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Managing cardiovascular risk in people with chronic kidney disease: a review of the evidence from randomized controlled trials

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***Abstract*:** Cardiovascular disease is the leading cause of death and morbidity in people with chronic kidney disease (CKD) making measures to modify cardiovascular risk a clinical priority. The relationship between risk factors and cardiovascular outcomes is often substantially different in people with CKD compared with the general population, leading to uncertainty around pathophysiological mechanisms and the validity of generalizations from the general population. Furthermore, published reports of subgroup analyses from clinical trials have suggested that a range of interventions may have different effects in people with kidney disease compared with those with normal kidney function. There is a relative scarcity of randomized controlled trials (RCTs) conducted in CKD populations, and most such trials are small and underpowered. As a result, evidence to support cardiovascular risk modification measures for people with CKD is largely derived from small trials and *post hoc* analyses of RCTs conducted in the general population. In this review, we examine the available RCT evidence on interventions aimed at preventing cardiovascular events in people with kidney disease to identify beneficial treatments as well as current gaps in knowledge that should be a priority for future research.

***Keywords*:** antioxidant, antiplatelet, blood pressure, bone mineral management, cardiovascular disease, chronic kidney disease, dialysis, end-stage kidney disease, fibrate, lipids

Introduction

Cardiovascular disease continues to be the leading cause of morbidity and mortality worldwide [Yach *et al.* 2005] with rates of cardiovascular events and mortality consistently increasing as kidney function deteriorates [Go *et al.* 2004]. Dialysis patients have mortality rates up to 40-fold higher than the general population [Sarnak and Levey, 2000] with cardiovascular disease being responsible for up to 50% of these deaths [Roberts *et al.* 2007].

Chronic kidney disease (CKD), defined as a glomerular filtration rate (GFR) less than 60 ml/min/1.73 m^2, or the presence of other markers of kidney damage including albuminuria or proteinuria [National Kidney Foundation, 2002], is common around the world, affecting up to 16% of the population [Perkovic *et al.* 2007; Chadban *et al.* 2003; Coresh *et al.* 2003]. The increasing prevalence of CKD [Imai *et al.* 2007; Coresh *et al.* 2003] and dialysis-dependent end-stage kidney disease (ESKD) will increase the number of people at high risk of cardiovascular events, thus increasing demands on health services.

CKD patients have higher rates of the general risk factors for cardiovascular disease, including hypertension, diabetes, obesity, and lipid abnormalities [Abboud *et al.* 2010; Rucker *et al.* 2009; Vaziri, 2006; Fox *et al.* 2004; Tozawa *et al.* 2002; Muntner *et al.* 2000; Manttari *et al.* 1995]. However, the relationship between risk markers and cardiovascular events in people with kidney disease often differs from that in the general population. Markers of cardiovascular disease such as elevated levels of cholesterol [Liu *et al.* 2004], blood pressure [Alborzi *et al.* 2007; Port *et al.* 1999], body mass index [Mafra *et al.* 2008] and homocysteine [Kalantar-Zadeh *et al.* 2004; Suliman *et al.* 2000] do not always have the same log-linear relationship with cardiovascular events observed in the general population.

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Indeed, a 'U'-shaped or inverse relationship has often been described such that people with the lowest levels of these risk factors have the worst outcomes. Postulated explanations for this 'reverse epidemiology' or 'reverse causality' phenomenon include confounding due to other unmeasured factors, such as heart disease, inflammation and malnutrition, as well as the survival bias inherent in observational studies [Kalantar-Zadeh *et al.* 2005; Kopple, 2005]. Poor precision in the measurement of factors such as blood pressure (particularly in haemodialysis patients where blood pressure varies markedly at different points in the dialysis cycle) may also contribute to this phenomenon.

Atherosclerotic disease may not follow identical pathways in people with ESKD compared with those with normal renal function, and indeed may be accelerated [Lindler *et al.* 1974]. For example, calcium phosphate flux may drive vascular calcification in ways not seen in people with normal kidney function [Goodman *et al.* 2000; Ribeiro *et al.* 1998]. Postulated cardiovascular risk factors specific to CKD include the loss of calcium and phosphorus regulation anaemia, hyperhomocysteinaemia, increased oxidant levels and increased chronic inflammatory rates [Francis *et al.* 2004; London *et al.* 2003; Astor *et al.* 2002; Stenvinkel *et al.* 1999; Roselaar *et al.* 1995; Luciak and Trznadel, 1991].

Recent years have seen the rise of the hypothesis that the burden of cardiovascular disease may not be as dominated by atherosclerotic disease in people with ESKD as it is in people with normal renal function. It is postulated that a substantial proportion of cardiovascular events in the ESKD population result from nonischaemic myocardial abnormalities, left ventricular hypertrophy and the fluctuations of electrolytes and fluid volumes characteristic of most intermittent haemodialysis regimens [Herzog *et al.* 2008]. The myocardial damage marked by fibrosis and microvascular disease ultimately induces arrhythmias, pump failure and sudden death [Foley *et al.* 1996; Hung *et al.* 1980]. The hypothesis has been fuelled by the negative results from trials of agents proven effective for the treatment of atherosclerotic disease in the general population, such as statins [Fellstrom *et al.* 2009; Wanner *et al.* 2005], and implies novel approaches will be needed to impact on the burden of disease.

Guidelines for the prevention of cardiovascular disease in the general population include recommendations for treatment with antiplatelet agents, beta-blockers, and blood pressure lowering agents [US Preventive Services Task Force, 2009; Rosendorff *et al.* 2007; Patrono *et al.* 2004]. The balance of potential benefits and harm associated with these treatments may be different for people with kidney disease due to differences in underlying physiology, pathophysiological mechanisms, side-effect profiles, and metabolism. It is thus not clear whether these guidelines should also apply to people with CKD, or whether they will result in similar net benefits. This uncertainty may explain, at least in part, why these medications are prescribed less frequently after cardiac events in people with kidney disease than the general population [Krause *et al.* 2004; Berger *et al.* 2003]. Furthermore, factors specific to and more commonly found in people with CKD (e.g. elevated homocysteine levels or oxidant stress, management of anaemia, or dialysis prescription) could potentially also be important in modulating risk.

This review aims to examine the available randomized controlled trial (RCT) evidence about interventions that potentially modify cardiovascular risk in people with kidney disease. It will examine measures that are of established benefit in other populations (blood pressure lowering, lipid lowering, antiplatelet agents) as well as those that are particularly pertinent to people with CKD, with a focus on data derived from randomized trials or systematic reviews of RCTs.

Blood pressure lowering in patients with chronic kidney disease

Blood pressure management has been advocated for both slowing the renal progression of CKD and for reducing cardiovascular risk. Current guidelines are supported predominantly by evidence for improvements in renal outcomes, where the benefits appear to be clearest for people who had proteinuria at baseline [Appel *et al.* 2010; Sarnak *et al.* 2005; Jafar *et al.* 2003; Peterson *et al.* 1995]. Agents acting via the renin–angiotensin system (RAS), including angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), are often recommended as first-line treatment on the basis of RCTs demonstrating a reduction in renal events such as kidney failure or doubling serum creatinine (SCr) in patients who have proteinuria, either with [Brenner *et al.* 2001;

Lewis *et al.* 2001] or without diabetes (Angiotensin-Converting Enzyme Inhibition in Progressive Renal Insufficiency study (AIPRI), Ramipril Efficacy in Nephropathy study (REIN)) [Jafar *et al.* 2003; GISEN Group, 1997; Maschio *et al.* 1996], or advanced CKD (SCr > 3 mg/dl) [Hou *et al.* 2006].

With most blood pressure trials designed around renal endpoints, there is less evidence for effects on cardiovascular endpoints for people with kidney disease. Evidence supporting cardiovascular benefits in people with CKD mainly comes from secondary subgroup analyses of large RCTs studying ACE inhibitors, such as the ADVANCE, PROGRESS, HOPE, and EUROPA studies [Heerspink *et al.* 2010; Brugts *et al.* 2007; Perkovic *et al.* 2007; Solomon *et al.* 2006; Mann *et al.* 2001]. Collectively, these trials have included many thousands of people with CKD and have found treatment with ACE inhibitors reduces the risk of major cardiovascular events by 13 to 35%. While the relative benefits appear similar to those in the non-CKD population in most of these studies, the increased cardiovascular risk observed in people with CKD mean the absolute benefits may be nearly doubled [Heerspink *et al.* 2010]. Comparative cardiovascular benefits for different classes of blood pressure lowering agents have not been established. A *post hoc* analysis of the ALLHAT study demonstrated that lisinopril was not superior to chlorthalidone or amlodipine in preventing coronary heart disease, stroke, or combined cardiovascular disease in patients with estimated GFR < 60 ml/min/1.73 m^2, and chlorthalidone was superior to both for preventing heart failure, independently of renal function [Rahman *et al.* 2006]. Similarly, in the AASK study, ramipril was not superior to amlodipine in preventing the occurrence of cardiovascular events [Norris *et al.* 2006] in African Americans with high blood pressure and kidney disease. Although agents acting via the RAS clearly reduce proteinuria more than other agents, paralleling a particular benefit in preventing kidney failure in people with proteinuria, the cardiovascular benefits of different classes of agents currently appear similar.

People with ESKD appear to derive similar relative benefits from blood pressure lowering as the general population as demonstrated in a recent systematic review of eight RCTs of 1679 patients on dialysis. Blood pressure lowering treatment with ACE inhibitors or ARBs (five trials), beta-blockers (two trials), and calcium channel blockers (one trial) were compared with placebo or conventional therapy over a period of 12–36 months. Cardiovascular events were reduced by 36% [95% confidence interval (CI) 65 to 57%] while all-cause mortality was reduced by 20% (95% CI 4% to 34%) [Heerspink *et al.* 2009]. There are no clear data on the effect on cardiovascular outcomes of fluid management as a means of blood pressure control despite clear evidence that volume adjustment is effective at reducing blood pressure for people on haemodialysis [Agarwal *et al.* 2009].

Blood pressure management has been traditionally based on the use of specified target levels, although recently the benefits of target-adjusted therapy over simple delivery of fixed dose therapy have been questioned [Kaplan and Kaplan, 2007]. The delivery of a fixed dose ACE inhibitor-based regime reduced cardiovascular events regardless of baseline blood pressure at varying stages of CKD in a trial of 11,140 people with diabetes [Heerspink *et al.* 2010]. A target-driven approach was assessed in 1094 African Americans with hypertension and CKD who were randomized to intensive [mean arterial pressure (MAP) ≤ 92 mmHg] or standard (MAP = 102–107 mmHg) blood pressure targets for 3.8 years and followed for a further 8.8–12.2 years [Appel *et al.* 2010]. Cardiovascular events were not different between the groups, either in the trial or the cohort phase. Similarly, the recently completed ACCORD study demonstrated that for people with type 2 diabetes, a systolic blood pressure target of less than 120 mmHg, compared with less than 140 mmHg, did not reduce the overall rate of fatal and nonfatal major cardiovascular events, although the risk of stroke was reduced [ACCORD Study Group, 2010]. People with impaired kidney function were included although subgroup analyses are not yet available.

In summary, the current evidence suggests that blood pressure lowering is effective at preventing cardiovascular events for people with hypertension and mild CKD. Increasing data suggest that routine blood pressure lowering therapy may also prevent cardiovascular events in high-risk people with CKD who do not meet traditional definitions of hypertension. The cardiovascular effects of different drug classes appear similar, although RAS blockade appears to

minimize the progression of proteinuric kidney disease. Whether this might translate into additional long-term cardiovascular benefits remains unproven.

Antiplatelet therapy

People with CKD have higher rates of thromboembolism than the general population [Mahmoodi *et al.* 2009; Wattanakit *et al.* 2008; Abbott *et al.* 2004; Tveit *et al.* 2002] but are simultaneously predisposed to bleeding through relative platelet dysfunction [Eleftheriadis *et al.* 2006; Kaw *et al.* 2006; Moal *et al.* 2003; Di Minno *et al.* 1986]. It is therefore plausible that both the benefits and harms of antiplatelet agents may be different in people with CKD and ESKD than in the general population, and furthermore that the net effect of benefits and harms may not be consistent in different stages of kidney disease.

Aspirin

The largest reported study of antiplatelet therapy in CKD is a *post hoc* analysis of the HOT study including 3619 people with an estimated GFR < 60 ml/min/1.73 m^2, which randomized people with hypertension to low-dose aspirin or placebo [Jardine *et al.* 2010]. The benefit of aspirin increased with advancing CKD stage for both the primary outcome of major cardiovascular events and for total mortality while bleeding events were nonsignificantly increased. The net effect was an increasing benefit with advancing CKD stage. In this study, the treatment of 1000 people with estimated GFR < 45 ml/min/1.73 m^2 with low-dose aspirin for 3.8 years would prevent 54 deaths and 76 major cardiovascular events at the cost of 27 major bleeding events. The small number of people with advanced CKD (only 98 people had a GFR < 30 ml/min/1.73 m^2) meant that the study was too small to examine the benefits and harms of aspirin for people with CKD stage 3 and 5.

The available studies of aspirin in ESKD are limited by their size and relatively short duration leading to low event numbers. In 2002, the Antithrombotic Trialists Collaboration pooled the results of 287 trials, including 14 trials and 2632 patients on dialysis [Antithrombotic Trialists, 2002]. Most of these trials were of relatively short duration (28 days to 18 months, average 6 months) and were predominantly conducted to assess the effect of antiplatelet agents on haemodialysis access events [Antithrombotic Trialists, 2002]. In an analysis limited by few events and variability in the interventional agent studied (aspirin in two trials, aspirin plus dypyridamole in two trials, picotamide in one, sulfinpyrazone in two, and ticlopidine in seven), active treatment produced a 41% reduction in the odds ratio for cardiovascular events (standard error 16%). This benefit was not significantly different from the 22% odds ratio reduction observed in the overall population. Reported bleeding events were also relatively infrequent with only 46 major extracranial bleeding events, 27 of 1333 (2.0%) in the antiplatelet arm and 31 of 1371 (2.3%) in the adjusted control arm (p not significant) making a confident interpretation difficult.

Further evidence on aspirin in ESKD may come from the ongoing FAVOURED study which aims to randomize 1200 people with CKD requiring an arteriovenous fistula to low-dose aspirin or placebo (and to fish oil or placebo in a factorial design) for 3 months [Irish *et al.* 2009].

Other antiplatelet agents

The available data on the benefits and harms of clopidogrel in people with CKD or ESKD is conflicting. CKD subgroup data from two studies in people with acute coronary events [Keltai *et al.* 2007; Steinhubl *et al.* 2002] showed that clopidogrel 75 mg daily did not significantly reduce the risk of cardiovascular events, while another study in stable patients found an increased risk of cardiovascular death [hazard ration (HR) 1.7, 95% CI 1.1 to 2.6; $p = 0.023$) [Dasgupta *et al.* 2009] in people with diabetic nephropathy randomized to clopidogrel. These results need to be interpreted with some caution because these trials were not designed nor powered to examine subgroup effects. Bleeding rates were elevated similarly in people with and without CKD. The combination of relatively high-dose aspirin (325 mg) plus clopidogrel (75 mg) led to increased bleeding in a randomized double-blind trial intended to assess the effect of the combination for 2 years on dialysis access thrombosis [Kaufman *et al.* 2003]. The study, conducted in US Veteran Affairs haemodialysis units, was stopped after the randomization of 200 patients when it became clear the incidence of bleeding events was almost doubled in the treatment arm (HR 1.98, 95% CI 1.19 to 3.28, $p = 0.007$). Overall the limited evidence available does not show clear benefit for clopidogrel in people with CKD with some suggestion of harm. Further studies and analyses are needed

given the use of this agent in current clinical practice.

Agents such as glycoprotein IIb/IIIa inhibitors (GPIs) and of the direct thrombin inhibitor, bivalirudin, have been studied mainly in the presence of acute coronary syndromes and are beyond the scope of this review. In brief, the available data suggest similar benefits and risks to those observed in the general population [Mehran *et al.* 2009; Chew *et al.* 2003; Reddan *et al.* 2003; Januzzi *et al.* 2002]. Of note, bivalirudin has been suggested to cause less major bleeding in people with CKD compared with heparin alone (OR 0.46, 95% CI 0.30 to 0.70) [Chew *et al.* 2003] or with heparin plus a GPI (6.2% *versus* 9.8%, $p = 0.008$) [Mehran *et al.* 2009].

Lipid lowering

A systematic review has examined the effect of statin therapy in people with CKD [Strippoli *et al.* 2008]. In 50 trials involving 30,144 participants, statins prevented fatal [relative risk (RR) 0.81, 95% CI 0.73 to 0.90] and nonfatal cardiovascular events (RR 0.78, 95% CI 0.73 to 0.84), but were not shown to have an effect on all-cause mortality (RR 0.92, 95% CI 0.82 to 1.03). Both the benefits and adverse effects of statins did not differ according to stage of kidney disease, although most data came from studies enrolling people with early stage CKD. The methodological quality of many of the trials was also considered suboptimal by the authors. Two major double-blind randomized trials, the 4D and the AURORA trials that included a combined 4028 patients, were unable to identify any benefit for statins in people with ESKD, reporting no significant effect in either study on cardiovascular events or all-cause mortality [Fellstrom *et al.* 2009; Wanner *et al.* 2005]. More recently, the SHARP (Study of Heart and Renal Protection) trial, the largest lipid-lowering trial to date in kidney disease, examined the effects of combination ezetimibe and simvastatin on cardiovascular and renal outcomes in 9438 patients with CKD and ESKD [Baigent *et al.* 2003]. The trial has been completed and the published results are eagerly awaited.

A recent meta-analysis has confirmed the benefits of fibrate therapy in the general population [Jun *et al.* 2010]. However, people with ESKD were excluded from the included studies and subgroup analyses of those with mild CKD were not possible, making conclusions about treatment for people with CKD speculative.

Nonclassical interventions

Dialysis-related interventions

Given cardiovascular mortality and morbidity rates are highest in people with ESKD, there has been great interest in the potential cardiovascular benefits that might be associated with improving dialysis technique. Studied interventions include earlier initiation of dialysis [Cooper *et al.* 2010], increased dialysis intensity driven by Kt/V (defined as a number used to quantify dialysis treatment adequacy where K = dialyzer clearance of urea, t = dialysis time, and V = volume of distribution of urea which approximately equates to the patient's total body water) targets or by haemofiltration volumes [Jun *et al.* 2010; Eknoyan *et al.* 2002; Paniagua *et al.* 2002], the use of different dialysis membranes [Locatelli *et al.* 2009; Eknoyan *et al.* 2002] and haemodiafiltration [van der Weerd *et al*. 2008]. Sadly, randomized trials and systematic reviews have failed to consistently demonstrate any benefits for these interventions on cardiovascular outcomes [Rabindranath *et al.* 2006; Eknoyan *et al.* 2002]. Several ongoing trials will provide substantial study power to assess the effects of haemodiafiltration in coming years [van der Weerd *et al.* 2008].

There is great interest in the potential for extended duration haemodialysis to improve outcomes. Observational studies demonstrate that various forms of extended haemodialysis are associated with a range of improved biochemical and clinical outcomes [Lacson *et al.* 2010; van Eps *et al.* 2010; Walsh *et al.* 2005; Innes *et al.* 1999]. However, it is widely recognized that patients who opt for such treatments have characteristics associated with better prognosis such that better outcomes would be expected even in the absence of a treatment effect [Lacson *et al.* 2010; van Eps *et al.* 2010; Powell *et al.* 2009; Innes *et al.* 1999]. The only published randomized evidence comes from a Canadian pilot [Culleton *et al.* 2007; Frequent Hemodialysis Network (FHN) Trial Group, 2010]. The Canadian pilot trial randomized 52 patients for 6 months to the equivalent of 30 minimum weekly hours of overnight home-based dialysis compared with three times weekly conventional dialysis targeted to a Kt/V > 1.2 [Culleton *et al.* 2007]. The primary outcome of change in left

ventricular mass (LVM) was significantly improved with a reduction of 15.3 g (95% CI 1 to 29.6 g; $p = 0.04$). A study comparing six times weekly nocturnal home haemodialysis with conventional three times weekly home haemodialysis aimed to recruit 250 participants but was terminated with 87 participants enrolled due to recruitment difficulties [Rocco and Kliger, 2010]. An ongoing study with an anticipated recruitment of 200 participants will compare the effect of extended hours of haemodialysis with conventional three times weekly treatment in Australia, New Zealand, Canada and the UK [ACTIVE Dialysis, ClinicalTrials.gov identifier: NCT00649298] and will provide further evidence on the potential benefits and harms of this treatment that has generated much interest but no definitive evidence.

Increasing the frequency of dialysis has similarly generated interest as a dialysis modality. The FHN trial assessed the effects of frequent daily dialysis (six sessions per week) compared with standard dialysis (three sessions per week) [FHN Trial Group, 2010] in 245 in-centre participants, on two sets of composite endpoints. With a delivered weekly dose of 12.7 ± 2.2 compared with 10.4 ± 1.6 h of dialysis per week, frequent daily dialysis improved the composite of increased LVM and death (HR for death or change in LVM 0.61; 95% CI 0.46 to 0.82) with a difference in adjusted mean change in LVM of −13.8 g (95% CI −21.8 to −5.8). Frequent daily dialysis similarly improved the composite of physical health composite scores (Rand 36-item quality of life with possible scores from 0 to 100) and death (HR for death or change in physical composite scores 0.70; 95% CI 0.53 to 0.92) with an improvement in change of scores of 3.2 (95% CI 1.0 to 5.4). Importantly, however, the study also suggested frequent haemodialysis increased the need for interventions due to vascular access complications (HR 1.35, 95% CI 0.84 to 2.18).

Antioxidant therapy

Oxidative stress due to increased generation of oxygen species has been suggested as a potentially important contributor to morbidity and mortality for people with CKD. Reports have associated oxidative stress with the pathogenesis of atherosclerosis [Galle *et al.* 2003; Galle, 2001; Maggi *et al.* 1994]. Studies in the general patient population have failed to demonstrate an effect of antioxidant therapy on cardiovascular events [Heart Protection Study Collaborative, 2002; Yusuf *et al.* 2000; GISSI-Prevenzione Trial Group, 1999]. However, inflammation, chronic uraemia, and dialysis treatment have been associated with elevated levels of oxidative stress compared with the general population [Stenvinkel *et al.* 1999; Roselaar *et al.* 1995; Luciak and Trznadel, 1991], raising the hypothesis that the intervention may be beneficial in the ESKD population. Two small RCTs have reported a reduction in cardiovascular events from antioxidant therapy in ESKD patients [Tepel *et al.* 2003; Boaz *et al.* 2000]. The SPACE study assessed the effect of vitamin E in 196 people with ESKD and pre-existing cardiovascular disease over a median of 1.4 years. Vitamin E significantly reduced cardiovascular events (RR 0.46, 95% CI 0.27 to 0.78, $p = 0.014$) but had no effect on overall mortality or cardiovascular mortality [Boaz *et al.* 2000]. A second RCT of 134 people receiving haemodialysis therapy for a median of 14.5 months found acetylcysteine reduced cardiovascular events by 40% (RR 0.60, 95% CI 0.38 to 0.95; $p = 0.03$) [Tepel *et al.* 2003]. However, the positive findings in these small studies are countered by the lack of benefit for the subgroup of 450 people with impaired kidney function in the larger HOPE-2 study [Steinberg *et al.* 2002]. It is conceivable that the different findings could reflect a difference in true effect between people with ESKD and those with better kidney function, but more data are required before routine use of these agents can be recommended.

Bone mineral management

Disturbances of bone and mineral metabolism are a well known complication of CKD. Hyperphosphataemia is an independently associated risk factor of cardiovascular morbidity and mortality both in people with CKD [Young *et al.* 2005; Stevens *et al.* 2004; Block *et al.* 2004, 1998] and those with normal renal function (≥ 60 ml/min/1.73 m^2) [Abramowitz *et al.* 2010]. Standard dialysis treatment alone often fails to maintain these markers at levels recommended by guidelines, leading to the use of pharmaceutical interventions. Traditionally, calcium-based binders have been prescribed to remove dietary phosphorus, however their association with arterial calcification [Goodman *et al.* 2000; Guerin *et al.* 2000], which in turn has been linked with increased mortality [Blacher *et al.* 2001, 1999], as well as the availability of alternative agents has focussed attention on the efficacy of noncalcium

based binders. The DCOR trial assessed the effect of unblinded sevelamer (a noncalcium-based binder) compared with calcium-based phosphate binders on all-cause mortality and cause-specific death, including cardiovascular mortality, in 2103 prevalent haemodialysis patients [Suki *et al.* 2007]. There was no effect on all-cause mortality rates (HR for sevelamer *versus* calcium-based binders 0.93, 95% CI 0.79 to 1.10, $p = 0.40$) or cardiovascular mortality (HR 0.93, 95% CI 0.74 to 1.17, $p = 0.53$). A prespecified subgroup analysis showed a significant treatment–age interaction, with sevelamer reducing all-cause mortality compared with calcium-based binders in participants aged 65 years and older (HR 0.77, 95% CI 0.61 to 0.96). However, surprisingly, no such interaction was observed for cardiovascular mortality, casting doubt on whether the intervention actually affected cardiovascular pathophysiology. Further methodological concerns include the lack of trial power to detect differences in cardiovascular or other specific causes of death, the lack of blinding, and the high withdrawal rate where nearly half of the participants discontinued treatment. The question of a benefit for treatment in older patients remains open.

Homocysteine lowering

Reducing homocysteine levels in the homozygous condition of homocysteinaemia has a profound effect on reducing cardiovascular events [Yap, 2003]. The association of elevated homocysteine levels with impaired kidney function led to the hope that reduction of homocysteine levels would reduce cardiovascular event rates. Individually, the results of trials in both CKD and ESKD populations [Armitage *et al.* 2010; Heinz *et al.* 2010; House *et al.* 2010; Jamison *et al.* 2007; Vianna *et al.* 2007; Zoungas *et al.* 2006] and in subgroup analyses of larger trials [VITATOPS Trial Study Group, 2010; Mann *et al.* 2008] have not shown a significant benefit from homocysteine lowering. A meta-analysis of trials in dialysis populations suggested that homocysteine lowering may be of benefit in populations without background supplementation or food fortification (RR 0.73, 95% CI 0.56 to 0.94) but not in populations with supplementation (RR 1.01, 95% CI 0.88 to 1.15) [Bostom *et al.* 2006]. Caution needs to be exercised in the interpretation of this finding given the small numbers of trials (five) and participants (1642) included. Trials are still under way and it is likely further analyses will contribute to a better understanding of the effect of homocysteine lowering in the future.

Anaemia management

Counter to expectations, full correction of anaemia in CKD appears to lead to worse rather than better cardiovascular outcomes. The introduction of erythropoeisis-stimulating agents dramatically reduced blood transfusion requirements and these agents were licensed for use as transfusing-sparing agents. The epidemiological association of anaemia with poor outcomes plus the compelling physiological rationale of improved oxygen delivery to tissues led to the hypothesis that a complete correction of anaemia would produce better outcomes than partial correction. However, harm was suggested by an early study among 1233 people with known heart disease [Besarab *et al.* 1998], leading to the early termination of the study. A number of subsequently completed trials conducted in the CKD and ESKD populations have in aggregate supported these findings. Among the 27 trials including 10,452 participants [Palmer *et al.* 2010], a higher haemoglobin target was associated with higher rates of stroke (RR 1.51, 95% CI 1.03 to 2.21) and trends towards harm for total cardiovascular events (RR 1.15, 95% CI 0.98 to 1.33) and mortality (RR 1.09, 95% CI 0.99 to 1.20) [Palmer *et al.* 2010].

Conclusions

Cardiovascular disease is the leading cause of death in patients with CKD and as such, its prevention and management is of the utmost importance to improve the long-term outcomes of this high-risk patient population. Most of the current evidence has been based on *post hoc* subgroup analyses of larger trials, predominantly testing pharmaceutical agents, which were generally not designed to specifically test benefits and harms in people with CKD and have few participants with ESKD. The trials conducted specifically in patients with CKD and ESKD are generally of relatively small size, restricting their capacity to determine effects in clinical outcomes. In the absence of rigorous randomized evidence, clinicians have two strategies on which to base practice. They can draw conclusions from observational relationships, although the reverse associations seen between risk factors and outcomes in CKD and ESKD can make this strategy problematic and lead to conclusions that are subsequently proven to be qualitatively incorrect in RCTs. A better approach is likely to be

one which generalizes from the results of trials conducted in the general population, particularly when CKD subgroup data are available.

Based on this, patients with stage 3 CKD appear to derive similar or greater cardiovascular benefits from blood pressure lowering, lipid lowering and aspirin-based antiplatelet therapy as the general population. There are far fewer data available in the ESKD population. The benefits of lipid lowering remain to be proven but should become clearer soon with the publication of SHARP. Systematic reviews suggest that blood pressure lowering and antiplatelet therapy are likely to be beneficial in ESKD, but study size and quality have been suboptimal (Figure 1).

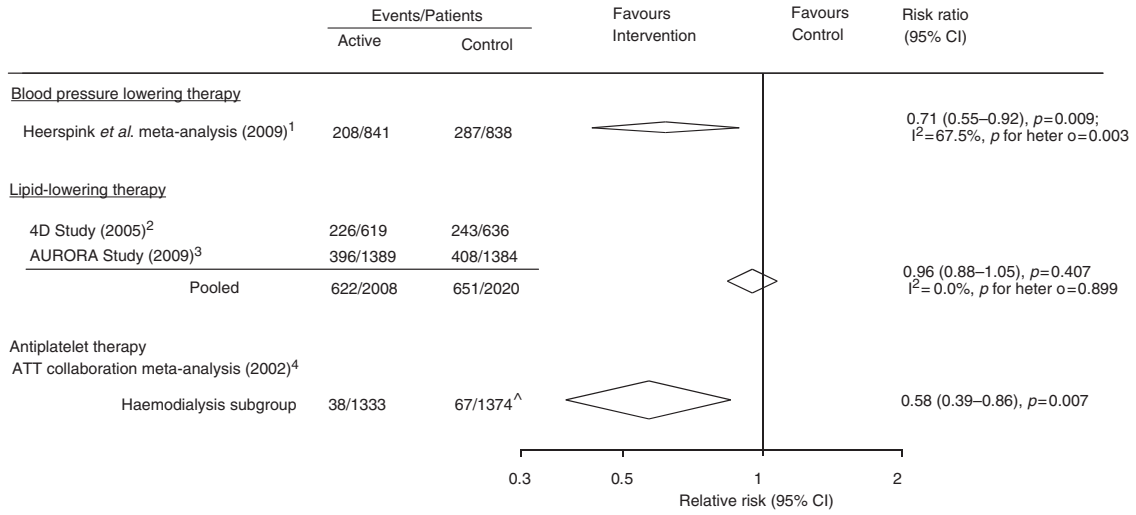

Figure 1. Current data from randomized trials or meta-analyses of randomized trials assessing the effects of interventions on cardiovascular outcomes in dialysis patients. CI, confidence interval. [1][Heerspink *et al.* 2009]; [2][Wanner *et al.* 2005]; [3][Fellstrom *et al.* 2009]; [4][Antithrombotic Trialists, 2002]. *The authors state that the adjusted control totals have been calculated after converting any unevenly randomized trials to even ones by counting the control group more than once.

Table 1. Risk factors for cardiovascular disease in patients with chronic kidney disease (CKD) and the likelihood of net cardiovascular benefit from various interventions in the treatment of CKD based on the totality of currently available evidence. See the text for details.

Risk factors contributing to cardiovascular disease in CKD	Interventions	CKD	ESKD
Hypertension from fluid retention and decreasing ability for blood pressure regulation	Blood pressure lowering therapy	Likely	Likely
Prothrombotic state	Aspirin therapy	Likely	Possible
Dysregulation of lipid metabolism	Lipid-lowering therapy	Likely	Possible
Not applicable	Extended hours dialysis	Not applicable	Possible
Increased oxidative stress (e.g. from inflammation)	Antioxidant therapy	Probably ineffective	Possible
Hyperphosphataemia	Bone mineral management (noncalcium-based binders) compared with calcium based binders	Unknown	Unknown
Hyperhomocysteinaemia	Homocysteine-lowering therapy	Probably ineffective	Probably ineffective
Anaemia from platelet dysfunction	Normalizing haemoglobin with erythropoeisis-stimulating agents	Likely harm	Likely harm

ESKD, end-stage kidney disease.

The design and conduct of a large randomized trial assessing these treatments should be an urgent priority for the nephrological community.

Few firm recommendations to alter current practice can be made on the basis of novel factors postulated to reduce cardiovascular events (Table 1). Haemoglobin normalization appears to be harmful. Homocysteine lowering appears ineffective, although reports from ongoing and completed trials are pending. Some approaches appear promising (e.g. extended hours of dialysis, antioxidant therapy) but remain to have their benefits demonstrated in appropriately powered and well conducted randomized trials assessing clinical endpoints.

The vast cardiovascular disease burden affecting the increasing number of people with CKD worldwide mean that the identification and implementation of appropriate risk reduction strategies needs to be a research priority.

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