F1000Prime REPORTS

Published: 01 August 2014

Recent advances in the management of hemodialysis patients: a focus on cardiovascular disease

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F1000Prime Reports 2014, **6**:72 (doi:10.12703/P6-72)

Abstract

The number of patients requiring chronic hemodialysis is rapidly growing worldwide. Hemodialysis both greatly reduces quality of life and is associated with extremely high mortality rates. Management of care of patients requiring chronic hemodialysis is complex, and randomized controlled trials aimed at reducing primary outcomes of cardiovascular disease events, mortality, or both in this population have largely been unsuccessful. Topics of major concern in the management of maintenance hemodialysis patients as related to these outcomes include the overall cardiovascular disease burden, blood pressure control, anemia, abnormalities in mineral metabolism, and inflammation. The focus of this review is a discussion of these topics on the basis of current recommendations from major organizations, expert opinion, and the available randomized controlled trials to date. These issues are further complicated by sometimes conflicting observational and randomized controlled trial data. Overall, treatment options for reducing these endpoints in maintenance hemodialysis patients are limited, and future randomized controlled trials are essential to continuing to advance care in this population, with the goal of ultimately improving hard outcomes. Such trials should consider new therapies to better target these factors, additional risk factors that have not been well tested to date, and therapies with new targets, including inflammation.

Introduction

The number of patients with end-stage renal disease (ESRD) is rapidly growing worldwide, and the most recent estimate (2011) is greater than 600,000 patients treated for ESRD in the US alone [1]. The cost associated with the care of patients requiring chronic dialysis is substantial, and the current annual estimate for the US exceeds $49 billion [1]. Chronic hemodialysis both greatly reduces quality of life and is associated with extremely high mortality rates, which are up to seven times greater than in the general population [1].

Management of patients requiring hemodialysis is complex, and randomized controlled trials (RCTs) aimed at reducing cardiovascular events and mortality in this population have largely been unsuccessful [2–7].

This review will consider topics of major concern in the management of maintenance hemodialysis patients as related to these outcomes, focusing on the overall cardiovascular disease (CVD) burden, blood pressure control, anemia, abnormalities in mineral metabolism, and inflammation. The focus will be on current recommendations from organizations, including Kidney Disease: Improving Global Outcomes (KDIGO) and the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (K/DOQI), expert opinion, and the available RCTs to date. It is expected that upon completion of this review the reader should have an appreciation for (a) the complex issues related to the management of care in maintenance hemodialysis patients, (b) controversies in management, including conflicting evidence from epidemiological studies

compared with RCTs, and (c) the need for future RCTs to further advance patient care and ultimately reduce mortality in this population.

Cardiovascular disease burden

Adjusted (for age, race, and gender) all-cause mortality rates are 7- to 8-fold greater in patients requiring chronic hemodialysis compared with the general population, and approximately 40% of deaths in this population are attributable to cardiovascular causes [1,8]. Risk factors for CVD in maintenance hemodialysis patients include both traditional risk factors such as diabetes and hypertension as well as unique non-traditional risk factors, including inflammation, oxidative stress, anemia, vascular calcification, and fluid and electrolyte shifts [9-11]. Notably, the National Kidney Foundation considers patients with chronic kidney disease (CKD) to be in the highest risk group (i.e. a coronary artery disease risk equivalent) for subsequent cardiovascular events [12]. As much as 50% of deaths in maintenance hemodialysis patients are attributable to cardiovascular causes [13], influenced in part by the development of atherosclerosis and arteriosclerosis, left ventricular hypertrophy (LVH), and sudden cardiac death.

The incidence and severity of coronary artery disease increases with declining estimated glomerular filtration rate (eGFR) and is present in over half of all patients with ESRD [14,15]. Atherosclerotic lesions are also characterized by vascular calcification. Intimal calcification occurs focally and is associated with both inflammation and overall atherosclerotic plaque burden [16]. Medial calcification also occurs, resulting from elastic fiber mineralization and vascular smooth muscle cell phenotypic changes resulting in upregulation of osteogenic programs [17]. This type of calcification is the more common form in ESRD and is associated with arterial stiffness, reduced myocardial perfusion, LVH, and heart failure [18]. The presence and extent of vascular calcification independently predicts future CVD and mortality in patients with ESRD [19,20].

Another important risk factor is the development of LVH, which occurs in over half of patients with an eGFR of less than 30 mL/minute per 1.73 m^2 [21]. Major mechanisms contributing to LVH are pressure overload, often resulting from long-standing hypertension and increased arterial stiffness and volume overload [22]. In addition, CKD-specific factors, including renin angiotensin aldosterone system (RAAS) activation, oxidative stress, inflammation, and severe anemia, play a role [22,23]. Finally, sudden cardiac death, resulting primarily from ventricular arrhythmias, accounts for the majority of cardiovascular deaths in patients with ESRD and this appears to be unrelated to the presence of coronary artery disease [1,24]. Contributing factors include electrolyte abnormalities, rapid electrolyte changes during hemodialysis, LVH, and sympathetic nervous system activation [24,25].

The major RCTs aimed at reducing CVD events or mortality in patients with ESRD are outlined in Table 1. Overall, these trials, which have included targeting anemia [2], altering hemodialysis dose and flux [3], lowering lipids [4,6,26], reducing homocysteine levels [5], and treating secondary hyperparathyroidism [7], have been largely unsuccessful in reducing primary outcomes of CVD events, mortality, or both. The exception is the Study of Heart and Renal Protection (SHARP), which demonstrated a 17% [rate ratio 0.83, 95% confidence interval (CI) 0.74 to 0.94] lower relative risk of first major atherosclerotic event in a combined population of patients with CKD (n = 6,247) and maintenance dialysis patients (n = 3,023) with a combined treatment of simvastatin plus ezetimibe [26]. There was no significant reduction in relative risk in the subgroup of dialysis patients alone; however, the study was not powered to assess CKD and dialysis subgroups separately.

Of note, in the Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events (EVOLVE) trial, there was a nominally significant reduction in risk in the primary composite endpoint (time to death, myocardial infarction, hospitalization for unstable angina, heart failure, or peripheral vascular event) with cinacalcet treatment in patients with moderate-to-severe hyperparathyroidism receiving maintenance hemodialysis after adjustment for baseline characteristics [7]. However, in the unadjusted, intent-to-treat analysis, there was no reduction in primary composite endpoint (hazard ratio 0.93, 95% CI 0.82 to 1.02). Finally, also included in Table 1 is a recent trial (Hypertension in Hemodialysis Patients Treated with Atenolol or Lisinopril, or HDPAL) comparing treatment with a beta-blocker (atenolol) with angiotensin-converting enzyme inhibitor (ACEI – lisinopril) to achieve home blood pressure control to less than 140/90 mm Hg [27]. Although the primary outcome of the study was change in left ventricular mass index rather than CVD events or mortality, the study is noteworthy because it was terminated early because of an increased incidence rate ratio of serious cardiovascular events (2.36, 95% CI 1.36 to 4.23) as well as an increased composite of myocardial infarction, stroke, congestive heart failure, and cardiovascular-related death (2.29, 95% CI 1.07 to 5.21) in the lisinopril group compared with the atenolol group. This study is discussed further in the following section.

Table 1. Major randomized controlled trials targeting a reduction in cardiovascular disease events, mortality, or both

Study	Population	Study design	Primary outcome	Average follow-up time	Major results
Normal Hematocrit Study [2]	N = 1233 maintenance HD patients with clinical evidence of congestive heart failure or ischemic heart disease	Epoetin alfa dosed to maintain Hct of 42% versus 30% (open-label)	Length of time to death or first non-fatal MI	14 months (median)	Although the difference in event-free survival between the two groups did not reach the pre-specified statistical stopping boundary, the study was halted early. Risk ratio for the high-Hct group versus low-Hct group 1.3 (95% CI 0.9-1.9)
HEMO [3]	N = 1846 maintenance HD patients undergoing treatment 3 times per week	2×2 factorial design with standard versus high dialysis dose and low-flux versus high-flux dialyzer	Death from any cause	2.8 years (mean)	No effect of dose or flux on primary outcome High- versus standard-dose relative risk 0.96 (95% CI 0.84-1.10) High- versus low-flux relative risk 0.92 (95% CI 0.81-1.05)
4D study [4]	N = 1255 type II diabetics receiving maintenance HD	Atorvastatin (20 mg/day) versus placebo	Composite of CV death, non-fatal MI, or stroke	4 years (median)	No reduction in 1° endpoint: relative risk 0.92 (95% CI 0.77-1.1) or total mortality Reduced 2° outcome of cardiac events combined: 0.82 (0.68-0.99), but increased risk of fatal stroke 2.03 (1.05-3.93)
HOST [5]	N = 2056 total; n = 751 ESRD (98% male)	Capsule with 40 mg folic acid, 100 mg B6, and 2 mg B12 versus placebo	All-cause mortality	3.2 years (median)	No reduction in all-cause mortality: hazard ratio 1.04 (95% CI 0.91-1.18) for entire study population For ESRD subgroup: hazard ratio = 1.04 (95% CI 0.83-1.28)
AURORA [6]	N = 2776 maintenance HD patients (50-80 years)	Rosuvastatin (10 mg/day) versus placebo	CV death, non-fatal MI, or non-fatal stroke	3.8 years (median)	Statin had no effect on 1° outcomes: hazard ratio 0.96 (95% CI 0.84-1.11)
SHARP [26]	N = 9270 total; n = 3023 receiving maintenance dialysis; no CVD history; at least 40 years of age	Simvistatin (20 mg/day) + ezetimibe (10 mg/day) versus placebo	First major atherosclerotic event (non-fatal myocardial infarction or coronary death, non-hemorrhagic stroke, or any arterial revascularization procedure)	4.9 years (median)	17% lower risk of 1° outcome: rate ratio 0.83 (95% CI 0.74-0.94) No change in rate ratio in the subgroup of dialysis patients (0.90; 95% CI 0.75-1.08), despite change in non-dialysis subgroup (0.78; 95% CI 0.67-0.91); however, not powered to assess these groups separately No change in mortality (vascular or total), but not primary outcome → would have needed larger sample size to detect based on the rate of event occurrence
EVOLVE [7]	N = 3883 patients with moderate-to-severe hyperparathyroidism receiving maintenance HD	Cinacalcet (progressive dose escalation) versus placebo	Composite of time to death, MI, hospitalization for unstable angina, heart failure, or peripheral vascular event	21.2 months (active) and 17.5 months (placebo (median)	In unadjusted, intent-to-treat analysis, no reduction in primary outcome with cinacalcet: hazard ratio 0.93 (95% CI 0.82-1.02) After adjustment for baseline characteristics, nominally significant reduction of 12% (hazard ratio 0.88; 95% CI 0.79-0.97) Power was lost because lower-than-anticipated event rate; higher dropout in active group
HDPAL [27]	N = 200 maintenance HD patients with LVH + hypertension	Beta-blocker (atenolol) versus ACE inhibitor (lisinopril) to achieve home blood pressure control to <140/90 mm Hg	Change in left ventricular mass index	12 months	Study terminated early because serious CV events (IRR 2.36, 95% CI 1.36-4.23), a composite of MI, stroke, congestive heart failure, and CV-related death (IRR 2.29, 95% CI 1.07-5.21) as well as all-cause hospitalizations (IRR 1.61, 95% CI 1.18-2.19) were all greater in the lisinopril versus atenolol group.

Abbreviations: ACE, angiotensin-converting enzyme; AURORA, A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events; CI, confidence interval; CV, cardiovascular; ESRD, end-stage renal disease; EVOLVE, Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events; Hct, hematocrit; HD, hemodialysis; HDPAL, Hypertension in Hemodialysis Patients Treated with Atenolol or Lisinopril; HEMO, the Hemodialysis study; HOST, Homocysteinemia in Kidney and End Stage Renal Disease ; IRR, incidence rate ratio; LVH, left ventricular hypertrophy; MI, myocardial infarction; SHARP, Study of Heart and Renal Protection.

Blood pressure control

Blood pressure is often poorly controlled and hypertension is very common in maintenance hemodialysis patients, and both are important predictors of all-cause mortality [1,28]. Though recommending pharmacologic treatment to lower blood pressure to a goal of less than 140/90 mm Hg in patients with non-dialysis-dependent CKD, the recently released Eighth Joint National Committee (JNC 8) guidelines issue no specific recommendation for maintenance dialysis patients [29]. Similarly, the recent KDIGO Blood Pressure Work Group clinical practice guidelines do not make specific recommendations for patients with ESRD, citing a lack of available robust evidence to guide such a recommendation [30]. Instead, the text refers the reader to the 2005 clinical practice guideline from K/DOQI, which recommends that pre-hemodialysis blood pressure and post-hemodialysis blood pressure targets be less than 140/90 and less than 130/80 mm Hg, respectively [31].

There is a controversy surrounding ideal blood pressure in maintenance dialysis patients, as epidemiological data have demonstrated a reverse J- or U-shaped curve of risk of morality with blood pressure [32,33]. This may be explained in part by confounding factors, such that blood pressure is lower in individuals with antecedent cardiac disease, poor overall health, or both [33]. In addition, the association between blood pressure and mortality may change over time in chronic hemodialysis patients [34]. Of note, this association has never been confirmed in an RCT. Chronic hemodialysis patients also exhibit great blood pressure variability, and this variability is a significant predictor of all-cause mortality [35,36]. To add a further complication, home blood pressure measurements may associate more closely with CVD than clinic blood pressure [37]. Although it is clear that pre- and post-hemodialysis blood pressure differ from interdialytic ambulatory blood pressure, which at times may be unsatisfactory, the former is more often used, as home and ambulatory blood pressure are often not feasible [38,39].

Overall, studies on antihypertensive agents in maintenance hemodialysis patients have been limited, and evidence available to guide practitioners is poor [39]. A 2010 recommendation from a KDIGO controversies conference stated that RAAS inhibitors, beta-blockers, and calcium channel blockers should all be strongly considered in this population, despite the lack of RCTs [39]. However, the very recently halted HDPAL study [27] (discussed above and in Table 1) suggests that beta-blockers may be superior to ACEI in preventing cardiovascular morbidity and all-cause hospitalization in this population of maintenance hemodialysis patients with LVH and hypertension. An ongoing Italian prospective open-label RCT called Angiotensin-Converting Enzyme Inhibitors in Hemodialysis (ARCADIA – ClinicalTrials.gov identifier NCT00985322), which is comparing 2 years of treatment with an ACEI to non-RAAS inhibitor therapy on a composite endpoint of cardiovascular death and non-fatal myocardial infarction and stroke in chronic hemodialysis patients with LVH and hypertension, will provide a more definitive answer.

Factors that complicate blood pressure control in maintenance hemodialysis patients include the roles of fluid status and sodium balance. ESRD is characterized by a positive sodium balance and increased extracellular fluid volume, both of which contribute to hypertension. Thus, normalizing fluid and sodium balance is key in controlling blood pressure and reducing cardiovascular risk [39,40]. Other unique considerations in selecting antihypertensive agents in this population include timing (due to clearance with hemodialysis), impaired kidney excretion of drugs, and increased propensity to side effects [39,41]. KDIGO recommends considering individual patient circumstances, including CVD history, occurrence of interdialytic hypotension, and vascular access thrombosis, in the treatment of hypertension of maintenance dialysis patients [39].

Anemia

In addition to hypertension, the frequency of anemia increases with CKD progression, affecting nearly all chronic hemodialysis patients [42]. The major cause of anemia is insufficient production of erythropoietin by the kidney [43]. Maintenance hemodialysis patients also have increased iron losses, resulting from impaired absorption, increased bleeding, frequent phlebotomy, and blood trapping by the hemodialysis apparatus [42]. KDIGO recommends testing for anemia in non-anemic ESRD patients when clinically indicated and every 3 months and diagnosing anemia in adults and children more than 15 years of age when the hemoglobin concentration is less than 13.0 g/dL in males and less than 12.0 g/dL in females [44]. KDIGO also recommends that treatment options, which include erythropoiesis-stimulating agents (ESAs) and intravenous iron as well as target hemoglobin levels, balance the potential benefits and risk of harm to the patient.

The goal of intravenous iron is to ensure adequate stores for erythropoiesis, correct iron deficiency, and prevent it from occurring if ESA is also used [44]. KDIGO recommends a trial of intravenous iron for adults on maintenance hemodialysis with anemia if serum transferrin saturation is less than 30%, ferritin is less than 500 ng/mL, and an increase in hemoglobin or a decrease in ESA dose or

both are desired, with subsequent iron therapy guided by clinical response [44]. Furthermore, KDIGO recommends that all correctable causes of anemia (e.g. iron deficiency and inflammation [45]) be addressed prior to initiating ESA therapy. The overall recommendation is that ESA be used to avoid hemoglobin levels falling to less than 9.0 g/dL, with an initiation when hemoglobin level is 9 to 10 g/dL, and that in general therapy not be used to maintain hemoglobin of greater than 11.5 g/dL or to intentionally increase hemoglobin to greater than 13 g/dL. Individual considerations need to be made regarding the frequency, dose, and type of ESA. Hemoglobin levels should continue to be tested when clinically indicated and at least monthly.

These recommendations have arisen from controversial and (by comparison) conflicting epidemiological and randomized controlled study data. Epidemiological data supported an inverse association of hemoglobin with mortality [46,47] and other adverse outcomes such as cardiovascular events [48] up to the normal range. However, correction of anemia has had opposing results in RCTs. The earliest trial was the Normal Hematocrit Study (Table 1), which compared partial (to a hematocrit of 31%) and full (to a hematocrit of 40%) correction of anemia with ESA (epoetin-alfa) in 1233 prevalent hemodialysis patients with symptomatic heart failure or ischemic heart disease on the composite primary outcome of time to death or first non-fatal myocardial infarction [2]. In contrast to the epidemiological data, full correction of anemia tended to increase cardiovascular events (risk ratio 1.3, 95% CI 0.9 to 1.9), and the trial was halted early.

Two subsequent RCTs, although performed in non-dialysis-dependent CKD patients, found similar results of increased risk (of cardiovascular events [49] and initiation of dialysis—with no change eGFR rate of fall—[50]) with ESA to correct anemia to a higher as opposed to a lower hemoglobin target. In contrast, the most recent and largest (n = 4038) study to date—the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT)—found no difference in the two primary endpoints of (1) a composite of death and cardiovascular events and (2) composite of death and progression to ESRD in patients with stage 3 to 4 CKD and type 2 diabetes mellitus treated with ESA (darbepoeitin-alfa) to achieve a target level of hemoglobin of 13 g/dL or placebo (with rescue if the hemoglobin level is less than 9 g/dL) [51]. However, the risk of stroke and venous thrombo-embolic events was increased in the treated group. Of note, an additional study in incident hemodialysis patients without symptomatic heart disease found no change in the primary endpoint of left ventricular mass index with full as opposed to partial correction of hemoglobin with ESA (epoetin-alfa) [52]. Overall, the randomized controlled study data are inconsistent with the epidemiological data, thus influencing KDIGO's more conservative recommendations in the treatment of anemia in CKD and ESRD. These differences in results may be partially explained by the fact that the epidemiological data included patients with more severe anemia than the RCTs, or perhaps by the fact that patients requiring the highest dose of ESA also have higher systemic inflammation [53].

Mineral metabolism

With declining kidney function, there are progressive alterations in mineral metabolism, including changes in levels of calcium, phosphorus, and parathyroid hormone (PTH), which associate with increased risk of mortality [54,55]. The most comprehensive evidence of this occurrence in maintenance hemodialysis patients is from the international Dialysis Outcomes and Practice Pattern Study (DOPPS), which collected data on 17,236 patients in the US, Europe, and Japan from 1996 to 2001 [56]. The majority of patients fell outside of the recommended range for calcium, phosphorus, and intact PTH (iPTH), and higher levels of all three metabolites were significantly associated with increased risk of all-cause and cardiovascular mortality.

In DOPPS, 50% of maintenance hemodialysis patients had albumin-corrected calcium above and 9% below the recommended guideline range [56]. Additional observational studies have also supported an increased relative risk of mortality with hypercalcemia [57,58]. KDIGO recommends checking serum calcium levels every 1 to 3 months in maintenance dialysis patients and maintaining serum calcium levels within normal limits [54]. In the presence of hypercalcemia, it is recommended to limit use of calcium-based phosphate binders, 1,25 dihydroxyvitamin D [$1,25(OH)_2D$ or calcitriol], and $1,25(OH)_2D$ analogs [54]. Finally, KDIGO suggests using a dialysate calcium concentration of between 1.25 and 1.50 mmol/L (2.5 and 3.0 mEq/L) [54].

Increased serum phosphorus level, even in the normal range, is consistently and independently associated with increased risk of cardiovascular events and mortality in maintenance hemodialysis patients [59-62]. KDIGO recommends checking serum phosphorus levels every 3 months in these patients and treating hyperphosphatemia toward the normal range (2.5 to 4.5 mg/dL) [54]. K/DOQI recommends treating hyperphosphatemia to a range of 2.5 to 5.5 mg/dL [63]. Options for the treatment of hyperphosphatemia include calcium-based phosphate binders and non-calcium binders (e.g. sevelamer hydrochloride (HCl), sevelamer carbonate, and lanthanum

carbonate) as well as dietary phosphate restriction [54]. KDIGO also suggests increasing dialytic phosphate removal in the treatment of persistent hyperphosphatemia [54].

Observational data support that treatment with a phosphate binder of any type provides a survival advantage in maintenance hemodialysis patients [64] and that sevelamer may reduce risk of mortality more effectively than calcium-based phosphate binders [65]. RCTs support that sevelamer may slow vascular calcification [59,66,67], but results are not consistent across all studies [68,69]. However, in the largest (n = 2013) RCT to date (Dialysis Clinical Outcomes Revisited, or DCOR), there was no difference in all-cause mortality in maintenance hemodialysis patients treated with sevelamer HCl as opposed to a calcium-based phosphate binder [70]. This is in contrast with a smaller (n = 127) study of incident hemodialysis patients which found an increased risk of mortality in the calcium-based binder group compared with the sevelamer HCl-treated group [59], and a recent meta-analysis that found a decreased risk of all-cause mortality in patients with CKD treated with non-calcium-based phosphate binders as opposed to calcium-based phosphate binders [71].

Finally, increased iPTH levels are also associated with increased cardiovascular events and mortality in maintenance hemodialysis patients, with an inflection point of around 400 to 600 pg/mL [55]. KDIGO recommends a target of two to nine times the upper limit of normal (i.e. 130 to 585 pg/mL) [54], and K/DOQI recommends a target of 150 to 300 pg/mL [63]. Treatment options include vitamin D [$1,25(OH)_2D$ and $1,25(OH)_2D$ analogs] and type II calcimimetics, which decrease PTH release by "mimicking" an increase in intracellular calcium through a conformation change in the calcium-sensing receptor [54]. Cinacalcet is the only type II calcimimetic available for clinical use and is approved by the US Food and Drug Administration to treat secondary hyperparathyroidism in dialysis patients. Observational data have shown that $1,25(OH)_2D$ analogs increase survival, but this is likely confounded by indication [58,72,73] and is not a consistent finding [74,75]. Observational data have also shown no further benefit of cinacalcet use in maintenance hemodialysis patients compared with $1,25(OH)_2D$ analogs [76].

In an RCT of maintenance hemodialysis patients with coronary calcification, treatment with cinacalcet plus low-dose $1,25(OH)_2D$ or an analog lowered the rate and extent of calcification progression [77]. However, the best evidence to date on the efficacy of treatment of secondary hyperparathyroidism for reducing risk of cardiovascular events or mortality in maintenance hemodialysis patients is from the EVOLVE study [7]. As discussed previously (see above and Table 1), in the unadjusted, intent-to-treat analysis, there was no reduction in primary composite endpoint with treatment with cinacalcet. Several editorials as well as letters to the editor regarding potential considerations in the interpretation of these results have been published [78–80].

Inflammation

An important future direction of RCTs to reduce cardiovascular events, mortality, or both is targeting systemic inflammation in chronic hemodialysis patients. Although no clear definition of inflammation is established in this population, levels of greater than 5 to 10 mg/L of the acute-phase reactant C-reactive protein (CRP) have been proposed by National Kidney Foundation K/DOQI guidelines as a marker of inflammation [31]. When CRP is used as a marker, chronic systemic inflammation is highly prevalent in hemodialysis patients and is an independent predictor of all-cause and cardiovascular mortality [81,82]. CRP expression is driven mainly by interleukin-1 (IL-1), a pleiotropic pro-inflammatory cytokine elevated in chronic hemodialysis patients [83,84] and also predictive of overall and cardiovascular mortality [85]. The pro-inflammatory cytokine IL-6 is also a strong predictor of cardiovascular mortality in this population [86,87].

Whether inhibiting inflammatory pathways in chronic hemodialysis patients may reduce cardiovascular and all-cause mortality is currently untested. Early work in this area supports that this may be an important future direction for randomized clinical trials. It was recently demonstrated that blockade of the pleiotropic pro-inflammatory cytokine IL-1β is efficacious in reducing circulating inflammatory markers in maintenance hemodialysis patients [88]. Determining whether reducing inflammation via inhibition of IL-1β or other pathways reduces cardiovascular mortality is a novel and important future direction for RCTs.

Conclusions

Morbidity and mortality in maintenance hemodialysis patients are extremely high, and management of care is complex. Among the issues important to care as related cardiovascular outcomes are the cardiovascular disease burden, blood pressure control, anemia, abnormalities in mineral metabolism, and inflammation. These topics are complicated by sometimes conflicting observational and RCT data. The RCTs to date have been largely unsuccessful in reducing primary outcomes of CVD events, mortality, or both. It is possible that, although RCTs to date have been ineffective, newer therapies targeting these factors may be more successful, such as

targeting inflammation to treat anemia and using fibroblast growth factor-23 inhibitors to treat abnormalities in mineral metabolism. In addition, certain risk factors, including the efficacy of phosphate lowering and adequate blood pressure control to reduce mortality, still have not been well tested in RCTs to date. Finally, new directions are key for future RCTs, with reductions in inflammation being one example of a very attractive target. As treatment options for reducing CVD events, mortality, or both in maintenance hemodialysis are currently limited, future RCTs related to each of these points should be considered, with the goal of ultimately improving hard outcomes.

Abbreviations

ACEI, angiotensin-converting enzyme inhibitor; CI, confidence interval; CKD, chronic kidney disease; CRP, C-reactive protein; CVD, cardiovascular disease; DOPPS, Dialysis Outcomes and Practice Pattern Study; eGFR, estimated glomerular filtration rate; ESA, erythropoiesis-stimulating agent; ESRD, end-stage renal disease; EVOLVE, Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events; HCl, hydrochloride; HDPAL, Hypertension in Hemodialysis Patients Treated with Atenolol or Lisinopril; IL, interleukin; iPTH, intact parathyroid hormone; KDIGO, Kidney Disease: Improving Global Outcomes; K/DOQI, Kidney Disease Outcomes Quality Initiative; LVH, left ventricular hypertrophy; PTH, parathyroid hormone; RAAS, renin angiotensin aldosterone system; RCT, randomized controlled trial.

Disclosures

The data reported here have been supplied by the United States Renal Data System (USRDS). The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy or interpretation of the U.S. government.

Acknowledgments

This work was supported by the American Heart Association (12POST11920023).

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