Tight glycaemic control and cardiovascular disease in type 2 diabetes

The role of tight glycaemic control in reducing cardiovascular events and mortality in type 2 diabetes has not yet been firmly established. Recent clinical trials have yielded unexpected outcomes. This review summarizes the background and outcome of these trials and the implications for management of glycaemia in type 2 diabetes.

Cardiovascular disease is the most frequent cause of mortality in patients with type 2 diabetes (Moss et al, 1994). The risk of death from cardiovascular causes in people with type 2 diabetes is two to four times that of people without diabetes (Feskens and Kromhout, 1992; Haffner et al, 1998). Non-fatal cardiovascular disease is also a major cause of morbidity (Wandell et al, 1997).

Prospective studies indicate a graded relationship between blood glucose levels and cardiovascular event rates in people with type 2 diabetes (Stratton et al, 2000; Selvin et al, 2004). It is tempting to assume that intensive glucose-lowering therapy targeting near-normal glucose levels could achieve a significant reduction in cardiovascular event rates. However, unlike the proven benefits of achieving tighter glucose control in reducing the risk of microvascular diabetes-related complications (retinopathy, nephropathy and neuropathy) in people with type 2 diabetes (UK Prospective Diabetes Study, 1998), such benefits have not yet been conclusively proven in reducing risk of cardiovascular disease. In the UK Prospective Diabetes Study (UKPDS), intensive glucose-lowering treatment in type 2 diabetes achieved a 16% non-significant reduction in the risk of myocardial infarction (P=0.052) (UK Prospective Diabetes Study, 1998).

This article reviews the results of recent major clinical trials that have aimed to verify whether intensive therapy targeting near normal glucose levels could achieve a reduction in the risk of cardiovascular events and mortality in type 2 diabetes.

The Action to Control Cardiovascular Risk in Diabetes study (ACCORD)

ACCORD was a randomized multi-centre trial designed to assess whether the effects of an intensive treatment strategy targeting glycosylated haemoglobin (HbA_{1c}) below 6% confer significant cardiovascular risk reductions compared to standard treatment targeting HbA_{1c} 7–7.9% (Gerstein et al, 2008). The study recruited 10 251 patients with type 2 diabetes between the ages of 40 and 79 years, with median HbA_{1c} of 8.1% and either established cardiovascular disease or at least two cardiovascular risk factors. No restriction was placed on the type of glucose-lowering treatment used to achieve glycaemic targets. A stable median HbA_{1c} of 6.4% and 7.5% were achieved within a year and maintained throughout the follow-up duration for the intensive and standard treatment arms respectively. The primary endpoint of this study was the first occurrence of the composite of non-fatal myocardial infarction, non-fatal stroke or cardiovascular death. Death from any cause was one of the specified secondary outcomes.

Hypoglycaemia requiring medical assistance occurred at a higher rate in the intensive therapy group (3.1% *vs* 1%). A lower incidence of the composite primary outcome was observed in the intensively treated group but this did not reach statistical significance (6.9% *vs* 7.2%, P=0.16). However, the rate of death from any cause was unexpectedly found to be higher in the intensively treated group (5.0% *vs* 4.0%; P=0.04). No obvious cause was identified to account for the excess mortality observed in this group. Possible explanations considered include a higher rate of severe hypoglycaemia and potential unidentified interactions between different combinations of drugs regimen used to achieve near-normal HbA_{1c}.

Thiazolidinediones were more frequently used in the intensively treated group compared to the standard group (92% *vs* 58%), with rosiglitazone being the most commonly prescribed drug. Although this initially raised suspicion as a possible culprit for the increased mortality in the intensively treated group owing to a previous meta-analysis report of increased cardiovascular death with the use of rosiglitazone (Nissen and Wolski, 2007), further analyses showed that the observed difference in mortality between the two groups was independent of the use of this drug.

Whether intensive glucose treatment for a mean duration of 3.5 years has any benefits in terms of improving long-term cardiovascular outcomes is the subject of a further follow-up study of the cohort of intensively treated patients.

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Action in Diabetes and Vascular Disease: preterax and diamicron modified release Controlled Evaluation (ADVANCE)

The ADVANCE study shares few salient features with ACCORD in terms of design and objective. In common with ACCORD, the randomized multi-centre study was conducted with the aim of evaluating the benefits of intensive glucose lowering on vascular outcomes in 11 140 patients with type 2 diabetes and a median HbA_{1c} of 7.5% (Patel et al, 2008). Study subjects were high risk with one third of them having had an established cardiovascular event. The target HbA_{1c} for the intensive treated patients in ADVANCE was <6.5% and the median duration of follow up was 5 years.

Notable differences with ACCORD were the choice of glucose-lowering drugs and the primary end-point of the study. Whereas there was no restriction on the use of drugs for glucose control in ACCORD, modified-release gliclazide, a sulphonylurea class of drug, was consistently used as first-line treatment in the intensive glucose control group in ADVANCE (Patel et al, 2008). The primary end-point was a composite of major macrovascular events (death from cardiovascular disease, non-fatal myocardial infarction or non-fatal stroke) and microvascular events (new or worsening nephropathy or retinopathy).

At the end of the follow-up period, a mean HbA_{1c} of 6.5% and 7.3% was achieved in the intensive and standard treated groups respectively. Hypoglycaemia occurred more often in the intensive than the standard treated group (2.7 *vs* 1.5%), although the overall risk was low.

Unlike ACCORD, no differences were found between the intensive and standard treated groups for death rates from any cause or cardiovascular disease. The primary end-point of the composite of macrovascular and microvascular events was lower in the intensive-control group (18.1% *vs* 20% in the standard control group, P=0.01). This difference is attributed to a 21% relative risk reduction in the incidence of nephropathy with no significant difference between the two groups when cardiovascular event rates were assessed independently.

Although there was no direct benefit with intensive control strategy in terms of reduction of cardiovascular event rates, the significant benefit achieved in lowering incidence of new onset nephropathy and microalbuminuria might translate to a positive outcome in macrovascular event rates given that established renal disease is associated with significant risk for cardiovascular disease and mortality (Hallan et al, 2007).

The UKPDS 10-year post trial follow-up study

UKPDS, the first large scale randomized trial, aimed to investigate the merits of tighter glucose control in reducing both microvascular and cardiovascular end-points in type 2 diabetes (UK Prospective Diabetes Study, 1998; Holman et al, 2008). Unlike ACCORD and ADVANCE, the 3867 subjects recruited for this study were newly diagnosed with type 2 diabetes and hence at lower risk for cardiovascular disease. Other major differences were the choice of glucose-lowering treatment (sulphonylureas or insulin in the intensive treated group with metformin reserved for overweight subjects *vs* diet only in the conventional treatment group), and the modest HbA_{1c} levels achieved (7% *vs* 7.9% in the intensive and conventional groups respectively). After a median follow up of 10 years, a 25% reduction in microvascular end-points was observed (UK Prospective Diabetes Study, 1998). This was mainly a result of the reduced risk of progression of retinopathy defined by the need for photocoagulation. The relative risk reduction achieved for macrovascular events did not reach statistical significance (16%: P=0.052) (UK Prospective Diabetes Study, 1998).

Recently, the outcome of a 10-year post-trial monitoring of the UKPDS survivor cohort was released (Holman et al, 2008). This study aimed to investigate whether improved glucose control achieved during the intensive treatment phase persisted beyond the duration of the study and if such an approach has long-term benefits in reducing macrovascular events. A total of 3277 patients with type 2 diabetes from the original UKPDS cohort were followed up with annual clinic visits for the first 5 years and through questionnaires thereafter.

During post-trial monitoring, the baseline difference achieved in HbA_{1c} level between the intensive and conventional treatment groups was lost within a year. Despite this, the significant risk reduction for any diabetes-related end-point and microvascular disease achieved during the trial period was maintained during post-trial monitoring. Interestingly, at the end of the post-trial follow-up period, a significant relative risk reduction for myocardial infarction (15%, P=0.01) and death from any cause (13%, P=0.007) was observed.

This extended effect of intensive glucose control, unravelled during post-trial follow up despite loss of the improved glycaemic control achieved during the trial (so-called legacy effect), holds promise for improving long-term cardiovascular outcomes. It is difficult to predict whether similar favourable long-term cardiovascular outcomes could be achieved for the ACCORD and ADVANCE cohort given that both studies have a different population attribute with a relatively high-risk profile and longer duration of sub-optimal diabetes control.

Discussion

The role of tight glycaemic control in reducing cardiovascular events and mortality in people with type 2 diabetes is a subject of utmost importance that remains unresolved. The lack of favourable cardiovascular outcomes with intensive treatment targeting near normal glycaemia both in ACCORD and ADVANCE should be interpreted in the context of shorter duration of follow up (3–5 years) in a high-risk population with longer duration of type 2 diabetes. The improved outcome observed in the UKPDS follow-up study only materialized with longer duration of post-trial monitoring and hence conducting a similar follow up on the ACCORD and ADVANCE cohort may prove to be useful.

The introduction of an intensive glucose-control strategy soon after the diagnosis of type 2 diabetes in the UKPDS cohort as opposed to long-established diabetes with several years of poor glycaemic control in the ACCORD and ADVANCE cohorts could also potentially account for the discrepancy in macrovascular outcome. In addition, the presence of cardiovascular risk factors or established cardiovascular disease in the ACCORD and ADVANCE population might have mitigated the benefits of intensive glucose control on improving major cardiovascular outcomes. The widespread use of aspirin, statin therapy and optimal blood pressure control in both studies could also have diminished the potential benefits of intensive glucose control.

The incidence of severe hypoglycaemia requiring medical assistance in ACCORD was much higher in the intensively treated group as compared to the standard treated group (10.5% *vs* 3.5%, $P<0.001$). The stress of acute hypoglycaemia in subjects with either high risk or established cardiovascular disease could provoke myocardial ischaemia or infarction and this might be one potential explanation for the excess mortality found in the intensively treated group (Desouza et al, 2003). The adrenergic response to hypoglycaemia could also trigger cardiac arrhythmias (Wright and Frier, 2008), although there is little evidence to support this hypothesis.

The unexpected increased death rate in ACCORD should not undermine the importance of tighter glycaemic control in the management of type 2 diabetes. Glycaemic targets should, however, be tailored to individual patients taking into account their cardiovascular risk profile and susceptibility to hypoglycaemia. A less intensive approach may be appropriate for those with established cardiovascular disease or multiple cardiovascular risk factors. This approach is advocated in the National Institute for Health and Clinical Excellence (2008) guidelines for type 2 diabetes which recommend a target HbA_{1c} of 6.5% or less while avoiding intensive treatment, aiming for lower glycaemic targets in those susceptible to hypoglycaemia. The American Diabetes Association (2008) likewise recommends a target HbA_{1c} of <7% in non-pregnant adults in general while reserving near normal HbA_{1c} (<6%) for individuals when it could be implemented without significant risk of hypoglycaemia.

KEY POINTS

- Achieving good glycaemic control in people with type 2 diabetes prevents microvascular complications but the benefits remains unclear for cardiovascular disease.
- Tight glucose control in type 2 diabetes should be practised as part of a comprehensive approach towards managing other coexistent cardiovascular risk factors to significantly reduce cardiovascular events and mortality rates.
- A target glycosylated haemoglobin of around 6.5% should be considered in most patients with type 2 diabetes, but in type 2 diabetes patients with established cardiovascular disease, those at high cardiovascular risk or those on complex intensive insulin treatments, a less stringent target glycosylated haemoglobin of 7.5% or higher may be reasonable to avoid hypoglycaemia.
- Intensive treatment targeting near normal glucose levels could be harmful in patients who are at high risk for cardiovascular events and severe hypoglycaemia.

Conclusions

Good glycaemic control aiming for a HbA_{1c} <6.5% will benefit patients with type 2 diabetes by reducing the incidence of microvascular complications such as retinopathy and nephropathy. The benefit of tight glycaemic control on cardiovascular disease is less clear. Recent clinical trials suggest that aggressive lowering of blood glucose using multiple agents and targeting for an HbA_{1c} below 6% may be unsafe in high-risk patients with type 2 diabetes leading to a higher mortality compared to less tight control. Thus high-risk patients with type 2 diabetes should have individualized HbA_{1c} targets. **BJHM**

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