Glycemic Control in Type 2 Diabetes: The Tighter the Better?

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STUDY

Hemmingsen B, Christensen LL, Wetterslev J, Vaag A, Gluud C, Lund SS, Almdal T: Comparison of metformin and insulin versus insulin alone for type 2 diabetes: systematic review of randomized clinical trials with meta-analyses and trial sequential analyses. *BMJ* 344:e1771, 2012

SUMMARY

Objective. The goal of this meta-analysis was to determine the effect of intensive versus conventional glycemic control on all-cause mortality and cardiovascular mortality, nonfatal myocardial infarction (MI), microvascular complications, and severe hypoglycemia in patients with type 2 diabetes.

Design and methods. This was a systematic review with both meta-analysis and trial-sequential analysis of randomized clinical trials. The researchers evaluated 28,614 participants with type 2 diabetes (15,269 randomized to intensive control and 13,345 randomized to conventional control). This analysis included 20 randomized trials, of which 14 dealt exclusively with glycemic control in the usual-care setting in patients without acute events at entry. Thirteen of the trials were published in English, and one was in Russian. The included trials were mainly conducted in North America and Europe. Ten of the trials described how the diagnosis of type 2 diabetes was established, whereas four did not describe how the diagnosis was made. Potential participants in the trials were excluded primarily for having liver, kidney, or other severe disease. The mean follow-up duration varied by study, although, for most, it was 5 years.

Results. Compared to conventional glycemic management, intensive treatment of blood glucose did not reduce all-cause mortality (relative risk [RR] 1.02, 95% CI 0.91–1.13; 28,359 participants, 12 trials). Data were insufficient to suggest that intensive control reduces the risk of cardiovascular mortality (RR 1.11, 95% CI 0.92–1.35; 28,359 participants, 12 trials). Intensive treatment reduced the risk for nonfatal MI (RR 0.85, 95% CI 0.76–0.95, $P = 0.004$; 28,111 participants, 8 trials) in meta-analysis, but this was not confirmed in trial-sequential analysis. Furthermore, intensive treatment reduced the risk for retinopathy (RR 0.80, 95% CI 0.67–0.94, $P = 0.009$; 10,793 participants, 7 trials). However, reduction in nephropathy was not significant (RR 0.83, 95% CI 0.64–1.06; 27,769 participants, 8 trials), and there was insufficient evidence to support these findings in trial-sequential analysis. The only finding of the meta-analysis that was supported by trial-sequential analysis was that of a 30% increase in the relative risk of severe hypoglycemia with intensive treatment.

Conclusion. Intensive treatment of blood glucose in type 2 diabetes did not reduce all-cause mortality. Available data remain insufficient to prove or refute a relative risk reduction for cardiovascular mortality, nonfatal MI, composite microvascular complications, or retinopathy at a magnitude of 1%. There is good evidence that intensive control of blood glucose increases patients' relative risk of severe hypoglycemia by 30%.

COMMENTARY

The link between hyperglycemia and cardiovascular risk has been well established by epidemiological[1,2] and pathophysiological[3,4] studies. However, the association between the extent of glucose lowering and the reduction in cardiovascular risk is less well defined. Clinical trials evaluating the effect of intensive versus conventional glycemic control on cardiovascular and microvascular outcomes in patients with type 2 diabetes have yielded mixed, sometimes contradictory results.[5–9]

The meta-analysis and trial-sequential analysis conducted by Hemmingsen et al. showed no meaningful reduction in relative risk for all-cause mortality from intensive compared to conventional glycemic control in patients with type 2 diabetes and found insufficient evidence to support or refute a meaningful reduction in relative risk for cardiovascular mortality, nonfatal MI, retinopathy, or a composite of microvascular complications. The authors did, however, find that intensive glycemic control increases the risk of severe hypoglycemia by 30% compared to conventional glycemic control.

This was the first comprehensive systematic review that used trial-sequential analysis to reanalyze current evidence of the effect of intensive glycemic control on mortality and micro- and macrovascular disease in patients with type 2 diabetes. The review yielded important findings of a lack of reduction in all-cause mortality and a 30% increase in hypoglycemia risk with intensive versus conventional glycemic control.

This systematic review used a search model that included the Cochrane Library, Medline, Embase, Science Citation Index Expanded, LILACS, and CINAHL. The authors searched in December 2010 for randomized clinical trials targeting intensive glycemic control versus conventional glycemic control in patients with type 2 diabetes. Moreover, they used a unique heterogeneity adjustment for the number of patients necessary to answer a specific question. As seen in many of the article's figures, there were not enough participants to answer some questions, whereas other figures reveal an adequate number of patients.

This analysis was not without limitations, however, and several questions remain unanswered. Only six of the 14 included trials had a low risk of bias according to the *Cochrane Handbook* risk of bias tool.[10] Consistent with existing literature, trial-sequential analysis confirmed that intensive glycemic control was associated with an increased hypoglycemic risk.

Although follow-up varied among the studies included in this meta-analysis, the mean follow-up in most of the studies was 5 years. It is noteworthy that the 10-year post-trial monitoring of patients in the U.K. Prospective Diabetes Study demonstrated long-term beneficial effects of intensive glucose control on macrovascular outcomes and all-cause mortality.[11] Hence, whether intensive glycemic control has a salutary effect on macrovascular disease at long-term follow-up warrants further exploration.

Also of interest, limited studies in patients with type 1 diabetes have suggested that the beneficial effects of pancreas transplantation on cardiovascular outcomes may not become apparent until 10 years after transplantation.[12] Similarly, reversal of microvascular complications after a successful pancreas transplant requires prolonged periods of euglycemia.[13,14]

Meta-analysis of pooled data from the Action to Control Cardiovascular Risk in Diabetes (ACCORD), Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE), and Veterans Affairs Diabetes Trial (VADT) studies showed low mortality rates from cardiovascular disease during the study periods in both intensive and conventional treatment groups (4.5 and 3.6% in the intensive and conventional treatment groups, respectively).[15] Trials with short follow-up durations and low cardiovascular event rates may lack the statistical power to detect the difference in clinical events between the intensively and conventionally treated groups.

The Diabetes Control and Complications Trial in type 1 diabetes[16] demonstrated a beneficial effect of intensive compared to conventional therapy on microvascular complications including retinopathy, microalbuminuria, and neuropathy. Furthermore, the relative benefits of intensive therapy on all complications were greater in the primary prevention cohort (absence of retinopathy at baseline) compared to the secondary prevention cohort (mild retinopathy at baseline), suggesting that initiation of intensive therapy early in the course of diabetes may be effective in reducing the long-term complications of diabetes.

Although similar studies in patients with type 2 diabetes are lacking, it is noteworthy that post hoc subgroup analysis of the VADT suggested that patients with a duration of diabetes < 12 years at the time of the study seemed to derive a cardiovascular benefit from intensive glycemic control, whereas those who had had diabetes for > 12 years showed no benefit or even an increased risk of cardiovascular events.[17] Of interest, patients in the ACCORD and ADVANCE trials had longstanding type 2 diabetes, and all participants in these studies had preexisting cardiovascular disease or cardiovascular risk factors.

In summary, although the current study demonstrated a lack of benefit of intensive versus conventional glycemic control in reducing all-cause mortality in patients with type 2 diabetes, studies with longer-term follow-up periods are needed. Future clinical trials should address whether intensive glycemic control in patients with type 2 diabetes using newer glucose-lowering agents that offer a low hypoglycemic risk profile (glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors) might be beneficial in reducing cardiovascular disease risk or mortality without the attendant risk of severe hypoglycemia.

The findings of the analysis by Hemmingsen et al. should not undermine the importance of achieving glycemic control in patients with type 2 diabetes because the ACCORD, ADVANCE, and VADT studies were not designed to evaluate whether glucose-lowering therapy reduces the risks of macrovascular complications, but rather to evaluate whether lowering A1C values below the currently recommended guideline of < 7% would result in further

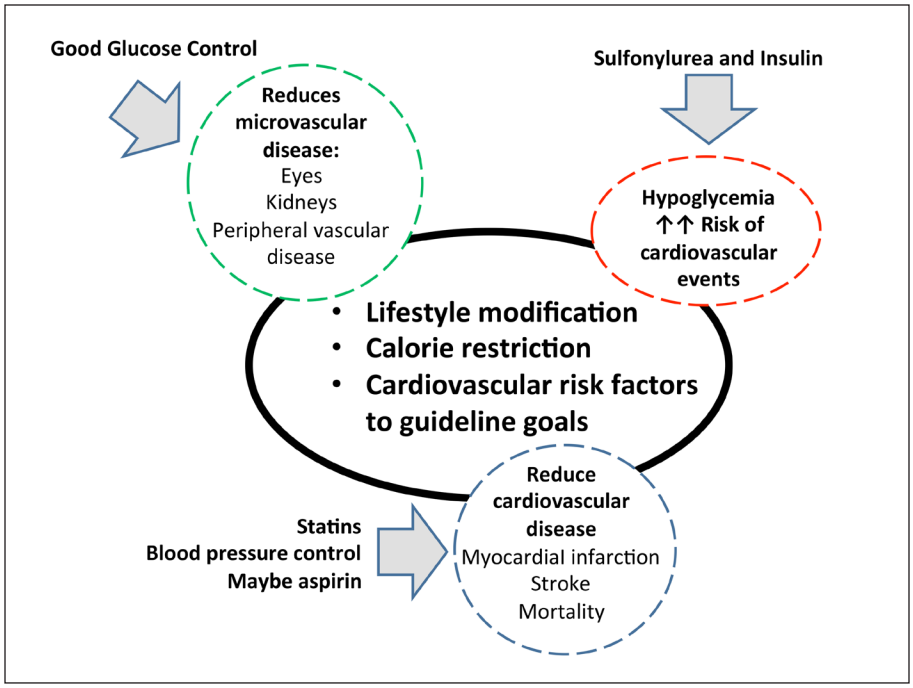

Figure 1. Balancing the risk and benefits of glucose control and proven cardiovascular treatments that reduce events.

reductions in all-cause mortality and micro- and macrovascular complications. Hence, maintaining good glycemic control should remain an important goal in the management of patients with type 2 diabetes. Determination of A1C targets should be individualized based on cardiovascular and hypoglycemia risks (Figure 1).

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