

## **Commentary for Kidney International**

### **PCSK9 inhibition: ready for prime-time in CKD?**

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#### **Abstract**

Lowering LDL cholesterol reduces the risk of atherosclerotic vascular disease in a wide range of patients with chronic kidney disease, with no evidence of a threshold below which further reductions no longer reduce risk. Statins safely lower LDL cholesterol, but novel inhibitors of proprotein convertase subtilisin kexin 9 (PCSK9) provide additional reductions which may reduce atherosclerotic vascular disease yet further in this high risk population.

#### **Keywords**

LDL cholesterol

Proprotein convertase subtilisin kexin 9 inhibitors

Cardiovascular disease

#### **Main body**

It is well-recognised that patients with chronic kidney disease (CKD) are at increased risk of cardiovascular disease (CVD) compared to their peers.<sup>1</sup> The reasons for this association, and the degree to which it is causal, have been debated. Nevertheless, the association remains and it is therefore incumbent on doctors caring for patients with kidney disease to address this risk in addition to considering the risk of progressive kidney disease and addressing associated problems (e.g. mineral-bone disease, anaemia). Structural heart disease appears early in the development of CKD and becomes increasingly prevalent as kidney function declines such that about 80% of patients starting dialysis have a structurally abnormal heart.<sup>2</sup> It is appropriate to consider therapies which address the consequences of this structural heart disease, which overlap with the clinical phenotype of heart failure.

However, the risk of atherosclerotic CVD (e.g. myocardial infarction, large vessel ischaemic stroke, peripheral arterial disease) also increases as kidney function falls. Unlike in other areas of nephrology, there are very good randomized trial data to support the use of therapies which address atherosclerotic CVD among patients with CKD. In large trials of individuals not selected on the basis of kidney function, lowering systolic blood pressure by 10 mmHg reduces the risk of coronary heart disease by 17% (95% CI 12-22%).<sup>3</sup> Lowering low density lipoprotein cholesterol (LDL-C) is also effective: the SHARP (Study of Heart and Renal Protection) trial demonstrated that simvastatin 20 mg plus ezetimibe 10 mg (which lowered LDL-C by 0.84 mmol/L) reduced the risk of major atherosclerotic events by 17% (95% CI 6-26%).<sup>4</sup> There is some evidence to suggest that the *proportional* benefits of lowering LDL-C become smaller as kidney function falls (although with the currently available data it is not possible to distinguish a gradual diminution with falling kidney function from a step-change such that the proportional effect is constant until dialysis commences, when lowering LDL-C becomes much less effective).<sup>5</sup> Because the risk of atherosclerotic disease increases as kidney function declines (by about 30% for every 30% fall in estimated glomerular filtration rate [eGFR]),<sup>6</sup> the risk of atherosclerotic disease increases four times with a change in eGFR of 60 to 10 mL/min/1.73m<sup>2</sup>. Since there is also a four-fold reduction in relative risk with lowering LDL-C across this range, the *absolute* benefits of lowering LDL-C are actually broadly similar across the range of kidney function.<sup>5</sup>

The proportional benefits of lowering LDL-C are strongly related to the absolute reduction achieved in LDL-C as can be seen in the figure. LDL-C lowering therapies generally cause (for a given dose) a fixed proportional reduction in LDL-C, so the absolute LDL-C reduction depends on the baseline concentration as well as the potency of the therapy being tested. Patients with CKD typically have low or low-normal LDL-C concentrations; therefore to maximise the benefit of LDL-C lowering, potent (and safe) therapies are needed which can achieve a significant reduction in LDL-C which will then translate into a meaningful reduction

in cardiovascular risk. Statins are effective at reducing LDL-C and there is good evidence to support the safety of moderate doses either alone or in combination with other LDL-C lowering agents like the absorption inhibitor ezetimibe. However, there are no direct data to assess the safety of high-dose statins among patients with CKD and high doses of certain statins are associated with excess risks of myopathy.

Circulating proprotein convertase subtilisin kexin 9 (PCSK9) binds to the LDL receptor on hepatocytes leading to lysosomal degradation of the PCSK9/LDL-receptor complex. Inhibitors targeting PCSK9 (PCSK9i) therefore result in increased recycling of the LDL receptor to the cell surface where it captures more LDL-C particles and removes them from the circulation, thus lowering blood concentration of LDL-C. The development of PCSK9i is a remarkable story which began with the identification of mutations in the PCSK9 gene as a rare cause of familial hypercholesterolaemia in 2003; subsequent epidemiological investigation demonstrated that PCSK9 variants that reduced PCSK9 function were associated with a lower risk of cardiovascular disease and the first phase 2 trials of monoclonal antibodies directed against PCSK9 started in 2011.<sup>7</sup> Several PCSK9i are now in development and in 2017 the FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) trial reported that evolocumab (140 mg every 2 weeks or 420 mg every month depending on patient preference) reduced LDL-C by 1.45 mmol/L (59%) and the risk of major cardiovascular events by 15% (95% CI 8-21%).<sup>8</sup> (Although this relative risk may seem small in comparison to the reduction in LDL-C, it is important to consider that LDL-C lowering therapies have little effect in the first year and the FOURIER trial was terminated early so median follow-up was only 26 months.)

PCSK9i is therefore a promising therapy and it is appropriate to consider its role in reducing cardiovascular risk among patients with CKD. The article by Toth and colleagues in this issue of *Kidney International* is therefore timely.<sup>9</sup> The authors present a pooled analysis of eight trials which compared alirocumab 150 mg every 2 weeks (some with an initial 12 week period of 75 mg every 2 weeks) with either placebo or ezetimibe 10 mg daily (with over 99% of participants taking a statin as background therapy). In total 4629 participants were included in the trials, of whom 467 (10%) had impaired renal function (IRF, defined as a baseline eGFR 30-59 mL/min/1.73m<sup>2</sup>). (The authors chose the term “impaired renal function” rather than CKD as they did not have proof that the reduction in eGFR was long-standing, although it was probably likely to be given that the participants were clinically stable at baseline.) The analysis shows that the proportional reduction in LDL-C observed with alirocumab 150 mg every 2 weeks (the dose chosen for the ongoing clinical outcome trials) was about 60% with similar effects among patients with or without IRF. The effect on LDL-C

also did not vary by baseline proteinuria, although the quantification of this was crude and most participants had minimal amounts.

PCSK9i seem to be well-tolerated with similar discontinuation rates compared to placebo in large trials. Similar results were shown here. As expected, participants with IRF had a higher rate of serious adverse events compared to participants with preserved kidney function, but the rates were similar between alirocumab and control groups, regardless of kidney function. No effect on kidney function was observed, with stable eGFR among participants with and without IRF (but no information on the effect on proteinuria was available).

So should nephrologists consider using PCSK9i in their patients? They have been proven to be effective at reducing cardiovascular risk in the general population and there do not seem to be reasonable grounds for thinking that they would not do the same among patients with CKD. Assuming statin-based therapy is now widely-used then a baseline LDL-C of around 1.7 mmol/L might be expected so an additional 60% reduction (with PCSK9i use) would equate to an approximate 1.0 mmol/L reduction. As shown in the figure, this could be predicted to reduce the risk of major vascular events by about 25% proportionally. Estimates of absolute benefit based on randomized trial are probably an underestimate as trial participants are typically at lower risk of disease than the population from which they are selected (although this does not mean that the proportional effects cannot be generalised). Whether such effects are worthwhile will depend on an individual patient's risk of atherosclerotic disease, preferences and – not least – the cost of such therapies.

However, before such determinations are made it is important to consider the population among whom PCSK9i have been tested to date. The alirocumab trials presented in this analysis excluded patients with an eGFR <30 mL/min/1.73m<sup>2</sup> and the FOURIER trial of evolocumab excluded patients with an eGFR <20 mL/min/1.73m<sup>2</sup>. Patients presented by Toth and co-workers did not have progressive CKD so there are remaining questions about their safety and efficacy in more advanced CKD and their effects on progression of CKD. Although atherosclerotic disease does not explain the majority of the excess of cardiovascular disease affecting patients with CKD, it is nonetheless a disease that can be targeted and patients with advanced or progressive CKD have too often been excluded from trials of new therapies. Hopefully the development of PCSK9i, which has set new standards in the speed of development, will also break the mould and assess the benefits of these exciting therapies in a population in significant need of further improvement in outcomes.

## **Disclosures**

CTSU has a staff policy of not accepting honoraria or other payments from the pharmaceutical industry, expect for the reimbursement of costs to participate in scientific meetings ([www.ctsu.ox.ac.uk](http://www.ctsu.ox.ac.uk)).

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## Figure legend

Association between absolute reduction in LDL-C and proportional risk reduction in major atherosclerotic events from 21 trials of statin versus control, 5 trials of more versus less statin and the SHARP trial of simvastatin plus ezetimibe versus placebo.

