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Clinicians should think twice before prescribing DPP-4 inhibitors for diabetes

Joshua J Fenton

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Correspondence to:

Dr Joshua J Fenton,
Department of Family and
Community Medicine, The
Center for Healthcare Policy and
Research, University of
California, Davis Health System,
4860 Y Street, Suite 2300,
Sacramento, CA 95817, USA;
jjfenton@ucdavis.edu

While reviewing abstracts in my role as an *Evidence Based Medicine* editor, I recently encountered a seemingly strange randomised trial of sitagliptin, one of the new dipeptidyl peptidase-4 (DPP-4) inhibitor antidiabetic drugs. Appearing in the *New England Journal of Medicine*, the trial evaluated the impact of sitagliptin on cardiovascular outcomes in patients with non-ideally controlled type 2 diabetes with established cardiovascular disease, concluding that sitagliptin was both non-inferior and non-superior to placebo in this high-risk group.¹ As a primary care physician, my hope for diabetic patients of mine is that a new medication, such as sitagliptin, would be superior to placebo in reducing their high cardiovascular risk. However, in this high-risk population with prevalent cardiovascular disease, sitagliptin seemed to have no impact on cardiovascular outcomes over the median 3-year follow-up of the trial, so the clinical implications of the findings for my patients seemed dubious. I wondered why a trial demonstrating the non-inferiority of sitagliptin to placebo merited appearance in the world's highest impact general medical journal.

Of course, a trial such as this—the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS)—has a broader audience than front-line physicians. Indeed, on closer inspection, one suspects that TECOS's principal audience is the regulatory regime, particularly the US Food and Drug Administration (FDA), and the European Medicines Agency (EMA), which now require trials of cardiovascular safety of new antidiabetic medications in view of the high incidence of adverse cardiovascular effects observed during the postmarketing phase with rosiglitazone.² Specifically, the FDA requires that new antidiabetic medications be shown to be associated with a risk ratio of new cardiovascular events of <1.8 (based on the upper bound the 95% CI) and to have a 'reassuring' point estimate. Hence, TECOS was designed with a non-inferiority margin of 1.3, a margin well below the FDA requirement (but still potentially consistent with an increased risk of cardiovascular events of up to 30%).

The TECOS investigators, however, recruited about twice as many patients than was necessary to provide 90% power for the non-inferiority analysis of safety. Indeed, by recruiting over 14 000 patients, the trial was adequately powered for both non-inferiority and superiority analyses, which ultimately showed no significant difference in the primary composite cardiovascular outcome in the sitagliptin versus placebo groups. The HR in the per-protocol, safety analysis was 0.98 (95% CI 0.88 to 1.09, $p < 0.001$ for non-inferiority), while the HR in the intention-to-treat, superiority analysis was 0.98 (95% CI 0.89 to 1.11, $p = 0.65$). Thus, the very low p value for the non-inferiority analysis implies that the likelihood is very small that sitagliptin increases the risk

of the composite cardiovascular outcome by the prespecified non-inferiority margin of 30% or greater.

For Merck, which manufactures sitagliptin and funded the study, this is very good news. Not only is the point estimate reassuring but the 95% CI for the safety analysis is far below the liberal 1.8 threshold specified by the regulatory agencies. However, for clinicians, there may still be reasons to be concerned about prescribing sitagliptin and other DPP-4 inhibitors. As these results demonstrate, sitagliptin does not reduce cardiovascular risk in high-risk patients, as patients and clinicians should want, despite its demonstrated ability to lower blood glucose levels. Indeed, the study data remain consistent with a 9% increase in the composite cardiovascular outcome (95% CI 0.88 to 1.09), and a 20% increase in the secondary outcome of congestive heart failure (intention-to-treat HR 1.00, 95% CI 0.82 to 1.20, $p = 0.98$). The latter finding is of particular concern, because a recent meta analysis of five trials (including TECOS) found a summary OR of heart failure admission with DPP-4 treatment of 1.13 (95% CI 1.00 to 1.26).³ Thus, despite TECOS, data from clinical trials remaining consistent with an increased risk of heart failure admission with DPP-4 use, so clinicians (and regulators) should not be blindly reassured by the TECOS findings.

Of course, it is conceivable that the benefits of improved glucose control with DPP-4 inhibitors may outweigh any associated risks of heart failure, so one should attempt to compare the potential benefits with the potential risks of DPP-4 drugs, notwithstanding many uncertainties regarding the long-term outcomes associated with DPP-4 use. In the UK Prospective Diabetes Study, approximately 20 patients needed to be treated with intensive antidiabetic therapy for 10 years to prevent one diabetes-related endpoint.⁴ We do not know if comparable glucose reductions achieved with DPP-4 inhibitors would confer similar benefits, but if we assume similar benefits with DPP-4 inhibitors, how does this benefit compare with the potential increased risk of heart failure associated with chronic DPP-4 use? The *BMJ* meta analysis of trial data estimates a pooled increased absolute risk of heart failure hospitalisation of approximately 16 per 1000 patients over 10 years (0.016%), so the number needed to harm over the period is 63 patients. Thus, the number needed to treat with DPP-4 inhibitors to benefit one patient is probably about 20 while the number needed to harm is about 60 with substantial uncertainty in both numbers due to short follow-up in safety trials, other potential trial biases, statistical imprecision, and uncertainty whether DPP-4 confer any long-term benefits in diabetes outcomes.

Trials such as TECOS are massive, astonishingly complex undertakings. TECOS enrolled patients from



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673 sites in 38 countries and followed them for a median of 3 years. Although TECOS was published in 2015, the trial protocol was initially registered 7 years earlier, probably after several years of development. Trials costs were surely enormous. For all this, TECOS enables a more precise assessment of how sitagliptin may alter cardiovascular risk in high-risk patients with inadequately controlled type 2 diabetes. However clinicians should remain wary that DPP-4 inhibitors may increase patients' cardiovascular risk, particularly for congestive heart failure, and that these risks could be comparable with any potential long-term benefits of glucose reduction that DPP-4 inhibitors may help to achieve.

Competing interests None declared.

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References

1. Green JB, Bethel MA, Armstrong PW, *et al.* Effect of sitagliptin on cardiovascular outcomes in type 2 Diabetes. *N Engl J Med* 2015;373:232–42.
2. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 2007;356:2457–71.
3. Li L, Li S, Deng K, *et al.* Dipeptidyl peptidase-4 inhibitors and risk of heart failure in type 2 diabetes: systematic review and meta-analysis of randomised and observational studies. *BMJ* 2016;352:i610.
4. Holman RR, Paul SK, Bethel MA, *et al.* 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008;359:1577–89.