Using individual patient data in meta-analyses of glucose-lowering studies

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Abbreviations

ACCORD	Action to Control Cardiovascular Risk in Diabetes
CONTROL	Collaborators on Trials of Lowering Glucose
CVD	Cardiovascular disease
IPD	Individual patient data
UKPDS	United Kingdom Prospective Diabetes Study

To the Editor: The Collaborators on Trials of Lowering Glucose (CONTROL) Group [1] have performed an excellent and important meta-analysis of the impact of intensive glucose-lowering on cardiovascular outcomes. The fact that the trialists of the four major glucose-lowering studies [2–5] were involved in the collaboration has the advantage of providing detailed understanding of the similarities and differences between studies, both in terms of protocol and for classifying and adjudicating pre-existing cardiovascular disease (CVD) and individual endpoints. We would nevertheless like to suggest some

ways in which the analyses might have been improved, together with some comments on the presentation of their data.

The results of this meta-analysis differ from the two recent attempts to combine the glucose-lowering studies [6, 7]. In part, this is because the authors have used hazard ratios rather than relative risks, and have truncated the United Kingdom Prospective Diabetes Study (UKPDS) data [2] at 5 years. They have also, correctly in our opinion [8], excluded data from UKPDS34 [9], and with it, the erroneous double-counting of UKPDS control participants in both of the other meta-analyses [6, 7]. Their results, using hazard ratios, come close to our own findings using relative risks for most endpoints [8]. What we find disappointing, however, is the fact that the opportunity to use individual patient data (IPD) in the classification both of pre-existing disease and of endpoints was not taken. This was apparently because the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study [3] is still ongoing, a logic that we do not understand in light of the fact that the UKPDS data were truncated at 5 years for the meta-analysis [1]. Even if the ACCORD study is ongoing, the authors might have used IPD for the median follow-up of 3.4 years, which was in any event integrated in their group-level analysis [1].

There are two reasons for the importance of IPD in the meta-analysis by the CONTROL Group [1]. The first is apparent from the clear incongruity in their ‘headline’ finding of a 9% reduction in risk of major cardiovascular events despite a 15% reduction in that of myocardial infarction. It might be argued that this degree of reduction in myocardial infarction risk arises in part from the decision to exclude sudden deaths (i.e. those from ‘unexpected or

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presumed cardiovascular disease' [3]) from the definition. The use of IPD would categorise such endpoints better for the purpose of meta-analysis. In the interim, however, it might be argued that intensive glucose-lowering reduces CVD risk by 9–10% because of a reduction in the risk of CHD by about 10–12% and virtually no effect on the risk of stroke [7, 8]. The second benefit of IPD would be a more precise classification of 'history of macrovascular disease', permitting exploration of whether the findings of the CONTROL Group, of greater benefits of intensive glucose-lowering in people without such a history [1], might be a consequence of the different definition of this category in the four trials.

The CONTROL Group [1] present hazard ratios, but unlike in other meta-analyses [6–8] the authors have not attempted to estimate absolute risk reductions or numbers-needed-to-treat. We argue that such estimates are necessary for interpreting the public health significance of the findings. We would suggest [8] that intensive glucose-lowering reduces the risk of CHD by some 10–12%, but is without significant impact on risk of stroke, or of CHD or total mortality. Such treatment has substantial impact on quality of life [10], in part because of the two- to threefold increased risk of serious hypoglycaemia, which in turn might increase the subsequent risk of dementia [11]. Treating 100 people for 10 years with such a regimen would prevent about two or three non-fatal cardiovascular events, to be set against some eight serious hypoglycaemic episodes [7]. Moreover, in terms of either number-needed-to-treat or absolute risk reduction, intensive glycaemic control achieves about one-third to one-half of the benefits of cholesterol- or blood pressure-lowering [8], with substantially greater complexity of treatment and of risk.

Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

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