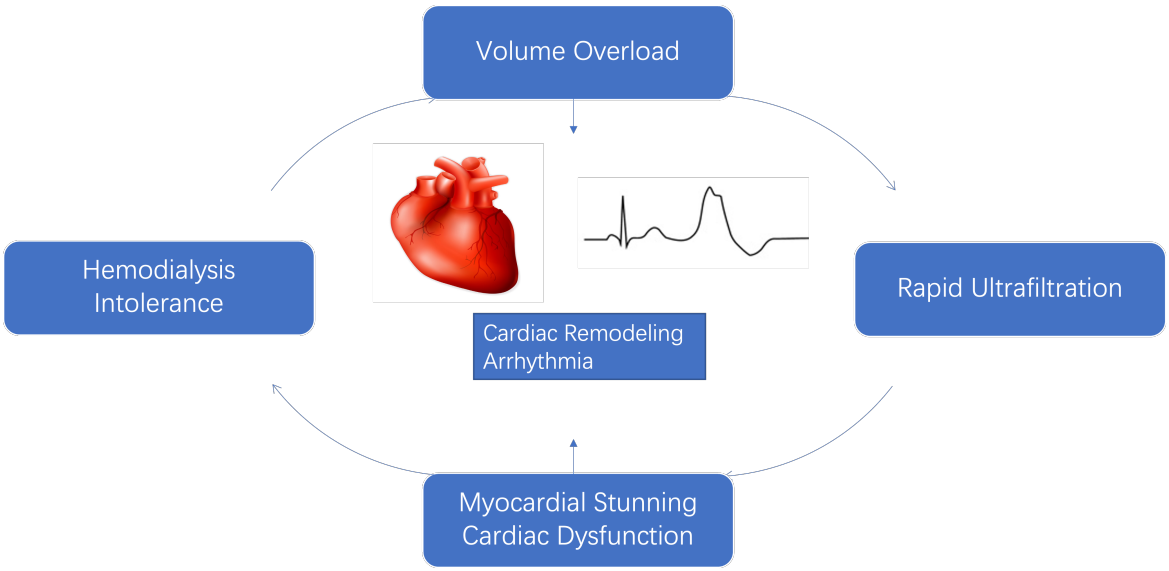

Fig. 1. Potential impact of volume overload, increased ultrafiltration rate and adverse cardiac outcome.

was found that 78.6% of SCA events were due to ventricular tachycardia (VT) or VF, while asystole accounted for 21.4% [16]. In addition, studies have shown that SCD is related to the timing of HD, and occurs during two time intervals, one at the end of a longer dialysis run, and the other during the initial dialysis period [17,18]. As expected, there is a significant correlation between pre-dialysis hyperkalemia and SCD. Patients are at a higher risk of conduction disorders when serum potassium is >5.0 mmol/L. A higher risk for ventricular arrhythmias was associated with a potassium <4.0 mmol/L [19]. In summary, during the dialysis interval, HD patients undergo a relatively rapid transition from mild hypokalemia or normokalemia to hyperkalemia and metabolic acidosis, both of which lead to cardiac electrophysiological instability, resulting in life-threatening arrhythmias.

2. Non-Traditional Risk Factors for CVD in HD Patients

In addition to traditional CVD risk factors such as hypertension, dyslipidemia, and smoking, non-traditional risk factors in HD patients also play an important role in the development of cardiovascular disorders. More effective control of risk factors may contribute to improved survival in HD patients.

2.1 VO and Dialysis-Induce Systemic Stress

VO is directly linked to cardiac remodeling, with recurrent stretching of cardiac chambers [20]. VO is strongly associated with cardiovascular morbidity and mortality. Patients with higher interdialytic weight gains (IDWG) had higher pre-dialysis blood pressure and a higher risk of all-cause and CV mortality [21]. Studies with more objective volume assessment using bioimpedance analysis found that baseline VO and chronic exposure to VO were associated with death in HD patients [22–24].

"Standard" 4-hour, thrice-weekly HD has been the major treatment schedule in most dialysis centers for decades. Unlike continuous urine production by the kidneys, HD is an intermittent therapy that rapidly removes fluid during each session. In anuric HD patients, the fluid volume accumulated between HD sessions almost equals the prescribed ultrafiltration volume. Observational data consistently demonstrated a strong association between high ultrafiltration rate (UFR) and greater mortality, with a threshold around 10–13 mL/kg/hr [25–27]. Rapid fluid removal from intravascular compartment during HD, if not compensated by plasma refilling and proper baroreflex, would impose hemodynamic stress and cause intradialytic hypotension (IDH), resulting in intolerance to HD sessions or inaccurate adjustment of dry weight, thus aggravating VO. High UFR could cause end-organ hypoperfusion even without IDH. Studies have demonstrated that HD could induce global and segmental myocardial ischemia and myocardial regional wall motion abnormalities (RWMAs) [28–31]. Repetitive myocardial injury would accelerate cardiac remodeling and compromise HD tolerance. Patients with HD-induced RWMAs have more premature ventricular complexes [32], decreased ejection fraction [28] and higher mortality [33] (Fig. 1).

Similar adverse effects also occur in other end-organs, including the gut, skeletal muscle, and brain, which may in turn accentuate HD intolerance and systemic inflammation. VO may induce inflammation by damaging the integrity of the bowel wall and the translocation of endotoxin [34]. Inflammation, by increasing capillary permeability and causing hypoalbuminemia, might induce interstitial fluid retention, compromise plasma refilling and ultrafiltration intolerance [35].

This vicious cycle derived from the unphysiologic nature of intermittent HD was summarized in the term "dialysis-induced systemic stress (DISS)", emphasizing the imperfection and flaws of current HD therapy [36,37]. The term DISS encompasses both hemodynamic and non-hemodynamic stress factors.

2.2 Uremic Toxin Retention

As kidney function decreases, uremic toxins accumulate and become biologically active, exerting adverse effects on the cardiovascular system.

Despite the introduction of high-flux dialysis and convective therapy, the removal of protein-bound solutes remains limited. The two iconic protein-bound toxins are p-cresol and indoxyl sulfate (IS). Studies have shown that p-cresol accumulation in CKD patients is closely associated with cardiovascular risk in CKD and is predictive of mortality [38]. *In vitro* studies have shown that p-cresol causes endothelial cell dysfunction *via* a toxic mechanism mediated by Rho kinase activity [39]. Another protein-bound uremic toxin, IS, is derived from tryptophan metabolism and is highly bound to albumin. IS has pro-oxidant and pro-inflammatory effects, triggers an immune response, accelerates CKD progression, and increases the occurrence of CVD events [40]. IS is also a potential CKD-associated pro-thrombotic uremic toxin, inducing tissue factor expression in vascular smooth muscle cells, and increasing the risk of pro-thrombotic properties after vascular intervention in a tissue factor-dependent manner [41].

2.3 Oxidative Stress, Endothelial Cell Dysfunction

The kidney is one of the most important sources of antioxidant enzymes, and decreased kidney function leads to an increase in pro-oxidant substances. Oxidative stress is common in ESKD, which accelerates renal injury by promoting renal ischemia, inducing apoptosis, and stimulating inflammatory responses. Increased levels of asymmetric dimethylarginine (ADMA) in ESKD lead to endothelial dysfunction by inhibiting endothelial cell NO synthase. ADMA levels in ESKD patients are closely associated with endothelial dysfunction as well as cardiovascular events [42]. The depletion of antioxidants and accumulation of oxidation products during HD also result in excessive oxidative stress. In addition, the HD procedure itself promotes the production and accumulation of oxidative products by activating platelets, complement and polymorphonuclear cells, and significantly increasing plasma ROS levels after the HD session [43].

2.4 Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) and Cardiovascular Calcification

Cardiovascular calcification is a well-established and widely acknowledged cardiovascular risk factor in ESKD and HD patients. Vascular calcification involves the trans-differentiation of vascular smooth muscle cells into osteoblast-like cells that induce a phenotypic shift by up-regulating the growth of osteochondrogenic markers, and ultimately initiating the local mineralization process [44]. In dialysis patients, cardiac valve calcification (CVC) in CKD-MBD increases the risk of arrhythmias, SCD, stroke, and mortality. Aortic stenosis is a common consequence of the calcification process, increasing cardiac afterload and further contributing to LVH. A meta-analysis confirmed that the higher the degree of CVC, the higher the mortality in dialysis patients, with CVC increasing cardiovascular mortality by 181% and all-cause mortality by 73% [45]. In addition, studies suggest that CKD-MBD biomarkers such as fetuin-A, osteoprotegerin, and osteopontin are associated with vascular calcification in HD patients. Fetuin-A is a hepatocyte-derived glycoprotein and a potent inhibitor of systemic calcification by facilitating clearance of mineral crystals deposited in the tissues. Compared with healthy controls, plasma fetuin-A concentrations are lower in HD patients, and are associated with vascular calcification and arterial stiffness, as well as increased all-cause and cardiovascular mortality [46].

2.5 Fibroblast Growth Factor-23 (FGF-23) and Klotho

Fibroblast growth factor-23 (FGF-23), a protein secreted by osteoclasts and osteoblasts, works with parathyroid hormone (PTH) in the regulation of phosphate excretion by interacting with the FGF receptor. FGF-23 requires the co-receptor α-Klotho for its physiological activity. FGF-23 reduces blood phosphorus levels in a Klotho-dependent manner by inhibiting 1,25-hydroxyvitamin D and PTH synthesis [47]. It was found that elevated plasma FGF-23 levels were independently associated with rapid CKD progression and CVDs in ESKD patients. FGF-23 caused pathological hypertrophy of isolated rat cardiomyocytes *via* FGF receptor-dependent activation of the calcineurin-NFAT signaling pathway, but this effect was independent of Klotho [48]. A growing body of evidence from animal experiments suggests that Klotho deficiency leads to vascular calcification, myocardial fibrosis and myocardial hypertrophy in patients with CKD [49]. In addition, reduced Klotho production makes the kidney more susceptible to injury and exacerbates uremic cardiomyopathy and vascular calcification.

2.6 Gut Microbes as a Potential Source of Uremic Toxins

The gut microbiome (GM) is now considered to be a metabolically active endogenous organ. Repeated ultrafiltration or fluid removal during HD sessions causes intestinal ischemia, which alters the integrity of the intestinal wall and disrupts the intestinal barrier, resulting in the translocation of bacteria and endotoxins in the circulatory system. Intestinal microecological dysregulation stimulates pro-inflammatory cytokine production, foam cell formation, and oxidative stress, which in turn increases the inflammatory state. Studies of GM alteration in CKD pa-

tients revealed that the proportion of microbiota (*Bifidobacterium spp.* and *Enterobacteriaceae*) is significantly reduced. Changes in the microbiota produce excess uremic toxins such as p-cresol sulfate, IS and trimethylamine nitrogen oxide, and these enteric-derived uremic toxins promote the progression of CKD and CVD [50].

3. HD Optimization for Prevention and Management of CVDs

In dialysis-dependent ESKD patients, the kidneys are incapable of producing sufficient urine to regulate salt and water balance in the body. HD removes fluid and solutes via diffusion and convection. In this section, we briefly describe the current understanding of the optimization of HD that may substantially improve CKD patients' CV outcomes.

3.1 HD Schedule and Volume Control

The first step to achieving desirable volume control is to accurately assess the volume status of the patients and probe the target post-dialysis weight or "dry weight". There is no gold standard for dry weight as the assessment methods are still hight subjective, largely depending on clinical judgment by the dialysis staff, taking into account edema, blood pressure, heart rate, HD tolerance and cardiac biomarkers. The recent application of more objective methods such as bioimpedance analysis is promising, but need to be tested and validated in larger populations [51].

As previously mentioned, aggressive ultrafiltration damages the cardiovascular system and leads to CVD. Increasing total HD time, by increasing the frequency, or prolonging the duration of each HD session, may attenuate the shortcomings of the conventional schedule and improve volume control, as well as solute removal. Two Frequent Hemodialysis Network (FHN) trials, daily and nocturnal, were conducted to assess the benefits of frequent HD compared with conventional HD [52,53]. In the FHN trials, HD performed 6 days per week was associated with improvements in mortality or 12-month change in left ventricular mass, and mortality or 12-month change in self-reported physical health. However, these benefits were not observed in nocturnal HD performed six times per week. Frequent nocturnal HD may improve blood pressure control, LVH, phosphate control, and reduce dialysis-induced myocardial stunning [54,55].

Contrary to frequent HD sessions, incremental HD, a less intensive HD modality with gradual dose increase from once- or twice-a-week to thrice-a-week, has been proposed to preserve residual kidney function (RKF). Preservation of RKF and intradialytic urine volume with incremental HD may provide a more patient-centered treatment [56]. RKF is associated with better volume control [57]. More importantly, patients with RKF experienced other advantages beyond volume compared with oligo-anuric patients, including better quality of life and anemia status, lower C-reactive protein (CRP) levels and erythropoiesis-stimulating agents (ESA) requirements, and ultimately, lower mortality [58–60].

3.2 Implementation of Convective Therapy

Convective therapy was expected to improve the prognosis of dialysis patients through greater and wider clearance of uremic toxins. The HEMO study demonstrated that increasing small molecule solutes (e.g., urea) alone would not improve patient prognosis [61].

Hemodiafiltration (HDF) is a mode of dialysis that combines diffusion and convection to achieve greater removal of solutes in a wide spectrum of molecular weights that includes small solutes and conventional middle molecules. The ESHOL study found that HDF had a lower all-cause and CV mortality when compared with high-flux HD [62]. However, in the convective transport study (CONTRAST), a difference in all-cause mortality vs. low-flux HD was only seen in post hoc analyses of patients with a convective volume $>$18 L [63]. Similarly, the post-hoc analyses of the Turkish (HDF vs. high-flux HD) study showed a difference in CV mortality only in patients with a convective volume $>$17.4 L [64]. In addition, the French Convective versus Hemodialysis in Elderly study did not find a significant benefit of HDF in all-cause and CV mortality [65]. The pooled individual analyses of these randomized controlled trials (RCTs) indicated that HDF reduces the risk of mortality in ESKD patients in a convective-volume-dependent fashion [66]. However, these findings, stratified by delivered convection volume, should be considered observational as the included trials were not designed to evaluate convection volumes, since high convection volumes can only be achieved in patients with sufficient blood flow, who tend to have fewer comorbidities such as diabetes and fewer vascular comorbidities.

3.3 Dialysate Temperature

It was hypothesized that lowering dialysate temperature can increase peripheral vascular resistance, thus reducing the risk of IDH and preserving myocardial perfusion. A study suggested an individualized cool HD abrogates myocardial stunning and stabilizes hemodynamics [67]. Data from other studies indicated that the potential benefits of cool dialysis in maintaining blood pressure comes at the cost of more frequent discomfort, such as shivering or cramps [68,69]. Unfortunately, the latest Personalised cooler dialysate for patients receiving maintenance hemodialysis (MyTEMP) trial, which included 15,413 patients, found that cool dialysis did not reduce the risk of major cardiovascular events after a 4 year follow-up [70].

3.4 Dialysate Composition

For HD patients, especially those with complete loss of kidney function, dialysis is the most important measure of electrolyte removal. The appropriate dialysate compo-

sition is crucial in regulating the electrolyte balance in the body. In this section, we focus on two key electrolytes: sodium and potassium.

3.5 Sodium

Currently, most dialysis centers adopt a dialysate sodium concentration (Na_d) of around 140 mEq/L. Studies have demonstrated that either a high or low Na_d has potential clinical risks and benefits. Higher Na_d usually improves intradialytic hemodynamic stability and HD tolerance at the expense of volume expansion, high blood pressure, and more IDWG. On the other hand, lower Na_d is associated with lower IDWG and blood pressure, but a higher incidence of IDH and intradialytic discomfort. According to the Dialysis Outcome and Practice Patterns Study (DOPPS) data, higher Na_d was associated with lower mortality in patients with a lower pre-dialysis serum sodium concentration [71]. Currently, there is no evidence supporting an optimal fixed sodium dialysate. Therefore, the choice of sodium concentration should be individualized, taking into account the pre-dialysis serum sodium level, HD tolerance, and volume status.

3.6 Potassium

Hyperkalemia is associated with poor outcomes in patients undergoing HD [72,73]. HD can efficiently reduce serum potassium concentration (K_s), but post-dialysis hypokalemia is associated with an increased incidence of ventricular arrhythmias and death [19,74]. Since high or low serum potassium levels can result in adverse effects, a fixed dialysate potassium concentration (K_d) may not be appropriate for all HD patients. In addition, the rapid dialytic removal of potassium due to a high serum-dialysate potassium gradient may provoke arrhythmias and sudden death, especially with low K_d. K_d profiling to maintain a constant serum-dialysate gradient appears to reduce ventricular arrhythmias [75]. Though the lack of automatic potassium profiling capabilities in current HD consoles limits the application of this approach, it raises further concerns about the potential harm of a low K_d dialysate. In a multicenter prospective study, patients using K_d of 1 mEq/L had a higher mortality compared to those receiving a 2 or 3 mEq/L [76]. In the DOPPS comparing K_d 2 vs. 3 mEq/L, no difference in the composite outcome of all-cause mortality and arrhythmias was observed [77].

4. Diagnosis and Treatment of CVDs in HD Patients

There are several explanations why the diagnosis and treatment of CVDs are more complex in HD patients compared to the general population. Most landmark RCTs in the cardiovascular field exclude dialysis patients, the risk stratification scoring tools, diagnostic tools (e.g., biomarkers), as well as therapeutic agents validated in these studies, cannot be directly applied to HD patients. Patients' symptoms, signs and laboratory measurements are, to a great extent, influenced by the HD schedule. It should also be noted that the advent and progress of CV abnormalities is a continuous procession starting long before the initiation of dialysis.

4.1 HF

4.1.1 Diagnosis

The 2021 ESC guidelines for the diagnosis and treatment of HF consider the diagnosis of HF to include (1) symptoms and/or signs; (2) LVEF (LVEF $\leq$40%, LVEF 41–49% or LVEF $\geq$50%); and (3) for the diagnosis of HF-pEF, objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including natriuretic peptide (B-type natriuretic peptide elevation) [8]. The New York Heart Association (NYHA) classification does not take into account the dynamic changes in volume status in dialysis patients, and that patients may have a worse NYHA class before HD than at the end of the HD session. For example, HD patients without clinically relevant cardiac structural abnormalities may exhibit typical manifestations of HF, such as nocturnal paroxysmal dyspnea and edema, due to pre-dialysis VO, which may completely disappear after appropriate dialysis and ultrafiltration. Therefore, the Acute Dialysis Quality Initiative (ADQI) Working Group XI proposed a cardiac function grading scheme dedicated to ESKD patients [78]. This HF staging schema includes the following three elements:

① Standardized echocardiographic evidence of structural and/or functional heart abnormalities;

② Dyspnea occurring in the absence of primary lung disease, including isolated pulmonary hypertension;

③ Response of congestive symptoms to renal replacement treatment (RRT)/ultrafiltration.

The ADQI classification can be summarized into the following classes: Class 1—echocardiographic evidence of heart disease and asymptomatic; Class 2R—dyspnea on exertion that is relieved by RRT/ultrafiltration to NYHA class I level; Class 2NR—dyspnea on exertion that CANNOT be relieved by RRT/ultrafiltration to NYHA class I level; Class 3R—dyspnea with activities of daily life (ADL) that is relieved by RRT/ultrafiltration to NYHA class II level; Class 3NR—dyspnea with ADL that CANNOT be relieved by RRT/ultrafiltration to NYHA class II level; Class 4R—dyspnea at rest that is relieved by RRT/ultrafiltration to NYHA class III level; and Class 4NR—dyspnea at rest that CANNOT be relieved by RRT/ultrafiltration to NYHA class III level. The strength of the proposed classification is the inclusion of nonphysiological periodical fluid removal and may be useful for clinicians to differentiate patients with VO alone, and then be able to adjust the dialysis schedule (e.g., more frequent HD). However, the clinical utility and prognostic value of this HF staging classification still need to be validated in future clinical studies.

In the general population, the biomarkers BNP and N-

terminal pro B-type natriuretic peptide (NT-proBNP) are important for the diagnosis of HF. However, BNP/NT-proBNP is affected by kidney function and is significantly increased in HD patients, making it challenging to establish a diagnostic cut-off value and accurately rule-in or rule-out the presence of HF. Our team found that the median NT-proBNP value is 4992 pg/mL in HD patients without HF symptoms. For HD patients with LVEF $\geq$60%, NT-proBNP $>$5741.5 pg/mL indicated VO in this population, however, it did not provide diagnostic criteria for HF [79]. Other biomarkers related to HF, such as soluble ST2 and galectin-3, though predictive of adverse cardiovascular events and/or outcomes in HD patients [80,81], still require validation to be adopted as a diagnostic tool.

Risk stratification tools generated from the general population or the CKD population are not suitable in dialysis patients, as patients undergoing HD are faced with a very distinct spectrum of risk factors and have an increased CV risk. The real challenge is not distinguishing dark sheep from white ones, but accurately identifying darker ones. A multimarker approach that simultaneously assesses novel biomarkers with conventional biomarkers, which has been tested in patients with HF, may offer additional clinical information and improve risk stratification in the ESKD population [82]. As demonstrated in a study by Zoccali *et al.* [83], compared to traditional risk models, the combined use of CRP, BNP and ADMA increases by about one fifth the explanatory power of all-cause and CV mortality. In a prospective cohort study, the combined use of soluble ST2 (serum stimulation-2) (sST2) and NT-proBNP or hs-cTnT helped identify HD patients at higher risk [80]. This multimarker strategy is pathophysiologically reasonable and clinically promising, since profiles of multiple biomarkers reflecting different aspects of CVDs show a more comprehensive picture in ESKD. However, the benefits gained from the inclusion of over three biomarkers appear modest, and their long-term utility requires further validation.

4.1.2 Treatment

The current recommended pharmacological treatment or guideline-directed medical therapy for HFrEF includes β-blockers, ARNi (angiotensin receptor/neprilysin inhibitor)/ACEI (Angiotensin Converting Enzyme Inhibitor)/ARBs (Angiotensin II receptor blockers), SGLT2i (sodium-glucose cotransporter-2 inhibitors), and mineralocorticoid receptor antagonists (MRAs). In addition, recommendations for HFpEF are made for SGLT2i, MRAs, and ARNi [84]. However, the evidence for these medications for HF in patients on dialysis is scarce and has yet to be validated [85]. A study of HD patients with HFrEF showed that ARNI reduced serum cTnT and sST2 levels and improved LVEF, supporting its safety and efficacy in the ESKD population [86].

At this time, for HD patients, optimal dialysis/ultrafiltration, including good volume control and adequate solute clearance, remains the cornerstone and the goal for the management of HF (See section 3).

4.2 CAD

4.2.1 Diagnosis

CAD is divided into two categories, chronic coronary syndrome (CCS) and acute coronary syndrome (ACS), depending on the onset of symptoms. The early detection of CAD in HD patients is challenging, mainly because of ① High prevalence of asymptomatic CAD. Typical angina pectoris is less common in HD patients; ② Non-specific changes in baseline electrocardiography (EKG) and non-specific elevation of myocardial injury markers due to subclinical myocardial injury induced by electrolyte disturbances (especially hyperkalemia), LVH and uremic pericarditis [87]; ③ Delayed coronary angiography or coronary computed tomographic angiography due to concerns of contrast damaging kidney function in the pre-dialysis CKD G4-G5 patients.

The prevalence of asymptomatic CAD in HD patients is high, and the reasons are multifactorial: diabetic or uremic neuropathy, atypical presentation with symptoms mimicking other conditions (e.g., IDH, anemia), reduced exercise capacity. Non-invasive screening techniques can help with early detection of CAD in asymptomatic patients. Dobutamine stress echocardiography and myocardial perfusion scintigraphy are the preferred screening tools. However, clinical screening is not widely adopted, except for kidney transplant candidates [88]. The Kidney Disease Outcomes Quality Initiative recommended screening for CAD in patients with a history of revascularization, a significant reduction in left ventricular function, and a change in clinical status suggestive of a cardiac problem. Because HD/ultrafiltration has been recognized as a circulatory stressor, pre- and post-HD serial measurements of troponin T and intradialytic EKG monitoring should be considered as screening tests. Nevertheless, besides the cost-utility concerns and accessibility of screening (which varies tremendously across different regions), the challenge of deciding whether to screen asymptomatic patients is the uncertainty of the benefits of coronary revascularization, which will be discussed in the next section. For patients who are candidates for coronary revascularization, invasive testing should be considered in those with a positive stress test or with signs and/or symptoms of CAD.

4.2.2 Treatment

There is limited evidence for the optimal medication strategy of CAD in patients with ESKD. In general, medication therapy focuses on three areas: antithrombotic therapy (anticoagulation/antiplatelet), lipid-lowering therapy and medications for ischemic symptoms [41]. It is important to note that certain anticoagulants are cleared by the kidneys, and their dosages need to be adjusted. For example, enoxaparin, the low molecular weight heparin

(LMWH) with the most clinical evidence in ACS, is mainly cleared by the kidneys, with 40% of the total dose being cleared by the glomerulus, which requires dose reduction in case of severe renal injury and therefore is not recommended for ST-elevation myocardial infarction (STEMI) patients with CKD G5. Among statins, atorvastatin and fluvastatin are mainly metabolized in the liver via Cytochrome P450 3A4 (CYP 3A4) and excreted in bile, only $<$5% is excreted by the kidneys, so no dose adjustment is needed when estimated glomerular rate (eGFR) decreases. However, pravastatin, simvastatin and rosuvastatin are metabolized in the kidneys, so the dose needs to be halved for patients with CKD G3-5. It should be noted that in dialysis-dependent patients, the benefits of statin treatment are inconclusive [89,90]. The Study of Heart and Renal Protection (SHARP) study is a placebo-controlled trial aimed to assess the efficacy of statins plus ezetimibe in patients with moderate-to-severe kidney disease, on or off dialysis. The SHARP trial showed that lowering low density lipoprotein (LDL) cholesterol with simvastatin plus ezetimibe safely reduced the risk of major atherosclerotic events in a wide range of patients with CKD. Though not powered to assess the risk reduction in dialysis-dependent patients, the benefit of statin/ezetimibe was significant in 34% of SHARP participants who began dialysis during the trial and were considered "non-dialysis" patients in the analysis [91]. Therefore, the 2013 Kidney Disease: Improving Global Outcomes (KDIGO) guideline did not recommend initiation of statins in dialysis patients. At the same time, KDIGO also suggested, in patients already receiving statin or the statin/ezetimibe combination at the time of dialysis initiation, that these agents be continued [92].

The role of coronary revascularization in CKD patients is also debated. For CCS, the ISCHEMIA-CKD trial, with 53% of the participants on dialysis and 44% on HD, found no benefit in reducing the risk of death or nonfatal myocardial infarction with an invasive strategy compared with conservative treatment [93]. For ACS, the evidence to date is limited and less robust. For STEMI, the EUDIAL Working Group supports the recommendation from the ESC guideline that the decision on immediate percutaneous coronary intervention (PCI) should be independent of the severity of kidney impairment [94]. In dialysis with non-STEMI, a large observational study suggested a potential benefit of PCI over only medical therapy [95]. When compared to coronary artery bypass graft (CABG) surgery, observational data indicated CABG is associated with higher short-term mortality, but better long-term survival for multivessel lesions [96].

Patients with CKD have a significantly higher risk of adverse clinical events following coronary revascularization compared to the non-CKD population. In particular, HD patients have a significantly increased risk of cerebrovascular events and hemorrhage. At 6 months after angioplasty in dialysis patients, recurrent ischemia was observed in 63% of patients, myocardial infarction in 23%, and death in 13% [97]. Therefore, the benefits of treatment and the potential risk of severe complications need to be weighed, and treatment decisions should be individualized.

4.3 Prevention of SCD

Evidence for the prevention of SCD in HD patients with antiarrhythmic drugs is inconsistent. Some studies have shown that β-blockers reduce the risk of SCD and all-cause mortality in HD patients [98,99]. Another randomized controlled trial that included 114 dialysis patients with dilated cardiomyopathy found that carvedilol was beneficial in reducing all-cause mortality but did not significantly reduce the risk of SCD [100]. Other drugs such as ACEI/ARB, calcium channel blocker (CCB), potassium binding agents and amiodarone have not consistently been found to be effective in preventing SCD in HD patients.

Implantable cardioverter-defibrillators (ICDs) are recommended for the primary prevention of sudden death in patients with LVEF $<$35% and a life expectancy of more than 1 year [101]. But this evidence is mainly derived from trials excluding HD patients. Observational studies suggested that ICD implantation is associated with a reduced risk of SCD in ESKD patients with reduced LVEF ($<$35%) [102,103].

However, ICD implantation in dialysis patients can also lead to undesirable complications, such as a significant increase in ESKD-related infectious complications [104].

In general, ICD implantation may reduce the incidence of lethal arrhythmias, but the benefits may be attenuated due to other causes of death. ICD-related complications and the complex comorbidities of the ESKD population make it difficult to estimate the benefit and risk of ICD implantation. Therefore, the European Dialysis Working Group did not recommend ICD implantation, and the effectiveness and applicability of ICDs for SCD prevention in the dialysis population require further study [105].

4.4 Treatment of Anemia And Iron Deficiency

Anemia is one of the most common complications among patients with advanced CKD. Observational studies have shown that anemia is a risk factor for the development of cardiovascular disease in dialysis patients [106–108]. Clinical treatment options other than blood transfusion were lacking until the use of ESAs. Unexpectedly, the use of ESAs to normalize hemoglobin level ($>$13 g/dL) may increase the risk of death and CVD, instead of improving patient prognosis [109–111]. Given this evidence, current guidelines have lowered the hemoglobin target for ESA treatment [112]. Additionally, ESA hyporesponsiveness (induced by iron deficiency, inflammation, and secondary hyperparathyroidism), rather than the hemoglobin level achieved, was associated with a higher risk of death and cardiovascular events [113].

Hypoxia-inducible factor (HIF) is a key transcription

factor that senses tissue oxygen concentration and regulates physiologic responses to restore oxygen balance. HIF-α subunit, combined with the β subunit, upregulates *EPO* gene expression and iron transport in hypoxia. HIF prolyl hydroxylase inhibitors (HIF-PHIs) are orally administered small molecule compounds that stabilize HIF-α by inhibiting prolyl hydroxylase domain enzymes. HIF-PHIs increase Hb levels and total iron-binding capacity, and decrease hepcidin and ferritin levels [114]. It is hypothesized that HIF-PHIs may better mimic the physiologic process of hypoxia, improving endogenous *EPO* synthesis while diminishing exogenous *EPO* exposure, therefore resulting in a safer treatment. Several HIF-PHIs have been evaluated as oral alternatives to conventional ESA in the CKD/ESKD population [115–119]. Although the noninferiority design of these trials precludes any conclusions on safety issues, HIF-PHIs failed to show a better safety profile than the conventional ESAs.

Iron deficiency (ID) is common in patients undergoing HD and is a notable cause of ESA hyporesponsiveness [120]. Intravenous (IV) iron supplementation is considered the gold standard for HD patients, due to its superiority to oral iron [120]. However, given the safety concerns that IV iron, especially at high-dose, may cause oxidative stress, tissue iron deposition and increased risk of infection, the current guidelines are still inconclusive regarding the optimal management of ID in this population. The PIVOTAL trial was a RCT of 2141 patients undergoing HD randomized to high-dose proactive IV iron sucrose administration or lower-dose reactive administration. After a mean follow-up of 2.1 years, patients receiving proactive IV iron had a lower ESAs dose and transfusion rate, and more importantly, lower incidence of death, nonfatal CV events, and hospitalization, supporting a more liberal IV iron supplementation approach [121]. Interestingly, in patients with HF, ID is also a major co-morbidity. Moreover, ID is a less examined demographic of the complex co-morbidities of HF, renal impairment, and anemia [122]. RCTs in HF patients with ID, demonstrated that IV iron supplementation was safe and effective in improving functional status and exercise capacity, as well as reducing HF hospitalization [123,124]. These findings showed that the CV benefits shown in the PIVOTAL trial were derived from physiological functions of iron beyond those of erythropoiesis.

5. Conclusions

HD patients have a high prevalence of CVD and mortality due to the presence of various cardiovascular risk factors. Optimized management of traditional and non-traditional risk factors may help prevent CVD and improve the prognosis of this population. Recent advances in medications for CVD are promising for ESKD patients, but their safety and efficacy need to be solidified in future well-designed clinical trials. In addition, advancements in dialysis technology may also provide new tools to treat CVD complications in the ESKD population.

Author Contributions

The authors ZZ and YQW were responsible for the design of the work. Both authors drafted and revised the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

References

[1] Fox CS, Matsushita K, Woodward M, Bilo HJG, Chalmers J, Heerspink HJL, *et al*. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. Lancet. 2012; 380: 1662–1673.

[2] Mahmoodi BK, Matsushita K, Woodward M, Blankestijn PJ, Cirillo M, Ohkubo T, *et al*. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without hypertension: a meta-analysis. Lancet. 2012; 380: 1649–1661.

[3] Agarwal R, Nissenson AR, Batlle D, Coyne DW, Trout JR, Warnock DG. Prevalence, treatment, and control of hypertension in chronic hemodialysis patients in the United States. The American Journal of Medicine. 2003; 115: 291–297.

[4] Foley RN, Parfrey PS, Harnett JD. Left Ventricular Hypertrophy in Dialysis Patients. Seminars in Dialysis. 1992; 5: 34–41.

[5] Parfrey PS, Foley RN, Harnett JD, Kent GM, Murray DC, Barre PE. Outcome and risk factors for left ventricular disorders in chronic uraemia. Nephrology, Dialysis, Transplantation. 1996; 11: 1277–1285.

[6] Amann K, Rychlík I, Miltenberger-Milteny G, Ritz E. Left ventricular hypertrophy in renal failure. Kidney International. 1998; 68: S78–S85.

[7] Levin A, Singer J, Thompson CR, Ross H, Lewis M. Prevalent left ventricular hypertrophy in the predialysis population: identifying opportunities for intervention. American Journal of Kidney Diseases. 1996; 27: 347–354.

[8] McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, *et al*. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. European Heart Journal. 2021; 42: 3599–3726.

[9] House AA, Wanner C, Sarnak MJ, Piña IL, McIntyre CW, Komenda P, *et al*. Heart failure in chronic kidney disease:

conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney International. 2019; 95: 1304–1317.
[10] Charytan D, Kuntz RE, Mauri L, DeFilippi C. Distribution of coronary artery disease and relation to mortality in asymptomatic hemodialysis patients. American Journal of Kidney Diseases. 2007; 49: 409–416.
[11] Shroff GR, Li S, Herzog CA. Trends in Mortality Following Acute Myocardial Infarction Among Dialysis Patients in the United States Over 15 Years. Journal of the American Heart Association. 2015; 4: e002460.
[12] Makar MS, Pun PH. Sudden Cardiac Death Among Hemodialysis Patients. American Journal of Kidney Diseases. 2017; 69: 684–695.
[13] Karnik JA, Young BS, Lew NL, Herget M, Dubinsky C, Lazarus JM, *et al*. Cardiac arrest and sudden death in dialysis units. Kidney International. 2001; 60: 350–357.
[14] Pun PH, Lehrich RW, Honeycutt EF, Herzog CA, Middleton JP. Modifiable risk factors associated with sudden cardiac arrest within hemodialysis clinics. Kidney International. 2011; 79: 218–227.
[15] Bayés de Luna A, Coumel P, Leclercq JF. Ambulatory sudden cardiac death: mechanisms of production of fatal arrhythmia on the basis of data from 157 cases. American Heart Journal. 1989; 117: 151–159.
[16] Wan C, Herzog CA, Zareba W, Szymkiewicz SJ. Sudden cardiac arrest in hemodialysis patients with wearable cardioverter defibrillator. Annals of Noninvasive Electrocardiology. 2014; 19: 247–257.
[17] Bleyer AJ, Hartman J, Brannon PC, Reeves-Daniel A, Satko SG, Russell G. Characteristics of sudden death in hemodialysis patients. Kidney International. 2006; 69: 2268–2273.
[18] Genovesi S, Valsecchi MG, Rossi E, Pogliani D, Acquistapace I, De Cristofaro V, *et al*. Sudden death and associated factors in a historical cohort of chronic haemodialysis patients. Nephrology, Dialysis, Transplantation. 2009; 24: 2529–2536.
[19] Sacher F, Jesel L, Borni-Duval C, De Precigout V, Lavainne F, Bourdenx JP, *et al*. Cardiac Rhythm Disturbances in Hemodialysis Patients: Early Detection Using an Implantable Loop Recorder and Correlation With Biological and Dialysis Parameters. JACC: Clinical Electrophysiology. 2018; 4: 397–408.
[20] Loutradis C, Sarafidis PA, Ferro CJ, Zoccali C. Volume overload in hemodialysis: diagnosis, cardiovascular consequences, and management. Nephrology, Dialysis, Transplantation. 2021; 36: 2182–2193.
[21] Kalantar-Zadeh K, Regidor DL, Kovesdy CP, Van Wyck D, Bunnapradist S, Horwich TB, *et al*. Fluid retention is associated with cardiovascular mortality in patients undergoing long-term hemodialysis. Circulation. 2009; 119: 671–679.
[22] Chazot C, Wabel P, Chamney P, Moissl U, Wieskotten S, Wizemann V. Importance of normohydration for the long-term survival of haemodialysis patients. Nephrology, Dialysis, Transplantation. 2012; 27: 2404–2410.
[23] Zoccali C, Moissl U, Chazot C, Mallamaci F, Tripepi G, Arkossy O, *et al*. Chronic Fluid Overload and Mortality in ESRD. Journal of the American Society of Nephrology. 2017; 28: 2491–2497.
[24] Kim YJ, Jeon HJ, Kim YH, Jeon J, Ham YR, Chung S, *et al*. Overhydration measured by bioimpedance analysis and the survival of patients on maintenance hemodialysis: a single-center study. Kidney Research and Clinical Practice. 2015; 34: 212–218.
[25] Saran R, Bragg-Gresham JL, Levin NW, Twardowski ZJ, Wizemann V, Saito A, *et al*. Longer treatment time and slower ultrafiltration in hemodialysis: associations with reduced mortality in the DOPPS. Kidney International. 2006; 69: 1222–1228.
[26] Assimon MM, Wenger JB, Wang L, Flythe JE. Ultrafiltration Rate and Mortality in Maintenance Hemodialysis Patients. American Journal of Kidney Diseases. 2016; 68: 911–922.
[27] Flythe JE, Kimmel SE, Brunelli SM. Rapid fluid removal during dialysis is associated with cardiovascular morbidity and mortality. Kidney International. 2011; 79: 250–257.
[28] Burton JO, Jefferies HJ, Selby NM, McIntyre CW. Hemodialysis-induced cardiac injury: determinants and associated outcomes. Clinical Journal of the American Society of Nephrology. 2009; 4: 914–920.
[29] Burton JO, Jefferies HJ, Selby NM, McIntyre CW. Hemodialysis-induced repetitive myocardial injury results in global and segmental reduction in systolic cardiac function. Clinical Journal of the American Society of Nephrology. 2009; 4: 1925–1931.
[30] McIntyre CW, Burton JO, Selby NM, Leccisotti L, Korsheed S, Baker CSR, *et al*. Hemodialysis-induced cardiac dysfunction is associated with an acute reduction in global and segmental myocardial blood flow. Clinical Journal of the American Society of Nephrology. 2008; 3: 19–26.
[31] Nie Y, Zhang Z, Zou J, Liang Y, Cao X, Liu Z, *et al*. Hemodialysis-induced regional left ventricular systolic dysfunction: HD-induced LV systolic dysfunction. Hemodialysis International. 2016; 20: 564–572.
[32] Burton JO, Korsheed S, Grundy BJ, McIntyre CW. Hemodialysis-induced left ventricular dysfunction is associated with an increase in ventricular arrhythmias. Renal Failure. 2008; 30: 701–709.
[33] Assa S, Hummel YM, Voors AA, Kuipers J, Westerhuis R, de Jong PE, *et al*. Hemodialysis-induced regional left ventricular systolic dysfunction: prevalence, patient and dialysis treatment-related factors, and prognostic significance. Clinical Journal of the American Society of Nephrology. 2012; 7: 1615–1623.
[34] Lau WL, Kalantar-Zadeh K, Vaziri ND. The Gut as a Source of Inflammation in Chronic Kidney Disease. Nephron. 2015; 130: 92–98.
[35] Dekker MJE, van der Sande FM, van den Berghe F, Leunissen KML, Kooman JP. Fluid Overload and Inflammation Axis. Blood Purification. 2018; 45: 159–165.
[36] McIntyre CW. Recurrent circulatory stress: the dark side of dialysis: recurrent circulatory stress in hemodialysis. Seminars in Dialysis. 2010; 23: 449–451.
[37] Canaud B, Stephens MP, Nikam M, Etter M, Collins A. Multitargeted interventions to reduce dialysis-induced systemic stress. Clinical Kidney Journal. 2021; 14: i72–i84.
[38] Meijers BKI, Bammens B, De Moor B, Verbeke K, Vanrenterghem Y, Evenepoel P. Free p-cresol is associated with cardiovascular disease in hemodialysis patients. Kidney International. 2008; 73: 1174–1180.
[39] Ying Y, Yang K, Liu Y, Chen QJ, Shen WF, Lu L, *et al*. A uremic solute, P-cresol, inhibits the proliferation of endothelial progenitor cells via the p38 pathway. Circulation Journal. 2011; 75: 2252–2259.
[40] Barisione C, Ghigliotti G, Canepa M, Balbi M, Brunelli C, Ameri P. Indoxyl sulfate: a candidate target for the prevention and treatment of cardiovascular disease in chronic kidney disease. Current Drug Targets. 2015; 16: 366–372.
[41] Shivanna S, Kolandaivelu K, Shashar M, Belghasim M, Al-Rabadi L, Balcells M, *et al*. The Aryl Hydrocarbon Receptor is a Critical Regulator of Tissue Factor Stability and an Antithrombotic Target in Uremia. Journal of the American Society of Nephrology. 2016; 27: 189–201.
[42] Małyszko J, Matuszkiewicz-Rowińska J. Endothelium, asymmetric dimethylarginine, and atherosclerosis in chronic kidney disease. Polish Archives of Internal Medicine. 2018; 128: 145–147.
[43] Liakopoulos V, Roumeliotis S, Gorny X, Dounousi E, Mertens

PR. Oxidative Stress in Hemodialysis Patients: A Review of the Literature. Oxidative Medicine and Cellular Longevity. 2017; 2017: 3081856.
[44] Vervloet M, Cozzolino M. Vascular calcification in chronic kidney disease: different bricks in the wall? Kidney International. 2017; 91: 808–817.
[45] Wang Z, Jiang A, Wei F, Chen H. Cardiac valve calcification and risk of cardiovascular or all-cause mortality in dialysis patients: a meta-analysis. BMC Cardiovascular Disorders. 2018; 18: 12.
[46] Liabeuf S, Okazaki H, Desjardins L, Fliser D, Goldsmith D, Covic A, *et al*. Vascular calcification in chronic kidney disease: are biomarkers useful for probing the pathobiology and the health risks of this process in the clinical scenario? Nephrology, Dialysis, Transplantation. 2014; 29: 1275–1284.
[47] Edmonston D, Wolf M. FGF23 at the crossroads of phosphate, iron economy and erythropoiesis. Nature Reviews Nephrology. 2020; 16: 7–19.
[48] Faul C, Amaral AP, Oskouei B, Hu MC, Sloan A, Isakova T, *et al*. FGF23 induces left ventricular hypertrophy. The Journal of Clinical Investigation. 2011; 121: 4393–4408.
[49] Xie J, Yoon J, An SW, Kuro-o M, Huang CL. Soluble Klotho Protects against Uremic Cardiomyopathy Independently of Fibroblast Growth Factor 23 and Phosphate. Journal of the American Society of Nephrology. 2015; 26: 1150–1160.
[50] Sircana A, De Michieli F, Parente R, Framarin L, Leone N, Berrutti M, *et al*. Gut microbiota, hypertension and chronic kidney disease: Recent advances. Pharmacological Research. 2019; 144: 390–408.
[51] Huang SHS, Filler G, Lindsay R, McIntyre CW. Euvolemia in hemodialysis patients: a potentially dangerous goal? Seminars in Dialysis. 2015; 28: 1–5.
[52] Chertow GM, Levin NW, Beck GJ, Depner TA, Eggers PW, Gassman JJ, *et al*. In-center hemodialysis six times per week versus three times per week. The New England Journal of Medicine. 2010; 363: 2287–2300.
[53] Rocco MV, Lockridge RS, Jr, Beck GJ, Eggers PW, Gassman JJ, Greene T, *et al*. The effects of frequent nocturnal home hemodialysis: the Frequent Hemodialysis Network Nocturnal Trial. Kidney International. 2011; 80: 1080–1091.
[54] Wong B, Collister D, Muneer M, Storie D, Courtney M, Lloyd A, *et al*. In-Center Nocturnal Hemodialysis Versus Conventional Hemodialysis: A Systematic Review of the Evidence. American Journal of Kidney Diseases. 2017; 70: 218–234.
[55] Jefferies HJ, Virk B, Schiller B, Moran J, McIntyre CW. Frequent hemodialysis schedules are associated with reduced levels of dialysis-induced cardiac injury (myocardial stunning). Clinical Journal of the American Society of Nephrology. 2011; 6: 1326–1332.
[56] Murea M, Moossavi S, Garneata L, Kalantar-Zadeh K. Narrative Review of Incremental Hemodialysis. Kidney International Reports. 2019; 5: 135–148.
[57] Mathew AT, Fishbane S, Obi Y, Kalantar-Zadeh K. Preservation of residual kidney function in hemodialysis patients: reviving an old concept. Kidney International. 2016; 90: 262–271.
[58] Shafi T, Jaar BG, Plantinga LC, Fink NE, Sadler JH, Parekh RS, *et al*. Association of residual urine output with mortality, quality of life, and inflammation in incident hemodialysis patients: the Choices for Healthy Outcomes in Caring for End-Stage Renal Disease (CHOICE) Study. American Journal of Kidney Diseases. 2010; 56: 348–358.
[59] Penne EL, van der Weerd NC, Grooteman MPC, Mazairac AHA, van den Dorpel MA, Nubé MJ, *et al*. Role of residual renal function in phosphate control and anemia management in chronic hemodialysis patients. Clinical Journal of the American Society of Nephrology. 2011; 6: 281–289.
[60] Suda T, Hiroshige K, Ohta T, Watanabe Y, Iwamoto M, Kanegae K, *et al*. The contribution of residual renal function to overall nutritional status in chronic haemodialysis patients. Nephrology, Dialysis, Transplantation. 2000; 15: 396–401.
[61] Eknoyan G, Beck GJ, Cheung AK, Daugirdas JT, Greene T, Kusek JW, *et al*. Effect of dialysis dose and membrane flux in maintenance hemodialysis. The New England Journal of Medicine. 2002; 347: 2010–2019.
[62] Maduell F, Moreso F, Pons M, Ramos R, Mora-Macià J, Carreras J, *et al*. High-efficiency postdilution online hemodiafiltration reduces all-cause mortality in hemodialysis patients. Journal of the American Society of Nephrology. 2013; 24: 487–497.
[63] Grooteman MPC, van den Dorpel MA, Bots ML, Penne EL, van der Weerd NC, Mazairac AHA, *et al*. Effect of online hemodiafiltration on all-cause mortality and cardiovascular outcomes. Journal of the American Society of Nephrology. 2012; 23: 1087–1096.
[64] Ok E, Asci G, Toz H, Ok ES, Kircelli F, Yilmaz M, *et al*. Mortality and cardiovascular events in online haemodiafiltration (OL-HDF) compared with high-flux dialysis: results from the Turkish OL-HDF Study. Nephrology, Dialysis, Transplantation. 2013; 28: 192–202.
[65] Morena M, Jaussent A, Chalabi L, Leray-Moragues H, Chenine L, Debure A, *et al*. Treatment tolerance and patient-reported outcomes favor online hemodiafiltration compared to high-flux hemodialysis in the elderly. Kidney International. 2017; 91: 1495–1509.
[66] Peters SAE, Bots ML, Canaud B, Davenport A, Grooteman MPC, Kircelli F, *et al*. Haemodiafiltration and mortality in end-stage kidney disease patients: a pooled individual participant data analysis from four randomized controlled trials. Nephrology, Dialysis, Transplantation. 2016; 31: 978–984.
[67] Jefferies HJ, Burton JO, McIntyre CW. Individualised dialysate temperature improves intradialytic haemodynamics and abrogates haemodialysis-induced myocardial stunning, without compromising tolerability. Blood Purification. 2011; 32: 63–68.
[68] Mustafa RA, Bdair F, Akl EA, Garg AX, Thiessen-Philbrook H, Salameh H, *et al*. Effect of Lowering the Dialysate Temperature in Chronic Hemodialysis: A Systematic Review and Meta-Analysis. Clinical Journal of the American Society of Nephrology. 2016; 11: 442–457.
[69] Tsujimoto Y, Tsujimoto H, Nakata Y, Kataoka Y, Kimachi M, Shimizu S, *et al*. Dialysate temperature reduction for intradialytic hypotension for people with chronic kidney disease requiring haemodialysis. The Cochrane Database of Systematic Reviews. 2019; 7: CD012598.
[70] Garg AX, Al-Jaishi AA, Dixon SN, Sontrop JM, Anderson SJ, Bagga A, *et al*. Personalised cooler dialysate for patients receiving maintenance haemodialysis (MyTEMP): a pragmatic, cluster-randomised trial. Lancet. 2022; 400: 1693–1703.
[71] Flythe JE, Mc Causland FR. Dialysate Sodium: Rationale for Evolution over Time. Seminars in Dialysis. 2017; 30: 99–111.
[72] Brunelli SM, Du Mond C, Oestreicher N, Rakov V, Spiegel DM. Serum Potassium and Short-term Clinical Outcomes Among Hemodialysis Patients: Impact of the Long Interdialytic Interval. American Journal of Kidney Diseases. 2017; 70: 21–29.
[73] Yusuf AA, Hu Y, Singh B, Menoyo JA, Wetmore JB. Serum Potassium Levels and Mortality in Hemodialysis Patients: A Retrospective Cohort Study. American Journal of Nephrology. 2016; 44: 179–186.
[74] Ohnishi T, Kimachi M, Fukuma S, Akizawa T, Fukuhara S. Postdialysis Hypokalemia and All-Cause Mortality in Patients Undergoing Maintenance Hemodialysis. Clinical Journal of the American Society of Nephrology. 2019; 14: 873–881.
[75] Redaelli B, Locatelli F, Limido D, Andrulli S, Signorini MG, Sforzini S, *et al*. Effect of a new model of hemodialysis potassium removal on the control of ventricular arrhythmias. Kidney

International. 1996; 50: 609–617.
[76] Ferrey A, You AS, Kovesdy CP, Nakata T, Veliz M, Nguyen DV, *et al*. Dialysate Potassium and Mortality in a Prospective Hemodialysis Cohort. American Journal of Nephrology. 2018; 47: 415–423.
[77] Karaboyas A, Zee J, Brunelli SM, Usvyat LA, Weiner DE, Maddux FW, *et al*. Dialysate Potassium, Serum Potassium, Mortality, and Arrhythmia Events in Hemodialysis: Results From the Dialysis Outcomes and Practice Patterns Study (DOPPS). American Journal of Kidney Diseases. 2017; 69: 266–277.
[78] Chawla LS, Herzog CA, Costanzo MR, Tumlin J, Kellum JA, McCullough PA, *et al*. Proposal for a functional classification system of heart failure in patients with end-stage renal disease: proceedings of the acute dialysis quality initiative (ADQI) XI workgroup. Journal of the American College of Cardiology. 2014; 63: 1246–1252.
[79] Wang Y, Cao X, Yu J, Zhang Y, Li X, Chen X, *et al*. Association of N-Terminal Pro-brain Natriuretic Peptide With Volume Status and Cardiac Function in Hemodialysis Patients. Frontiers in Cardiovascular Medicine. 2021; 8: 646402.
[80] Zhang Z, Shen B, Cao X, Liu Z, Chen X, Nie Y, *et al*. Increased Soluble Suppression of Tumorigenicity 2 Level Predicts All-Cause and Cardiovascular Mortality in Maintenance Hemodialysis Patients: A Prospective Cohort Study. Blood Purification. 2017; 43: 37–45.
[81] Hogas S, Schiller A, Voroneanu L, Constantinescu D, Timar R, Cianga P, *et al*. Predictive Value for Galectin 3 and Cardiotrophin 1 in Hemodialysis Patients. Angiology. 2016; 67: 854–859.
[82] Ortiz A, Massy ZA, Fliser D, Lindholm B, Wiecek A, Martínez-Castelao A, *et al*. Clinical usefulness of novel prognostic biomarkers in patients on hemodialysis. Nature Reviews Nephrology. 2011; 8: 141–150.
[83] Mallamaci F, Tripepi G, Cutrupi S, Malatino LS, Zoccali C. Prognostic value of combined use of biomarkers of inflammation, endothelial dysfunction, and myocardiopathy in patients with ESRD. Kidney International. 2005; 67: 2330–2337.
[84] Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, *et al*. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022; 145: e895–e1032.
[85] Quach K, Lvtvyn L, Baigent C, Bueti J, Garg AX, Hawley C, *et al*. The Safety and Efficacy of Mineralocorticoid Receptor Antagonists in Patients Who Require Dialysis: A Systematic Review and Meta-analysis. American Journal of Kidney Diseases. 2016; 68: 591–598.
[86] Lee S, Oh J, Kim H, Ha J, Chun KH, Lee CJ, *et al*. Sacubitril/valsartan in patients with heart failure with reduced ejection fraction with end-stage of renal disease. ESC Heart Failure. 2020; 7: 1125–1129.
[87] Chuang AMY, Nguyen MT, Kung WM, Lehman S, Chew DP. High-sensitivity troponin in chronic kidney disease: Considerations in myocardial infarction and beyond. Reviews in Cardiovascular Medicine. 2020; 21: 191–203.
[88] De Vriese AS, Vandecasteele SJ, Van den Bergh B, De Geeter FW. Should we screen for coronary artery disease in asymptomatic chronic dialysis patients? Kidney International. 2012; 81: 143–151.
[89] Wanner C, Krane V, März W, Olschewski M, Mann JFE, Ruf G, *et al*. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. The New England Journal of Medicine. 2005; 353: 238–248.
[90] Fellström BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J, *et al*. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. The New England Journal of Medicine. 2009; 360: 1395–1407.
[91] Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, *et al*. 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.
[92] Wanner C, Tonelli M, Kidney Disease: Improving Global Outcomes Lipid Guideline Development Work Group Members. KDIGO Clinical Practice Guideline for Lipid Management in CKD: summary of recommendation statements and clinical approach to the patient. Kidney International. 2014; 85: 1303–1309.
[93] Bangalore S, Maron DJ, O'Brien SM, Fleg JL, Kretov EI, Briguori C, *et al*. Management of Coronary Disease in Patients with Advanced Kidney Disease. The New England Journal of Medicine. 2020; 382: 1608–1618.
[94] Burlacu A, Genovesi S, Basile C, Ortiz A, Mitra S, Kirmizis D, *et al*. Coronary artery disease in dialysis patients: evidence synthesis, controversies and proposed management strategies. Journal of Nephrology. 2021; 34: 39–51.
[95] Bhatia S, Arora S, Bhatia SM, Al-Hijji M, Reddy YNV, Patel P, *et al*. Non-ST-Segment-Elevation Myocardial Infarction Among Patients With Chronic Kidney Disease: A Propensity Score-Matched Comparison of Percutaneous Coronary Intervention Versus Conservative Management. Journal of the American Heart Association. 2018; 7: e007920.
[96] Wu P, Luo F, Fang Z. Multivessel Coronary Revascularization Strategies in Patients with Chronic Kidney Disease: A Meta-Analysis. Cardiorenal Medicine. 2019; 9: 145–159.
[97] Sadeghi HM, Stone GW, Grines CL, Mehran R, Dixon SR, Lansky AJ, *et al*. Impact of renal insufficiency in patients undergoing primary angioplasty for acute myocardial infarction. Circulation. 2003; 108: 2769–2775.
[98] Jadoul M, Thumma J, Fuller DS, Tentori F, Li Y, Morgenstern H, *et al*. Modifiable practices associated with sudden death among hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study. Clinical Journal of the American Society of Nephrology. 2012; 7: 765–774.
[99] Foley RN, Herzog CA, Collins AJ. Blood pressure and long-term mortality in United States hemodialysis patients: USRDS Waves 3 and 4 Study. Kidney International. 2002; 62: 1784–1790.
[100] Cice G, Ferrara L, D'Andrea A, D'Isa S, Di Benedetto A, Cittadini A, *et al*. Carvedilol increases two-year survivalin dialysis patients with dilated cardiomyopathy: a prospective, placebo-controlled trial. Journal of the American College of Cardiology. 2003; 41: 1438–1444.
[101] Al-Khatib SM, Yancy CW, Solis P, Becker L, Benjamin EJ, Carrillo RG, *et al*. 2016 AHA/ACC Clinical Performance and Quality Measures for Prevention of Sudden Cardiac Death: A Report of the American College of Cardiology/American Heart Association Task Force on Performance Measures. Journal of the American College of Cardiology. 2017; 69: 712–744.
[102] Genovesi S, Porcu L, Luise MC, Riva H, Nava E, Stella A, *et al*. Mortality, sudden death and indication for cardioverter defibrillator implantation in a dialysis population. International Journal of Cardiology. 2015; 186: 170–177.
[103] Hiremath S, Punnam SR, Brar SS, Goyal SK, Gardiner JC, Shah AJ, *et al*. Implantable defibrillators improve survival in end-stage renal disease: results from a multi-center registry. American Journal of Nephrology. 2010; 32: 305–310.
[104] Polyzos KA, Konstantelias AA, Falagas ME. Risk factors for cardiac implantable electronic device infection: a systematic review and meta-analysis. Europace. 2015; 17: 767–777.
[105] Genovesi S, Boriani G, Covic A, Vernooij RWM, Combe C, Burlacu A, *et al*. Sudden cardiac death in dialysis patients: dif-

ferent causes and management strategies. Nephrology, Dialysis, Transplantation. 2021; 36: 396–405.
[106] Li S, Foley RN, Collins AJ. Anemia, hospitalization, and mortality in patients receiving peritoneal dialysis in the United States. Kidney International. 2004; 65: 1864–1869.
[107] Ma JZ, Ebben J, Xia H, Collins AJ. Hematocrit level and associated mortality in hemodialysis patients. Journal of the American Society of Nephrology. 1999; 10: 610–619.
[108] Brookhart MA, Schneeweiss S, Avorn J, Bradbury BD, Liu J, Winkelmayer WC. Comparative mortality risk of anemia management practices in incident hemodialysis patients. The Journal of the American Medical Association. 2010; 303: 857–864.
[109] Pfeffer MA, Burdmann EA, Chen CY, Cooper ME, de Zeeuw D, Eckardt KU, *et al*. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. The New England Journal of Medicine. 2009; 361: 2019–2032.
[110] Besarab A, Bolton WK, Browne JK, Egrie JC, Nissenson AR, Okamoto DM, *et al*. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. The New England Journal of Medicine. 1998; 339: 584–590.
[111] Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, Wolfson M, *et al*. Correction of anemia with epoetin alfa in chronic kidney disease. The New England Journal of Medicine. 2006; 355: 2085–2098.
[112] Kliger AS, Foley RN, Goldfarb DS, Goldstein SL, Johansen K, Singh A, *et al*. KDOQI US commentary on the 2012 KDIGO Clinical Practice Guideline for Anemia in CKD. American Journal of Kidney Diseases. 2013; 62: 849–859.
[113] Solomon SD, Uno H, Lewis EF, Eckardt KU, Lin J, Burdmann EA, *et al*. Erythropoietic response and outcomes in kidney disease and type 2 diabetes. The New England Journal of Medicine. 2010; 363: 1146–1155.
[114] Gupta N, Wish JB. Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitors: A Potential New Treatment for Anemia in Patients With CKD. American Journal of Kidney Diseases. 2017; 69: 815–826.
[115] Fishbane S, Pollock CA, El-Shahawy M, Escudero ET, Rastogi A, Van BP, *et al*. Roxadustat Versus Epoetin Alfa for Treating Anemia in Patients with Chronic Kidney Disease on Dialysis: Results from the Randomized Phase 3 ROCKIES Study. Journal of the American Society of Nephrology. 2022; 33: 850–866.
[116] Singh AK, Cizman B, Carroll K, McMurray JJV, Perkovic V, Jha V, *et al*. Efficacy and Safety of Daprodustat for Treatment of Anemia of Chronic Kidney Disease in Incident Dialysis Patients: A Randomized Clinical Trial. JAMA Internal Medicine. 2022; 182: 592–602.
[117] Singh AK, Carroll K, McMurray JJV, Solomon S, Jha V, Johansen KL, *et al*. Daprodustat for the Treatment of Anemia in Patients Not Undergoing Dialysis. The New England Journal of Medicine. 2021; 385: 2313–2324.
[118] Eckardt KU, Agarwal R, Aswad A, Awad A, Block GA, Bacci MR, *et al*. Safety and Efficacy of Vadadustat for Anemia in Patients Undergoing Dialysis. The New England Journal of Medicine. 2021; 384: 1601–1612.
[119] Chertow GM, Pergola PE, Farag YMK, Agarwal R, Arnold S, Bako G, *et al*. Vadadustat in Patients with Anemia and Non-Dialysis-Dependent CKD. The New England Journal of Medicine. 2021; 384: 1589–1600.
[120] Johnson DW, Pollock CA, Macdougall IC. Erythropoiesis-stimulating agent hyporesponsiveness. Nephrology. 2007; 12: 321–330.
[121] Macdougall IC, White C, Anker SD, Bhandari S, Farrington K, Kalra PA, *et al*. Intravenous Iron in Patients Undergoing Maintenance Hemodialysis. The New England Journal of Medicine. 2019; 380: 447–458.
[122] Macdougall IC, Canaud B, de Francisco ALM, Filippatos G, Ponikowski P, Silverberg D, *et al*. Beyond the cardiorenal anaemia syndrome: recognizing the role of iron deficiency. European Journal of Heart Failure. 2012; 14: 882–886.
[123] Ponikowski P, Kirwan BA, Anker SD, McDonagh T, Dorobantu M, Drozdz J, *et al*. Ferric carboxymaltose for iron deficiency at discharge after acute heart failure: a multicentre, double-blind, randomised, controlled trial. Lancet. 2020; 396: 1895–1904.
[124] Loncar G, Obradovic D, Thiele H, von Haehling S, Lainscak M. Iron deficiency in heart failure. ESC Heart Failure. 2021; 8: 2368–2379.