# PCSK9 inhibition and type 2 diabetes

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The focus of cardiovascular disease prevention has shifted from normalisation of risk factors to absolute risk reduction. Reducing low-density lipoprotein cholesterol (LDL-C) concentration by 1 mmol/L for around 5 years is consistently associated with a 23-25% lower risk of major cardiovascular events, for statin and non-statin therapies alike, regardless of the baseline LDL-C level.[1] In high and middle income countries, statins are now routinely recommended as first line LDL-C-lowering therapy for people with 10 year modelled risk above somewhat arbitrary, country-specific thresholds defined by economic and clinical considerations. This high-risk category includes most patients with type 2 diabetes. Statins achieve similar reductions in relative risk among people with and without diabetes.[2] However, even among patients on maximum doses, with LDL-C levels in the normal range, further reductions in LDL-C and modelled risk are possible.

Proprotein convertase subtilisin/kexin type 9 (PCSK9) enzyme catalyses the degradation of the LDL receptor, thereby reducing LDL-C uptake by cells and increasing circulating levels. In this issue, Sabatine and colleagues report the efficacy and safety of PCSK9 inhibition in people with and without diabetes.[3] They undertook a pre-specified secondary analysis of data from FOURIER, a randomised controlled trial of subcutaneous injections of the monoclonal antibody Evolocumab or placebo every 2 or 4 weeks, in 27,564 patients with atherosclerotic disease and prescribed statin therapy. The effect of Evolocumab on LDL-C concentration (~1.5 mmol/L reduction at 48 weeks) and risk of the composite cardiovascular endpoint over 2.2 years (hazard ratio 0.83; 95%CI:0.75 to 0.93) was similar in participants with diabetes compared to those without. Consideration of adverse effects is particularly important given the historical controversy over statins. Evolucumab was well tolerated. The frequency of adverse effects (for example muscle-related and neurocognitive) was similar in the two study arms,

as was drug discontinuation, which occurred less often (5.7%/year) than in the IMPROVE-IT trial of the addition of once daily oral Ezetimibe to statin therapy (7%/year).[4]

One concern related to statins is the increased risk of type 2 diabetes,[5] albeit the net effect on risk of cardiovascular disease, the most burdensome complication of diabetes, strongly justifies their use. Meta-analyses of statin trials including over 90,000 patients followed for 4.2 years, and Mendelian randomisation studies of LDL-C lowering variants near the gene encoding the HMG-coenzyme A reductase protein (the target for statins) confirm an adverse effect of statins on weight (0.24kg higher) and incidence of diabetes (12% higher).[5] Genetic studies including data from more than half a million individuals have demonstrated associations between PCSK9 variants and weight (1.03kg higher), fasting glucose (0.09 mmol/L higher) and odds of diabetes (19 to 29% higher).[6,7] The FOURIER investigators report no evidence of an association between Evolocumab and weight, glycated haemoglobin and incidence of diabetes (hazard ratio 1.05; 95% CI:0.94 to 1.17). These results reassure us that PCSK9 inhibition is unlikely to have a major impact on diabetes risk. FOURIER was adequately powered to detect effect sizes observed in genetic studies. However, estimates from genetic studies are scaled to a 1mmol/l lower LDL-C concentration and reflect a life-long exposure to differences in PCSK9 function in the general population. By contrast, FOURIER investigated pharmacological PCSK9 inhibition reducing LDL-C by 1.5mmol/l over 2.2 years of follow-up, in the setting of a high-risk population previously exposed to statin treatment. Hence, a small to moderate effect of Evolocumab on diabetes risk will only be excluded by pooling of data from several trials, as undertaken for statins. The consistency of results of genetic studies and trials highlights as yet unexplained mechanisms in the aetiology of diabetes that merit further investigation. The discrepancy in effect sizes between genetic studies and trials raises the possibility that cardiovascular risk reductions of greater than 25% could be achieved through longer term treatment from an earlier age. As the rationale for basing prescribing decisions on absolute risk assumes a consistent effect size, perhaps we should consider incorporating age-sex standardised rather than absolute risk into guidelines and shared decision-making.

Ezetimibe is the recommended additional LDL-C lowering therapy for patients prescribed maximum tolerated dose statin. While considerably cheaper than Evolocumab, it has a smaller effect on LDL-C. In IMPROVE-IT, adding Ezetimibe to statins achieved a reduction of 0.43 mmol/L in LDL-C compared to placebo, and was associated with a greater reduction in relative risk of cardiovascular events among people with diabetes than those without. FOURIER data suggest that Evolucumab is an effective and safe option for patients with diabetes and atherosclerotic disease. If PCSK9 inhibitors, or other emerging therapies, have few adverse effects, including minimal impact on diabetes risk, this might influence prescribing decisions. However, for the vast majority of the half a billion people with type 2 diabetes worldwide, access to PCSK9 inhibitors is likely to be limited for the forseable future by their cost.[8]

## Conflict of interest

Simon Griffin receives an honorarium and reimbursement of travel expenses from Eli Lilly associated with membership of an independent data monitoring committee for a randomised cardiovascular endpoint trial of a medication to lower blood glucose. He received an honorarium from Janssen for speaking at an educational meeting in 2015 and from Astra Zeneca for speaking at an educational meeting in 2017.

Luca Lotta declared no conflicts of interest.

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