Is tight glycemic control in type 2 diabetes really worthwhile?

YES

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Since the first big landmark trial on glycemic control and complications in type 1 diabetes (DCCT [Diabetes Control and Complications Trial])[1] was published in 1993, almost every major trial for type 1 and type 2 diabetes has consistently demonstrated the beneficial effects of lowering glucose on diabetes complications. According to large randomized trials, there is no question that the lower the hemoglobin A_{1c} (HbA_{1c}) levels, the lower the risk of microvascular disease.[2] The relationship between macrovascular disease and increased glycemia has been shown in many epidemiologic studies, including the epidemiologic analysis of the relationship between HbA_{1c} and vascular disease in the UKPDS (United Kingdom Prospective Diabetes Study).[3]

The EDIC (Epidemiology of Diabetes Intervention and Complications)[4] trial, the 10-year posttrial monitoring of the DCCT, showed a 40% reduction in cardiovascular events and an almost 60% reduction in myocardial infarction (MI), stroke, and cardiovascular death in those patients who were, initially, intensively controlled compared with those less intensively controlled, even though their HbA_{1c} values were the same at the end of the trial. (Although this study involved individuals with type 1 diabetes, it is in a sense a better demonstration of the singular effect of glucose lowering on macrovascular disease without the other confounding vascular risk factors found more frequently in type 2 diabetes.) Original data from the UKPDS, which included subjects with type 2 diabetes, showed a significant 25% reduction in microvascular complications ($P=.0099$) and a non-significant 16% reduction in MI ($P=.052$). In addition, the UKPDS's 10-year follow-up[5] continued to show a reduction in microvascular complications, despite similar HbA_{1c} values between the intensive and control groups, during most of the posttrial period. There was also a significant reduction in MI (15%, $P=.01$) and death from any cause in the sulfonylurea insulin–treated group (13%, $P=.007$) and MI (33%, $P=.005$) and death from any cause (27%, $P=.002$) in the Metformin-treated group.

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Woodcut by Thomas Murner, circa 1500.

The implication is that tight glycemic control in newly diagnosed diabetes patients has a lasting effect on the reduction of both microvascular and macrovascular complications. This is the case even if glycemia increases over time. The same "legacy" effect seen in the EDIC trial and the UKPDS follow-up has also been demonstrated in the Steno-2 Study.[6] This 8-year trial of a multifactorial risk-reduction strategy, including a target HbA_{1c} value of 6.5%, clearly showed reduced macrovascular and microvascular complications with tight glycemic control. The 5-year follow-up study similarly showed a significant reduction in cardiovascular mortality ($P=.04$) and death from any cause ($P=.02$).

So why the debate? One recent trial, the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study,[7] demonstrated a small increased risk of death in individuals with long-standing diabetes who were treated aggressively to target HbA_{1c} levels of less than 6%; this has led to the question of whether or not tight glycemic control is worthwhile.

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Treating early gives the best benefits

Three trials, designed to look at whether near-normal glycemic control reduces cardiovascular disease in type 2 diabetes, have just been completed. These are the ACCORD,[7] the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation),[8] and the VADT (Veterans Affairs Diabetes Trial)[9] studies. There are 2 big differences between these studies and the ones mentioned previously. First, these trials were all short (3.5 to 5 years). Second, the patient populations in these 3 trials were older, had had diabetes for longer (eg, an average of 10 years in the ACCORD study), and were at higher risk of cardiovascular events, compared with the DCCT and UKPDS studies in which the patient populations were younger or recently diagnosed.

All 3 trials were able to achieve sustained reductions in HbA_{1c} levels for the duration of the studies, something that was difficult to achieve in previous trials, particularly the UKPDS. The ADVANCE study showed a significant reduction in microvascular complications (14%, 95% confidence interval 3% to 23%) and a non-significant reduction in the macrovascular events. By choosing an HbA_{1c} target of 6.5%, there was a 21% reduction in new or worsening nephropathy. Neither the VADT nor the ADVANCE studies showed increased mortality or cardiovascular event rate; however, the ACCORD study, which attempted the most aggressive lowering of HbA_{1c} levels (targeting <6% in 6 months), showed a slight increase in deaths—1.7% versus 1.1%. This was, however, less than the predicted rate (4%), and overall the cardiovascular event rates in the intensive and standard groups (6.9% and 10.6%, respectively) were much lower than expected. Moreover, a prespecified subanalysis in the ACCORD study showed that patients treated intensively who showed the greatest reduction in primary macrovascular end points were at earlier stages of disease, with lower baseline HbA_{1c} values and no known baseline vascular diseases.[7] Likewise in the VADT study, those with the shortest duration of diabetes (< 15 years) benefited the most from intensive control.[9]

Don't throw the baby out with the bathwater

From the trials cited above, we can see that tight glycemic control in type 2 diabetes, with HbA_{1c} target levels of less than 7%, reduces the microvascular complications of diabetes. It might also reduce macrovascular complications if initiated early, although it might take longer for the benefits to become evident. According to the Diabetes In Canada Evaluation (a study of diabetes care in primary practice),[10] physicians have difficulty helping their patients to achieve HbA_{1c} target values of less than 7%. The "headlines" of the ACCORD trial might suggest, to some, that physicians can "relax" in treating diabetes to target. This might be "throwing the baby out with the bathwater." As advocated in the 2008 Canadian Diabetes Association clinical practice guidelines,[11] an HbA_{1c} value of less than 7% will reduce microvascular complications. To further reduce the risk of nephropathy, an HbA_{1c} value of less than 6.5% is beneficial. In terms of reducing macrovascular disease, the most worthwhile approach is to target an HbA_{1c} value of less than 7% and begin a multifaceted cardiovascular risk-reduction approach as early as possible.

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Competing interests
None declared

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CLOSING ARGUMENTS

- Diabetes trials have consistently shown that lower hemoglobin A_{1c} levels decrease complications of the disease.
- Longer trials, such as the DCCT and the EDIC follow-up, the UKPDS, and the Steno-2 Study, have demonstrated the additional macrovascular benefits of tight glycemic control.
- The "legacy" effect of tight control at an earlier stage of disease has a lasting influence on the reduction of both microvascular and macrovascular complications.
- The ACCORD trial findings should not be generalized to younger, healthier patients.