# Reducing cardiovascular risk in people with diabetes and kidney disease

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We need to move beyond managing end organ complications to reducing cardio-renal risk across the spectrum of kidney function

Type 2 diabetes mellitus is one of the greatest challenges facing the Australian health care system. The number of Australians living with diabetes has tripled over the past 25 years, and by 2025 it is expected that 3 million adults will have been diagnosed with the disease, one of the most rapid rises for any chronic condition in Australia.[1]

More than one-third of these people will develop chronic kidney disease, making diabetes the leading cause of end-stage kidney disease (ESKD) in Australia, as it is overseas. In many countries, more than 50% of people requiring renal replacement therapy have diabetes-related kidney damage.[2] As perhaps the most debilitating complication of diabetes, ESKD has a calamitous impact on patients and their families and caregivers, and also has substantial consequences for the Australian health care system, with an estimated cost of more than $12 billion over the past decade alone.[3]

In this issue of the *MJA*, Lim and colleagues describe the impact of diabetes on the risk of cardiovascular mortality in patients with ESKD, having analysed three decades of data from the Australia and New Zealand Dialysis and Transplant Registry, a key global contributor to our understanding of ESKD and kidney transplantation.[4]

The findings underscore the fact that patients with ESKD and diabetes — especially those with ESKD attributable to diabetic nephropathy — are at exceptionally high risk of cardiovascular disease-related mortality. But even more striking is that the relative likelihood of cardiovascular disease-related death is substantially higher for younger patients. This is particularly worrying, as the burden of type 2 diabetes in young people is rapidly increasing worldwide; in little more than a decade, the number of people aged 20–39 years with type 2 diabetes has almost tripled, rising from 23 to 63 million.[5]

The study by Lim and colleagues is therefore timely, refocusing our attention on the need to improve cardiovascular outcomes, not only for patients with ESKD and diabetes, but also for the many Australians with diabetic nephropathy who do not yet require dialysis and are more likely to die from cardiovascular disease than to progress to ESKD. How can we achieve this aim?

Clinical trials of a number of interventions for reducing the risk of cardiovascular events and mortality in patients with ESKD have not yielded clear evidence of benefit. The Kidney Disease Improving Global Outcomes guidelines recommend lipid-lowering therapy for people with chronic kidney disease who do not require dialysis, but there is insufficient evidence to support commencing lipid-lowering therapy in most patients with ESKD who do require dialysis, despite several large randomised trials.[6] While trials of blood pressure-lowering interventions have collectively suggested a benefit for cardiovascular outcomes, the trials have been small and inadequate for clearly guiding therapy.[7] The role of antiplatelet therapy is less well established than for people without kidney disease, with more complex risk–benefit considerations because of the increased bleeding risk in patients with kidney disease.[8]

The best way to improve cardiovascular outcomes for patients with ESKD is to redouble our efforts to increase the number and improve the quality of clinical trials. Despite cardiovascular disease causing more than half of all deaths in people with ESKD, trials reporting cardiovascular outcomes for this population are generally shorter than 6 months in duration, and most enrol fewer than 100 participants.[9] The outcomes assessed are heterogeneous, with an over-reliance on surrogate outcomes of unclear significance for patients. As a result, it has been difficult to synthesise and interpret the available evidence and to identify the best strategies for preventing cardiovascular disease. A range of recent





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collaborative efforts, such as the Australian-led Standardising Outcomes in Nephrology (SONG) initiative, will go some way to redressing these problems by involving patients, their caregivers, and health professionals in developing a core outcome set, including cardiovascular outcomes, for haemodialysis trials applying a consensus methodology.[10]

But we also need to urgently identify treatments that slow the loss of kidney function and prevent cardiovascular disease in people with diabetes, especially those with established nephropathy. If we do not, the rapidly growing number of people with diabetic nephropathy will inevitably translate into an increased burden of ESKD that is more complex and expensive to treat. Promising new glucose-lowering agents, such as the sodium/glucose cotransporter 2 inhibitors and some glucagon-like peptide 1 receptor agonists, reduce the risk of adverse cardiovascular events and may slow the progression of kidney disease in people with type 2 diabetes; they are now recommended by a number of guidelines as second line treatments (after metformin) for people with diabetes and established cardiovascular disease.[11,12] Further trials that assess the impact of promising interventions on the risk of ESKD and its complications must be a priority for the diabetes and nephrology communities.

It is clear that new treatments alone will not reduce the burden of diabetes and its complications. Multifaceted population health strategies that prevent type 2 diabetes are desperately needed to achieve the best outcomes. We should embrace opportunities to take a lead role in advocating policies that recognise the environmental and behavioural drivers of diabetes and other chronic health conditions.

As Lim and his co-authors point out, reducing cardiovascular risk is one of the most important aspects of care we can provide for people with ESKD. We clearly can and must do much better. A concerted effort to generate better evidence and apply tested treatments will enable us to move beyond simply managing end organ complications, towards more comprehensively reducing cardio-renal risk across the entire spectrum of kidney function in partnership with general practice, where most kidney disease care is provided.

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