More Intensive Glycemic Control Reduces Nonfatal Myocardial Infarction But Not All-Cause Mortality

Reviewed by Michael Pignone, MD, MPH

STUDY

Ray KK, Seshasai SR, Wijesuriya S, Sivakumaran R, Nethercott S, Preiss D, Erqou S, Sattar N: Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. *Lancet* 373:1765–1772, 2009

SUMMARY

Design. A meta-analysis of randomized, controlled trials.

Subjects. The meta-analysis included five trials with a total of 33,040 participants. Entry criteria differed among trials, but overall mean age was 62 years and 62% were male. Participants had an average of 8 years' duration of diabetes at entry.

Methods. The goal of the meta-analysis was to compare the effect of more intensive versus conventional glycemic control on cardiovascular outcomes and mortality. Main outcomes of interest included coronary heart disease (CHD) events, including nonfatal myocardial infarction (MI) and CHD death and all-cause mortality. Secondary outcomes included stroke, heart failure, and hypoglycemia. Random effects models were used to combine outcome data across the five trials. Heterogeneity among trials was examined using χ^2 and I^2 statistics.

Results. Across the trials, intensive glycemic control was associated with a mean A1C 0.9% lower than for conventional glycemic control (6.6 vs. 7.5%). Intensive control was associated with a consistent, statistically significant reduction in nonfatal MIs (odds ratio [OR] 0.83, 95% confidence interval [CI] 0.75–0.93) but had no clear effect on all-cause mortality (OR 1.02, 95% CI 0.87–1.19). For stroke, intensive control was associated with a small, non–statistically significant reduction in events (OR 0.93, 95% CI 0.81–1.06). Heart failure seemed to be increased for intensive regimens that involved the use of thiazolidinediones; intensive regimens were also associated with increased risk of hypoglycemia, including severe hypoglycemia. Available data were insufficient to assess the effects of patient characteristics (e.g., age, duration of diabetes, history of cardiovascular disease, and other concurrent therapies) on outcomes.

Conclusion. More intensive glycemic control that achieves an A1C of 7.0% and a difference of approximately 1 percentage point compared to conventional therapy can produce a moderate reduction in nonfatal MIs.

COMMENTARY

The question of whether intensive glycemic control reduces cardiovascular events in patients with type 2 diabetes has engendered a great deal of debate and controversy. Epidemiological evidence has demonstrated a consistent relationship between glycemic control and the risk of cardiovascular events.[1] Based on this relationship, many have assumed that interventions that improved glycemic control would also reduce cardiovascular events. However, the publication of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, which found that the more intensive regimen (target A1C < 6%) was associated with an increased risk of cardiovascular death and all-cause mortality, led to questions about whether interventions to achieve more intensive glycemic control were actually beneficial for cardiovascular health in patients with diabetes.[2]

Since the publication of ACCORD, investigators have attempted to synthesize, with systematic review and meta-analysis, the full body of evidence with respect to whether more intensive glycemic control reduces cardiovascular events.[3] In this context, systematic review and meta-analysis offer several important benefits; they include all available and relevant evidence, allow a more precise estimate of effect than any single trial, and offer the opportunity to systematically examine reasons for heterogeneous results across trials. Disadvantages include limitations imposed by differences in the patient populations, interventions, usual care, or outcomes across trials; inability to overcome methodological limitations of the individual trials; and limited ability to examine covariables at the individual patient level that may be important for understanding differences in the effect of the interventions being considered.

This meta-analysis by Ray et al. offers several important insights but

also has several important limitations. Based on a synthesis of five major trials, it found that more intensive glycemic control (defined differently across trials) produced a consistent 17% reduction in the risk of nonfatal MIs compared to less intensive ("conventional") control. This difference was achieved with a mean 0.9% difference between groups in glycemic control using a variety of different treatment regimens and goal A1C levels. The amount of risk reduction did not appear to differ across trials. There appears to be little difference between groups in fatal CHD events, although this outcome was not presented separately, and little difference in stroke. All-cause mortality did not differ between groups, but the confidence interval was relatively wide, and there was heterogeneity across trials. Secondary analyses suggested increased heart failure only for intensive regimens that featured thiazolidinediones, a finding that is not surprising given previous systematic reviews of these agents,[4] and an increased risk of hypoglycemia, a well-recognized adverse effect of more intensive regimens.

This meta-analysis is limited by an inability to examine at the study level or individual patient level whether certain characteristics (e.g., history of cardiovascular events, sex, age, initial A1C, degree of A1C reduction, and type of glycemic control regimen used) affect the degree of cardiovascular risk reduction achieved. Other limitations include limited data on the concurrent use of other risk-reducing therapies and their effect on the absolute and relative risk reduction with intensive glycemic control and the relatively wide confidence intervals for some key outcomes such as all-cause mortality. Another meta-analysis of the same set of trials reached similar conclusions and did not identify strong moderators of the effect through meta-regression.[3]

Despite these limitations, this meta-analysis provides evidence that more intensive glycemic control is a moderately effective means of reducing nonfatal MIs, in addition to its benefits in reducing the risk of microvascular complications.[5] The degree of risk reduction from intensive glycemic control is smaller than that achieved with statins[6] or more intensive blood pressure control[7] and should be considered in the context of these other well-proven treatments.

The trials considered included a range of initial A1C levels and goals for treatment. Based on the totality of evidence, it appears that aiming for an A1C of 7.0% makes sense, assuming that the risk of hypoglycemia is low and that the regimens used are similar to those employed in the trials considered here. To better refine our approach to glycemic control, an individual-patient-level meta-analysis of existing trials and perhaps additional trials that better compare specific treatment regimens, including risk of adverse effects, are warranted.

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