Strategies to manage cardiovascular risk in CKD

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Background

Cardiovascular disease (CVD) remains the leading cause of death across the spectrum of chronic kidney disease (CKD), including CKD not requiring dialysis, and for patients requiring dialysis or kidney transplantation. There is high prevalence of 'conventional' cardiovascular risk factors in patients with CKD such as hypertension, dyslipidaemia, diabetes mellitus, smoking, low physical activity/obesity and prior cardiovascular events. Many risk factors contribute to the aetiology and pathogenesis of CKD or are shared risk factors for CKD progression[1]. Furthermore, there are contributors to accelerated CVD specific to, or exaggerated in CKD. Examples include left ventricular hypertrophy (LVH), fluid and electrolyte shifts, proteinuria, functional vitamin D deficiency, hyperphosphataemia, chronic inflammation, vascular stiffness and/or vascular calcification. There are multiple other putative mechanisms for accelerated CVD in CKD patients, identified by phenotyping using state of the art imaging, physiological studies and molecular biology, although these are yet to translate to clinical practice. This NDT Digest will discuss current clinical evidence for addressing CVD risk in CKD.

Personalised CVD risk reduction in CKD patients

To have maximum acceptability, strategies to reduce CVD risk should be tailored to the individual. Interventions targeting CVD risk reduction should be specific to CKD stage or renal replacement therapy modality. The evidence base for many interventions varies by CKD stage. Not all interventions have a strong evidence base, either due to challenges of undertaking large randomised controlled trials (RCTs) of lifestyle interventions, or due to the lack of specific RCTs in patients with CKD. Non-pharmacological interventions may include addressing lifestyle such as smoking,

obesity, salt intake and physical activity. RCTs inform best practice for management of dyslipidaemia and blood pressure in CKD to reduce cardiovascular risk[1].

Optimal treatment of dyslipidaemia in CKD

The benefits of lowering LDL-cholesterol in with HMG-CoA reductase inhibitors (statins) is established in patients without renal dysfunction. Their safety and efficacy as secondary and primary CVD prevention in high risk patients is established in large RCTs. The overwhelming nature and magnitude of benefits in high risk populations is summarized in meta-analyses from the Cholesterol Treatment Triallists collaboration[2].

The SHARP trial clearly demonstrated benefit of lowering LDL-cholesterol with simvastatin/ezetimibe compared to placebo as primary prevention of atherosclerotic vascular events in patients with CKD not requiring dialysis[3]. By contrast, two large RCTs in dialysis patients, 4D and AURORA, showed no demonstrable benefit of statin therapy (atorvastatin in 4D, rosuvastatin in AURORA) in dialysis patients[4, 5]. The ALERT trial of lipid lowering with fluvastatin to prevent cardiovascular events in renal transplant recipients showed that statin therapy was associated with a reduction in non-fatal myocardial infarction and cardiac deaths[6].

The combined weight of these trials in patients with varying degrees of CKD have led meta-analyses studying the effect of lipid lowering with statins and/or lowering of LDL-cholesterol. The most comprehensive of these meta-analyses from 28 trials in patients with various degrees of renal impairment[7] gives the overall message that lowering of LDL-cholesterol has a beneficial effect on prevention of major atherosclerotic vascular events in CKD patients not requiring dialysis (including renal transplant recipients). As eGFR declines, there is a trend towards smaller relative risk reductions

for major coronary events and strokes. There appears to be little benefit derived from commencing lipid lowering in patients once they start dialysis treatment.

Targeting blood pressure to reduce CVD risk – SPRINT into action?

Leaving aside that treatment of hypertension is a therapeutic goal in reducing risk of CKD progression, it is well established that hypertension is a major modifiable global risk factor for reducing risk of CVD. Until recently most guidelines including Kidney Disease Improving Global Outcomes (KDIGO) in 2012 recommended aiming for target systolic blood pressure (BP) of <140mmHg and <130mmHg with preferential use of renin angiotensin system inhibition in the presence of significant proteinuria. However, recent compelling data from the 2646 non-dialysis CKD patients in the SPRINT trial suggests that there is additional mortality benefit in reduction of systolic BP to <120mmHg compared to 140mmHg[8]. Although this was a large trial, the overall difference in number of patients experiencing an event between the intervention groups was small, with more adverse events in the intensive BP group. Further studies would be useful to inform whether targeting this lower blood pressure achieves greater benefits on CVD risk in CKD without an excess of adverse events such as falls or acute kidney injury.

In dialysis patients, defining an optimum BP is challenging. Whilst there is clear epidemiological evidence that extremes of BP are associated with increased CVD risk, it is less clear that reduction in BP with any specific strategy such as medication or alterations to ultrafiltration regimens, is associated with consistent definitive benefit. Interestingly, a meta-analysis of trials of antihypertensive therapy in dialysis patients did show benefit with intervention, although it should be noted that the many patients in this analysis did not actually have hypertension *per se* [9].

Sodium and CVD risk

The data on the association between salt (or sodium) intake and cardiovascular risk is controversial. Recent data suggests that in patients with hypertension, excretion of >7g/day of sodium, as a marker of salt intake, is associated with increased risk of CVD. Excretion of <3g/day was also associated with increased CVD risk[10]. CKD populations tend towards hypertension and fluid retention, and these data suggest that in many patients with CKD, reduction of sodium intake is likely to be beneficial for reducing CVD risk, especially in the setting of most Western diets where sodium consumption is high.

The future of CVD risk management of CKD

Several treatment strategies which might have specific benefits in CKD patient are currently being tested in clinical trials. Further refinement of algorithms addressing CKD mineral-bone disease is required following the EVOLVE trial with cinacalcet and various recently reported trials with vitamin D analogues. Ongoing trials include vitamin K supplementation, which may reduce vascular calcification (NCT01742273), mineralocorticoid receptor antagonism which may target LVH non-atherosclerotic CVD deaths (NCT01848639) and. Until these trials report and are digested, a suggested approach to primary prevention of CVD in CKD is shown in Figure 1.

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Figure 1. Issues to address for primary prevention of CVD in CKD. Abbreviations: GFR- glomerular filtration rate, BP-blood pressure, ACR- urinary albumin:creatinine ratio, RASi- renin angiotensin system inhibition

Conflict of interest statement. The results presented in this paper have not been published previously in whole or part.