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LETTER

Diabetes prevention and cardiovascular complications

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Abbreviations

ACT NOW	Actos Now for Prevention of Diabetes
ASCVD	Atherosclerotic cardiovascular disease
CV	Cardiovascular
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
IRIS	Insulin Resistance Intervention after Stroke
MI	Myocardial infarction
RRR	Relative risk reduction

To the Editor: The review by Nathan et al recently published in *Diabetologia* provides an excellent discussion of the relationship between diabetes prevention and microvascular and cardiovascular (CV) complications [1]. We agree that the existing data are quite limited, although somewhat more robust for microvascular disease. This is not unexpected, given that hyperglycaemia is more closely aligned with retinopathy and nephropathy than with atherosclerotic CV disease (ASCVD). We noted one important omission, however, from this otherwise complete review. Insulin Resistance Intervention after Stroke (IRIS) was a large, multi-national clinical trial, funded by the US National Institutes of Health, that randomised insulin-resistant (but non-diabetic) individuals with recent stroke or transient ischaemic attack to receive the thiazolidinedione pioglitazone or placebo and assessed the impact on future CV events as well as the diagnosis of diabetes [2].

Pioglitazone is a potent insulin-sensitising drug and, as Nathan et al point out, it prevented diabetes in individuals with impaired glucose tolerance (IGT) in the Actos Now for Prevention of Diabetes (ACT NOW) trial [3]. That study, which predominately involved patients without known ASCVD, also demonstrated a simultaneous benefit of pioglitazone on the progression of early carotid atherosclerosis, but was too small (N=602) and brief (2.4 years) to adequately assess clinical CV events. In contrast, IRIS, which included 3876 patients with known cerebrovascular disease and a median follow-up of 4.8 years, demonstrated a 24% relative risk reduction (RRR) in the primary outcome of fatal/non-fatal stroke or myocardial infarction (MI) (p=0.007) with pioglitazone vs placebo (Fig. 1) [2]. Subsequently, using updated outcome definitions, we also reported statistically significant RRRs with pioglitazone for stroke alone (25%), exclusively driven by ischaemic stroke (28%) [4], as well as for acute coronary syndrome (29%), predominately driven by a large effect on type 1 MI (38%) [5].

Both insulin resistance and ASCVD are important risk factors for type 2 diabetes. IRIS provided a unique opportunity to simultaneously assess, as a prespecified secondary outcome, the preventive effect of pioglitazone on diabetes in a large group of insulin-resistant individuals both with and without 'prediabetes' (defined and analysed separately as impaired fasting glucose [IFG; fasting plasma glucose ≥5.6 mmol/l] or elevated HbA_{1c} [5.7–6.4% or 39–46 mmol/mol]). Overall, diabetes developed in 7.7% of IRIS participants randomised to placebo and 3.8% of those assigned to pioglitazone (HR 0.48, 95% CI 0.33, 0.69; p<0.0001) (Fig. 1) [6]. The effect size was nominally larger in those with baseline IFG (HR 0.41, 95% CI 0.30, 0.57]) or elevated HbA_{1c} (HR 0.46, 95% CI 0.34, 0.62]). In a more recent report, focusing on the combined 2885 IRIS participants with either definition of prediabetes (i.e. by fasting glucose or HbA_{1c} criteria), the RRRs for the primary

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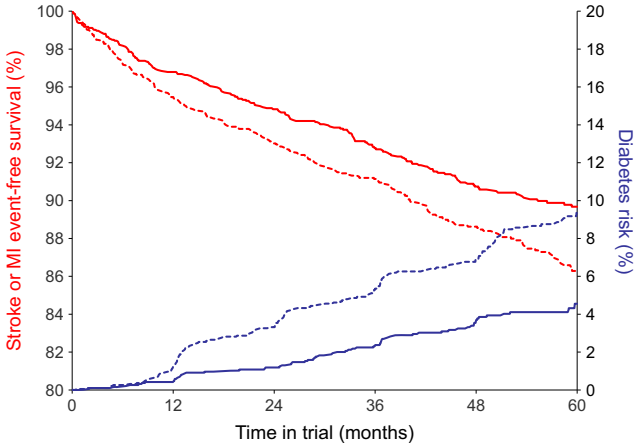

Fig. 1 Prevention of CV events [2] and diabetes [6] with pioglitazone in the IRIS trial. The figure displays the event-free survival for the primary outcome (fatal/non-fatal stroke and fatal/non-fatal MI) (red lines, left *y*-axis) and the incidence of the secondary outcome of diabetes diagnosis (blue lines, right *y*-axis) in the IRIS trial. Solid lines, participants randomised to pioglitazone; dashed lines, participants randomised to placebo

outcome of stroke/MI and the secondary outcome of a diagnosis of type 2 diabetes (intent-to-treat analyses) were 30% (p=0.002) and 54% (p<0.001), respectively, increasing to 43% (p=0.004) and 82% (p=0.001) in those with good adherence to pioglitazone [7], a drug with known side effects of weight gain and oedema.

So, pioglitazone is the first glucose-lowering medication proven to not only prevent diabetes, but also to reduce major CV events in a single trial involving high-risk CV individuals. In a similar vein, Nathan et al discussed the Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) trial, which assessed type 2 diabetes prevention with the α-glucosidase inhibitor acarbose in 1429 individuals with IGT and IFG. That study found not only a 25% RRR for diabetes (p=0.0015), but also a 49% risk reduction for any CV event (p=0.03) [8]. However, the latter estimate was based on few patients with events (n=47), not surprisingly, given that the STOP-NIDDM population was low-risk, with <5% having established CVD at baseline. A subsequent larger trial (Acarbose Cardiovascular Evaluation [ACE]) involving 6522 Chinese individuals with both IGT *and* coronary heart disease could not replicate the benefit of acarbose (HR 0.98, 95% CI 0.86, 1.11) for major CV events [9].

Accordingly, while we agree with the authors that there is a paucity of data to support the notion that preventing diabetes results in a CV benefit, pioglitazone stands out as an example of one intervention that has done so in high-risk patients with established ASCVD. We recognise that pioglitazone has pleiotropic actions and its diabetes prevention effect is likely responsible for only a part of its CV benefits. Nonetheless, the IRIS trial provides convincing evidence that it is indeed possible to prevent both diabetes and CV events simultaneously—if the right drug is used and if the right patients are targeted.

Data availability All data generated or analysed during this study are included in these published articles [2, 6] and associated supplementary information files.

Duality of interest SEI has served on clinical trial steering or executive committees for Eisai (through the Thrombolysis in Myocardial Infarction [TIMI] Study Group) and AstraZeneca, which have examined diabetes prevention through weight loss or glucose lowering medications. The other authors declare no dualities of interest associated with their contribution to this manuscript.

Contribution statement All authors were responsible for drafting the article or revising it critically for important intellectual content, and all authors approved the version to be published.

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