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## EDITORIALS

## Intensive glucose lowering treatment in type 2 diabetes

The effect on microvascular disease seems to be modest at best

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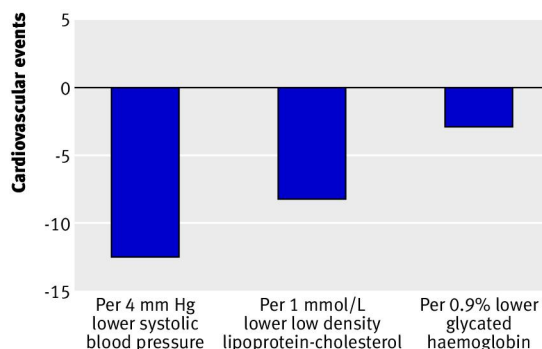
The recognition that diabetes is an independent risk factor for cardiovascular disease has led to trials of different glucose lowering strategies in an attempt to reduce the risk of such disease. The effect of glucose lowering on cardiovascular disease outcomes is one of the most contentious in recent history, as indicated by the class IIb recommendation from the joint American Diabetes Association, American Heart Association, and American College of Cardiology guidelines.<sup>1</sup> In the linked meta-analysis (doi:10.1136/bmj.d4169), Boussageon and colleagues assess both microvascular complications and cardiovascular events related to the intensity of glycaemic control and the quality of randomised studies.<sup>2</sup>

Before considering individual trials several factors warrant consideration. For example, it is possible that glucose lowering is a much weaker intervention than previously envisaged so that individual trials may be underpowered to detect changes in a chosen end point. Also, current treatments may partly negate any benefit of glucose lowering by exchanging one risk factor for another—for example, weight gain, which has concomitant effects on blood pressure and lipids.<sup>3</sup>

The largest study to date, which compared the effects of intensive glucose lowering with standard treatment on cardiovascular outcomes, reported data from five randomised controlled trials on 33 040 patients in whom 1497 non-fatal myocardial infarctions, 2318 coronary events, 1127 strokes, 2892 deaths, and 1391 cases of new or worsening heart failure occurred.<sup>4</sup> It found that a 0.9% lowering of glycated haemoglobin (HbA<sub>1c</sub>) 7.5% v 6.6%) was associated with a 17% reduction in non-fatal myocardial infarctions, 15% reduction in coronary events, and a trend towards lower stroke risk with no statistical evidence of heterogeneity. Mortality and heart failure did not differ significantly between intensive and standard treatment arms. These data are consistent with literature based analyses that excluded PROactive,<sup>5</sup> and a meta-analysis of four major trials with individual participant data, which also suggested that cardiovascular benefit after intensive glucose lowering was limited to people without known cardiovascular disease.<sup>6</sup>

Boussageon and colleagues' meta-analysis adds eight extra studies with information on a further 1493 participants in whom 54 additional non-fatal myocardial infarctions, 209 deaths, and 187 cases of new or worsening heart failure occurred.<sup>2</sup> The cardiovascular data are broadly consistent with earlier reports,<sup>4,6</sup> showing a 15% reduction in non-fatal myocardial infarctions but no clear effect on other cardiovascular disease events. This is despite inclusion of some small studies with incomplete randomisation (UGDP), studies that lack end point adjudication (Kumamoto study, HOME trial), and trials of agents that are now withdrawn because of safety concerns (UGDP). The authors provide sensitivity analyses based on trial quality (Jadad score >3 for high quality v ≤3 for low quality). However, the supposedly high quality studies provide data for only 6465 subjects with 323 non-fatal myocardial infarctions and 195 strokes, thereby reducing the available data by more than 80%. Also the sensitivity analysis of intensive glucose lowering and heart failure events is dominated by the PROactive study, in which pioglitazone was the active treatment under investigation.<sup>7</sup> It seems unlikely that there would be any clear significant difference between low and high quality studies for the various cardiovascular outcomes on the basis of conventional statistical interaction analyses.

The meta-analysis is consistent with earlier evidence that the cardiovascular benefit of intensive glucose lowering seems to be modest at best, and that glucose lowering is probably less efficacious and more difficult to achieve than lipid lowering and blood pressure control (figure). A combined approach that targets glucose lowering, lipid lowering, and blood pressure control seems to be most beneficial,<sup>8</sup> and available data also suggest a long lasting beneficial effect on diabetes related clinical events many years after an intensive regimen.<sup>9</sup> The authors rightfully say that an improvement in surrogate markers (such as HbA<sub>1c</sub>) is not conclusive evidence of clinical benefit. This was highlighted by the Food and Drug Administration in guidance published in December 2008, which includes specific targets for investigators to satisfy the cardiovascular safety of new glucose lowering drugs.<sup>10</sup>



Absolute number of events prevented by different interventions per 1000 patient years of treatment (data taken from Cholesterol Treatment Trialists' Collaboration and Blood Pressure Lowering Treatment Trialists' Collaboration)

Boussageon and colleagues' study provides large scale quantification of the effect of intensive glucose lowering on microvascular disease.<sup>2</sup> Intensive glucose lowering reduced new or worsening microalbuminuria, with a trend towards a reduction in new or worsening retinopathy, but it had little effect on other end points. The fact that many of the analyses are dominated by ADVANCE<sup>11</sup> suggests that there is considerable heterogeneity in the definitions of microvascular end points between trials. Nonetheless, it again seems that any effect of intensive glucose lowering on microvascular disease is modest, at best. The data also confirm a doubling in serious hypoglycaemic events in patients receiving intensive treatment, as previously documented,<sup>4</sup> but the link between treatment, severity of hypoglycaemia, and cardiovascular outcomes remains unresolved.<sup>12</sup>

Clinicians should consider these benefits and risks carefully because the most sensible treatment strategy will vary substantially between patients. Further studies are needed to determine whether an absolute HbA<sub>1c</sub> target should be established for everyone or whether HbA<sub>1c</sub> should be reduced by a target percentage from baseline, so that benefits and harms can be balanced.

Competing interests: All authors have completed the ICMJE uniform disclosure form at [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; KKR has received honorariums for lectures and serving on advisory boards and steering committees for Novo Nordisk, Roche, and AstraZeneca; no other relationships or activities that could appear to have influenced the submitted work.

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