Glycemic Control and CV Outcomes In Type 2 Diabetes:
On to the Meta-analyses

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Type 2 diabetes is often associated with a cluster of metabolic abnormalities, including obesity, insulin resistance, dyslipidemia, and arterial hypertension. Additionally, endothelial dysfunction and increased platelet activity observed in this condition adds to the hypercoagulable state. This translates into a "residual risk" that leaves diabetics with CHD at greater odds of having adverse cardiovascular events compared to non diabetics with CHD, despite optimal lipid management with statins.

Need for meta-analyses

In the past, we talked about the evidence gathered from trials regarding the role of intensive glucose control in reducing diabetic complications. According to the evidence gathered, it is undeniably favourable for microvascular events (U.K. Prospective Diabetes Study 33 [UKPDS 33]), but macrovascular complications were recorded, including coronary heart disease (CHD).[1, 2] Initial data from UKPDS 33 reported a 16% reduction in MI with tight glucose control that failed to reach statistical significance. This led to three large-scale trials designed to specifically test intensive vs. standard glycemic control in preventing cardiovascular events. While two (Action in Diabetes and Vascular Disease [ADVANCE] and Veteran Affairs in Diabetes Trial [VADT]) failed to show any significant difference in mortality or composite cardiovascular outcomes, one (The Action to Control Cardiovascular Risk in Diabetes [ACCORD]) trial had to be prematurely stopped due to excess (22%) all-cause mortality in the intensively treated group.[3-5] These inconsistent results prompted trialists to turn to meta-analyses, with the hope that any design issues that reduced statistical power –lower than expected event rates, smaller than expected differences in glycemic control between groups or shorter than needed follow-up¬– would be resolved with a pooled sample.

Results from meta-analyses

In one meta-analysis, investigators pooled events from five trials (Proactive Prospective Pioglitazone Clinical Trial In Macrovascular Events [PROactive] trial plus the four trials discussed above, UKPDS 33 data was combined with UKPDS 34) comparing intensive vs. standard glucose lowering to include 1,497 non-fatal MIs, 2,318 CHD events (fatal and non-fatal MIs), 1,127 strokes, and 2,892 all-cause deaths in 33,040 patients over about 163,000 person-years of follow-up.[6] The mean HbA1c concentration was 6.6% with intensive control compared to 7.5% with standard care. Intensive glucose-lowering reduced non-fatal MI by 17% (odds ratio 0.83, 95% confidence interval 0.75 to 0.93) and CHD events by 15% (odds ratio 0.85, confidence interval 0.77 to 0.93), with these effects being consistent across studies. However, intensive therapy failed to significantly influence stroke (odds ratio 0.93, confidence interval 0.81 to 1.06) or all-cause mortality (odds ratio 1.02, confidence interval 0.87 to 1.19). Heterogeneity was high across studies for all-cause mortality, suggesting that the increased death rates noted in ACCORD were not consistent across trials and might not be a true representation. In terms of adverse effects, more participants on intensive treatment reported a hypoglycemic episode (weighted averages 38.1% vs. 28.6%), and a near doubling

was noted for severe hypoglycemia events (weighted averages 2.3% vs. 1.2%). Additionally, intensively treated patients were 2.5 kg heavier by the end of the study compared to those on standard treatment. The authors concluded that intensive glycemic control did reduce coronary events significantly without increasing the risk of death. While intensive glucose management had modest effects compared to cholesterol and blood pressure reduction, it could nevertheless reduce some of the residual risk associated with type 2 diabetes

Another recent meta-analysis also looked at similar trials (except PROactive) involving a total of 27,802 patients.[7] The authors noted that compared to the earlier UKPDS trials, HbA1c targets were tighter in the 2008 ACCORD, ADVANCE and VADT trials, which led them to separately assess endpoints for earlier and more recent studies. Overall, compared with conventional therapy, intensive glucose control reduced cardiovascular risk (relative risk 0.90, 95% confidence interval 0.83 to 0.98, risk difference per 1,000 patients over 5 years, -15) and CHD risk (relative risk 0.89, confidence interval 0.81 to 0.96, risk difference -11.00) with similar results across trials. Cardiovascular mortality (relative risk 0.97, confidence interval 0.76 to 1.24, risk difference -3.00) and all-cause death (relative risk 0.98, confidence interval 0.84 to 1.15, risk difference -4.00) were not affected overall, though significant heterogeneity was noted, with the UKPDS trials showing a favourable trend for these outcomes with intensive treatment and the 2008 trials demonstrating non-significant increase in risk. Overall, a 16% reduced risk for nonfatal MI was observed along with absolute risk reductions of nine events per 1,000 patients over five years of treatment. Fatal MI, nonfatal stroke, fatal stroke, or peripheral artery disease were not affected. Rates of severe hypoglycemia were doubled with tight glucose control (relative risk 2.03, confidence interval 1.46 to 2.81, risk difference 39).

Implications

These recent meta-analyses provide reassuring evidence that intensive glucose control can provide small but significant reduction in residual cardiovascular risk without increasing mortality, albeit at the cost of increased hypoglycemic episodes and weight gain. Meta-analyses, as retrospective studies, are subject to several sources of bias. The quality as well as variations in study design of the included trials, can substantially affect the final results. Until we have more robust data from larger-scale randomized controlled trials, it is prudent to manage diabetes with multiple interventions including lifestyle changes, antihypertensive and lipid-lowering medication, as well as glucose control. The HbA1c target should be < 7, especially for young subjects with recently detected diabetes, to avail the proven microvascular benefits of tight glucose control. For elderly or long-standing/poorly controlled diabetes patients at risk of "hypoglycemia unawareness," a slightly higher target HbA1c is acceptable.

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