NEPHROLOGY – EDITORIAL

Cardiovascular events in chronic dialysis patients: emphasizing the importance of vascular disease prevention

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Abstract Cardiovascular disease is the leading cause of death in both chronic kidney disease and peritoneal dialysis/hemodialysis patients. Vascular disease prevention in these patients is therefore important to reduce the incidence of cardiovascular events and the high morbidity and mortality. This Editorial discusses the traditional, (1) smoking, (2) dyslipidemia, (3) body mass index, (4) glycemic control and (5) blood pressure, and non-traditional, (1) anemia, (2) vitamin D/hyperparathyroidism, (3) calcium/phosphorus metabolism and (4) magnesium, risk factors in renal patients. Current evidence does not support routine statin use and antiplatelet medication to dialysis patients. Patient compliance and adherence to proposed measures could be essential to reduce cardiovascular events and mortality rates in this high-risk population.

Keywords Hemodialysis · Peritoneal dialysis · Vascular disease prevention · Mortality · Chronic kidney disease

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Introduction

Kim et al. [1] in this issue of *International Urology and Nephrology* report that plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) levels can predict the risk of acute ischemic stroke episodes in patients on chronic hemodialysis. Cardiovascular disease (CVD) is the leading cause of death in patients with chronic kidney disease (CKD) stages 4 [2, 3] and 5, as well as in those on maintenance peritoneal dialysis or hemodialysis [4–6]. Cardiovascular mortality is 10–20 times higher in dialysis patients compared with age-matched individuals in the general population [5].

Peritoneal dialysis and hemodialysis have improved considerably during the last decades and both peritoneal dialysis [6] and hemodialysis [7] demonstrate excellent long-term (5–10 years) results. Assisted peritoneal dialysis also offers important advantages, particularly for the elderly population [8]. In addition to promoting physical and cognitive functioning [9], the establishment and strict adherence to vascular disease prevention measures offers the opportunity to reduce the high cardiovascular events and mortality

rates in dialysis patients. This Editorial will discuss the role of traditional as well as non-traditional risk factors of cardiovascular mortality in dialysis patients and the importance of their control. Among traditional risk factors, the role of body mass index [10–12] and blood pressure [13–17] is discussed more extensively elsewhere; these risk factors are therefore not covered in this Editorial.

Traditional risk factors

Smoking

A study in the early 1980s suggested that smoking may have more detrimental effects on patients undergoing dialysis compared with non-CKD individuals [18]. Serum nicotine levels were assessed in 10 patients with end-stage renal disease (ESRD) undergoing maintenance hemodialysis at three pre-specified periods: before and after smoking a single cigarette, as well as following hemodialysis. Similar measurements were carried out in control subjects (before and after smoking one cigarette, as well as after an equivalent period to dialysis). Not only were serum nicotine levels higher at baseline in ESRD patients compared with controls (76.6 ± 16.8 vs. 19.0 ± 7.2 ng/ml, respectively; $P < 0.004$), but also this difference increased after smoking (132.9 ± 19.7 vs. 36.1 ± 8.2 ng/ml, respectively; $P < 0.001$), as well as following dialysis or the equivalent period in control subjects (51.9 ± 10.5 vs. 9.3 ± 3.5 ng/ml, respectively; $P < 0.001$) [18]. It was thus concluded that the markedly higher nicotine levels in dialysis patients may contribute to the higher CVD risk seen in these patients [18].

Another study demonstrated that smoking negatively influences survival rates in dialysis patients with diabetes mellitus [19]. The 1- and 5-year survival rates were compared in 22 diabetic patients undergoing hemodialysis who smoked >10 cigarettes/day with 30 non-smoking counterparts. Smokers demonstrated worse 1- and 5-year survival rates compared with non-smokers (68 vs. 80% and 9 vs. 37%, respectively; for both associations, $P < 0.05$). Furthermore, smokers had higher systolic blood pressure (154 ± 12 vs. 146 ± 13 mm Hg, respectively; $P < 0.05$) and a higher incidence of myocardial infarction (77 vs. 13%, respectively; $P < 0.005$)

compared with non-smokers [19]. In another large registry ($n = 15,246$ dialysis patients), smoking was independently associated with an increased risk of death during the first 90 days of initiation of dialysis ($P < 0.001$) [20].

In the Veterans Affairs Population ($n = 6,432$ men with CKD 3–5), tobacco use was independently associated with increased cardiovascular mortality ($P < 0.001$) [2]. The United States Renal Data System Wave 2 ($n = 4,024$ dialysis patients) study searched for associations between smoking and cardiovascular outcomes and death [21]. Current smoking was associated with an almost 60% higher risk for new-onset congestive heart failure ($P = 0.004$), an almost 70% higher risk for new-onset peripheral vascular disease ($P < 0.001$) and a 37% increased mortality ($P < 0.001$) compared with either non-smokers or former smokers [21]. Peripheral vascular disease (PVD) with critical limb ischemia is the single most important independent predictor of poor cardiovascular outcomes and one of the main causes of death in dialysis patients [22, 23]. Therefore, smoking cessation is crucial and should be strictly advised/reinforced to dialysis patients.

Dyslipidemia

Hypertriglyceridemia is the primary lipid abnormality in dialysis patients [24]. On the other hand, dyslipidemia is a strong risk factor for ischemic stroke [25]. Statins, a group of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, are a family of pleiotropic lipid-lowering drugs, known to have additional non-lipid effects, such as anti-inflammatory, stabilization of atherosclerotic plaques, decreased vascular smooth muscle cell migration and inhibition of platelet aggregation [26–30]. It was thus suggested that their use could be associated with a beneficial effect on cardiovascular events and survival rates in these patients. A recent meta-analysis and meta-regression of randomised controlled trials showed that although statins cause no significant reduction in all-cause mortality risk in CKD patients, they reduce cardiovascular mortality risk by approximately 20% (heterogeneity $\chi^2 = 8.45$, $I^2 = 0\%$; $P = 0.23$ for interaction) and no apparent difference in the treatment effect across pre-dialysis, dialysis and transplant populations [31]. Compared with placebo, statins also decrease the risk of non-fatal cardiovascular events by

>20%, with no significant heterogeneity among the studies (heterogeneity $\chi^2 = 7.68$; $I^2 = 8.9\%$). This effect was consistent across pre-dialysis and dialysis patients, with no significant interaction ($P = 0.18$ for interaction) [31].

In the United States Renal Data System Dialysis Morbidity and Mortality Study Wave-2 ($n = 3,716$ patients; 362 [9.7%] statin users) [32], statin users exhibited lower all-cause and cardiovascular mortality rates compared with non-users (143/1,000 vs. 202/1,000 person-years and 61/1,000 vs. 88/1,000 person-years, respectively). Statin use was independently associated with a 37% reduced risk of cardiovascular mortality ($P = 0.014$) and a 32% reduced risk of all-cause mortality rates ($P = 0.002$) [32]. Similarly, in the Dialysis Outcomes and Practice Patterns Study (DOPPS; $n = 7,365$ dialysis patients) [33], statin use was associated with a 31% lower risk for all-cause mortality ($P < 0.0001$) and a 23% lower cardiac mortality ($P = 0.03$).

However, two recent multicentre studies, the German Diabetes and Dialysis Study (Die Deutsche Diabetes Dialyse Studie; 4D) [34] and the Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA) [35] failed to show a reduction of cardiovascular mortality in dialysis patients by treatment of lipid abnormalities with statins. The 4D study compared the long-term (4-year) effects of atorvastatin 20 mg/day versus placebo on diabetic patients undergoing hemodialysis (619 vs. 636 patients, respectively) [34]. The primary end-point was a composite of death from cardiac causes, fatal stroke, non-fatal myocardial infarction or non-fatal stroke, whichever occurred first. The cumulative incidence of the primary end-point at 1 year was 12.6 versus 11.2%, for patients receiving atorvastatin versus placebo, respectively. At 3 years, the same incidence was 31.9 versus 30.5%, for the atorvastatin and placebo groups, respectively. A similar number of patients died from cardiac causes in the two groups (20 vs. 23% for the atorvastatin and placebo groups, respectively; relative risk [RR], 0.81; 95% CI, 0.64–1.03; $P = 0.08$) [34]. A myocardial infarction occurred in 70 vs. 79 patients receiving atorvastatin and placebo, respectively (11 vs. 12%, RR, 0.88; 95% CI, 0.64–1.21; $P = 0.42$). More patients died of stroke in the atorvastatin group than in the placebo group (27 vs. 13, respectively; RR, 2.03; 95% CI,

1.05–3.93; $P = 0.04$). Secondary end-points included death from all causes, all cardiac events combined, as well as all cerebrovascular events combined [34]. Death from all causes was similar in the atorvastatin and the placebo groups (48 vs. 50%, respectively; RR, 0.93; 95% CI, 0.79–1.08; $P = 0.33$) [34]. However, atorvastatin therapy resulted in a significant reduction of all cardiac events combined compared with placebo (205 vs. 246 events, or 33 vs. 39%, respectively; $P = 0.03$). Finally, the incidence of all cerebrovascular events combined in the atorvastatin group was not different from that in the placebo group (RR, 1.12; 95% CI, 0.81–1.55; $P = 0.49$) [34].

In the AURORA study [35], men and women 50–80 years old ($n = 2,776$) with ESRD who had been treated with regular hemodialysis or hemofiltration for >3 months were randomised to receive either rosuvastatin 10 mg/day or placebo. After a mean follow-up of 3.2 years, the primary end-point (non-fatal myocardial infarction, non-fatal stroke or death from cardiovascular causes) occurred in 396 patients assigned to rosuvastatin and in 408 individuals receiving placebo ($P = 0.59$). The lack of an effect of rosuvastatin therapy on the primary end-point was consistent in all prespecified subgroups, including patients with diabetes mellitus, preexisting cardiovascular disease, hypertension, high low-density lipoprotein (LDL) cholesterol level or elevated C-reactive protein (CRP) level [35]. Although both studies show that starting statins in ESRD patients (either diabetics or non-diabetics) is not beneficial [34, 35], these trials excluded patients who were already on statin therapy and therefore these findings do not justify stopping statins in patients who are already on statin therapy for coronary artery disease.

In conclusion, there is evidence that starting treatment of lipid abnormalities with statins is not associated with a reduction in cardiovascular mortality in dialysis patients.

Diabetes mellitus

Diabetes mellitus is the most important cause of ESRD in many countries [7]. Although survival of diabetic patients with ESRD has improved during the last years, it is still considerably worse than in non-diabetic ESRD patients [7]. Diabetic ESRD patients have various comorbidities. Cardiac diseases, including ischemic heart disease and congestive heart

failure, are more common in diabetic than in non-diabetic ESRD patients [7]. The same applies to stroke and peripheral vascular disease. Cardiovascular events including myocardial infarction, sudden cardiac death and stroke are the most common causes of death in this population [7].

Peroxisome proliferator-activated receptor (PPAR)-γ agonists are promising drugs for improving the survival of diabetic ESRD patients [36, 37]. PPAR-γ agonists may increase lipogenesis in adipose tissue and insulin sensitivity in muscles and liver, reduce free fatty acids and increase adiponectin levels. Additionally, PPAR-γ agonists reduce the levels of cardiovascular disease and inflammation markers such as metalloproteinase-9, interleukin-6, CRP and plasminogen activator inhibitor type 1 [38]. Despite these beneficial effects, recent trials reported that the use of PPAR-γ agonists is associated with an increased risk of myocardial infarction and heart failure, thus suggesting that their disadvantages or harmful effects may outweigh their benefits [39, 40]. Furthermore, the use of renally excreted hypoglycemic agents (e.g., metformin [41]) in this population should be considered with caution.

Maintenance of optimal blood glucose levels, improved nutrition and fluid balance and optimal preservation of residual renal function are essential steps for improving the survival of diabetic ESRD patients [37].

Antiplatelet medication

Although antiplatelet medication is recommended for vascular disease prevention, this may not apply to renal patients. A study designed to determine the efficacy of the combination of aspirin and clopidogrel in the prevention of hemodialysis access graft thrombosis was stopped prematurely by the Data Safety and Monitoring Board because of a significantly increased risk of bleeding among the participants receiving antiplatelet therapy. The cumulative incidence of bleeding events was significantly greater for those participants compared with participants receiving placebo ($P = 0.007$) [42]. Furthermore, there was no significant benefit of active treatment in the prevention of thrombosis ($P = 0.45$) [42]. Another study showed that the risk of major bleeding episodes in hemodialysis patients increases significantly with antiplatelet medication [43], while a large retrospective cohort study showed that the use of warfarin, clopidogrel or aspirin among 41,425 incident hemodialysis patients was associated with increased risk of mortality compared with 24,740 patients not receiving any of these medications [44]. A recent systematic review ($n = 16$ studies; 40,676 patients) concluded that the bleeding risk is increased in hemodialysis patients treated with combination antiplatelet therapy, while no definite conclusion can be drawn regarding the use of a single antiplatelet agent [45].

Thus, there is currently insufficient evidence to recommend routine antiplatelet medication to dialysis patients.

Non-traditional risk factors

The previously mentioned traditional risk factors may explain about half of all-cause and cardiovascular mortality in the ESRD population [46]. A number of non-traditional risk factors have been associated with elevated mortality rates among dialysis patients. A brief description of these emerging risk factors is presented.

Hemoglobin levels

Currently, whether anemia is associated with an increased risk of cardiovascular events in dialysis patients is a subject of debate. The prospective multicentre Morbidity-and-mortality in Anaemia Renal (MAR) study reported that hemoglobin levels predicted 1-year survival and hospitalization rates in 1,428 dialysis patients [47]. On the other hand, the recent Trial to Reduce cardiovascular Events with Aranesp Therapy (TREAT) compared cardiovascular outcomes between patients with hemoglobin levels of approximately 13 g/dl ($n = 2,012$; median achieved hemoglobin level: 12.5 g/dl; interquartile range, 12.0–12.8 g/dl) with patients with hemoglobin levels of approximately 10 g/dl ($n = 2,026$; median achieved hemoglobin level: 10.6 g/dl; interquartile range, 9.9–11.3 g/dl; $P < 0.001$) [48]. Although the two groups did not vary in mortality and cardiovascular event rates, patients with high hemoglobin levels suffered more fatal or non-fatal strokes compared with patients with low hemoglobin levels (101 vs. 53, respectively; $P < 0.001$) [48]. Furthermore, cardiac

revascularization procedures were performed less frequently in patients with high hemoglobin values compared with those with low hemoglobin values (84 vs. 117 patients, or 4.2 vs. 5.8%, respectively; hazard ratio, 0.71; 95% confidence interval [CI], 0.54–0.94; $P = 0.02$) [48]. These findings supported the results of two earlier studies, the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) trial [49] and the Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE) study [50]. In CHOIR [49], the primary end-point was the time the composite of death, myocardial infarction, hospitalization for congestive heart failure (excluding renal replacement therapy) or stroke. In this trial [49], 1,432 CKD patients were randomly assigned to epoetin alfa aiming to achieve a hemoglobin level of either 13.5 g/dl ($n = 715$) or 11.3 g/dl ($n = 717$). Elevated hemoglobin levels were associated with a higher incidence of composite events (death, myocardial infarction, hospitalization for congestive heart failure without renal replacement therapy or stroke: 17.5 vs. 13.5%, respectively; $P = 0.03$) compared with the low-hemoglobin group [49]. In contrast, the primary end-point in CREATE [50] was the time to a first cardiovascular event, including sudden death, myocardial infarction, acute heart failure, stroke, transient ischemic attack and angina pectoris, resulting in hospitalization for 24 h or more or prolongation of hospitalization, complication of peripheral vascular disease (amputation or necrosis) or cardiac arrhythmia resulting in hospitalization for 24 h or more. In CREATE [50], correction of anemia by administration of epoetin beta to target hemoglobin values of 13.0–15.0 g/dl was not associated with a reduction of cardiovascular events compared with subnormal target hemoglobin values of 10.5–11.5 g/dl ($P = 0.20$).

According to international guidelines [51], dialysis patients should maintain hemoglobin values within a target window of 11–12 g/dl. Maintaining these hemoglobin levels in dialysis patients may therefore be associated with lower cardiovascular event rates.

Vitamin D and hyperparathyroidism

With worsening renal function there is a progressive decline in the activity of 1-α-hydroxylase, the enzyme responsible for the conversion of 25(OH)-vitamin D_2 to 1,25-(OH)-vitamin D_3 (calcitriol) [52]. The net effect is secondary hyperparathyroidism.

There is evidence suggesting that vitamin D treatment with vitamin D receptor activators reduces mortality in dialysis patients [53–56]. A recent study examined the association between decreased levels of 25(OH)-vitamin D with an increased risk for early all-cause mortality [57]. Patients were divided into two groups based on 25(OH)-vitamin D levels (<50 nmol/l and >50 nmol/l). The presence of 25(OH)-vitamin D levels ≤50 nmol/l was associated with higher all-cause early mortality ($P < 0.033$) [57]. In another trial [58], chronic hemodialysis patients receiving injectable vitamin D had a lower cardiovascular-related mortality compared with patients not receiving injectable vitamin D ($P < 0.001$). Finally, vitamin D deficiency is associated with early mortality among incident hemodialysis patients [59]. These consistent findings suggest an association between hyperparathyroidism and vitamin D levels with mortality rates in dialysis patients. Nevertheless, randomized controlled trials are required to test the hypothesis that decreased levels of 25(OH)-vitamin D are associated with an increased risk for early all-cause mortality in dialysis patients.

Calcium and phosphorus

Mineral metabolism derangements in CKD patients (particularly changes in calcium and phosphate metabolism) may have a negative effect on the vascular calcification process [60]. Vascular calcifications are a strong risk factor for increased morbidity and mortality in ESRD patients [61, 62].

Hyperphosphatemia is among the most common metabolic complications of ESRD [63]. A large registry ($n = 40,538$ hemodialysis patients) showed that phosphate concentrations >5.0 mg/dl were associated with an increased relative risk of death (RR, 1.07, 1.25, 1.43, 1.67 and 2.02 for serum phosphate levels 5.0–6.0, 6.0–7.0, 7.0–8.0, 8.0–9.0 and ≥9.0 mg/dl, respectively) [64]. The multicentric DOPPS study attempted to identify significant predictors and potential consequences of abnormal mineral metabolism in representative groups of hemodialysis facilities ($n = 307$) and patients ($n = 17,236$) [65]. All-cause mortality was significantly and independently associated with serum concentrations of phosphorus (RR, 1.04 per 1 mg/dl; $P = 0.0003$), calcium (RR, 1.10 per 1 mg/dl; $P < 0.0001$) and calcium-phosphorus product (RR, 1.02 per 5 mg^2/dl^2; $P = 0.0001$). There were strong

associations between cardiovascular mortality with serum concentrations of phosphorus (RR, 1.09; $P < 0.0001$), calcium (RR, 1.14; $P < 0.0001$) and calcium-phosphorus product (RR, 1.05; $P < 0.0001$) [65]. These results were verified in a large independent study ($n = 12,833$ hemodialysis patients) [66]. Patients with elevated phosphorus levels (>6.5 mg/dl) had an increased relative risk for death resulting from coronary artery disease (RR, 1.41; $P < 0.0005$), sudden death (RR, 1.20; $P < 0.01$), infection (RR, 1.20; $P < 0.05$) and unknown causes (RR, 1.25; $P < 0.05$) compared with patients with low phosphorus levels (≤6.5 mg/dl) [66]. Finally, low parathyroid hormone (PTH) levels (<100 pg/ml) are associated with all-cause mortality among hemodialysis patients (adjusted RR, 2.03; 95% CI, 1.12–3.69; $P = 0.02$) [67].

Similarly, several studies have suggested that excess calcium intake is associated with vascular calcification and increased mortality in ESRD and dialysis patients [62, 68, 69]. According to the most recent DOPPS data [70], PTH levels between 101 and 300 pg/ml are associated with the lowest mortality risk whereas PTH levels >600 pg/ml are associated with the greatest mortality risk. Current evidence thus suggests that elevated serum phosphate and calcium levels are associated with increased relative risk of death in dialysis patients. It should be emphasized, however, that there is currently no prospective randomized study demonstrating that the reduction of vascular calcifications decreases mortality in dialysis patients.

Magnesium

As mentioned earlier, vascular calcifications are a strong risk factor for increased morbidity and mortality in ESRD patients [61, 62]. Low magnesium levels are associated with vascular calcification and cardiovascular mortality among ESRD patients [71, 72]. In contrast, elevated magnesium levels inhibit PTH secretion, which is an independent risk factor for vascular calcification, left ventricular hypertrophy and mortality in ESRD patients [66].

A recent comprehensive review provides an in-depth analysis of the role of magnesium in CKD [73]. There is increasing evidence suggesting an association between magnesium with cardiovascular disease in subjects with, as well as without CKD.

Conclusions

Cardiovascular mortality in ESRD and dialysis patients has a dual cause, the traditional and the non-traditional risk factors. Current evidence suggests that the non-traditional risk factors are more frequently and strongly associated with cardiovascular mortality and event rates in these patients.

Vascular disease prevention measures may offer the opportunity to reduce the high cardiovascular event and mortality rates in dialysis patients. The evidence regarding the control of some risk factors (e.g., smoking cessation) is more robust than for others (e.g., statins), where current evidence does not show a reduction in cardiovascular mortality. Unfortunately, there is a surprising lack of evidence from intervention trials in this population. Future trials should investigate the potential benefits associated with vascular disease prevention in dialysis patients, as well as the exact role of the emerging non-traditional risk factors.

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