Commentary

Cardiovascular disease and intensive glucose lowering in type 2 diabetes

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The leading cause of death in type 2 diabetes is cardiovascular disease accounting for an increased risk of up to two to four times compared with those without diabetes. Prospective studies have shown positive associations of blood glucose and glycated haemoglobin levels with higher risks of cardiovascular events. To date the benefits of intervention of long-term reduction in blood glucose levels on cardiovascular events is unclear. This article reviews the results of recent major clinical trials that address whether near normal glucose levels in patients with type 2 diabetes can reduce the risk of cardiovascular events.

The leading cause of death in type 2 diabetes is cardiovascular disease accounting for an increased risk of up to two to four times for ischaemic heart disease and stroke compared with those without diabetes.\(^1,2\) Prospective epidemiological studies have shown associations of increasing blood glucose and glycosylated haemoglobin levels with higher risks of cardiovascular events.\(^3\) This article reviews the results of recent major trials to address whether near normal glucose levels in patients with type 2 diabetes can reduce the risk of cardiovascular events.

In both diabetes (types 1 and 2), interventional studies have demonstrated that the development and progression of microvascular complications such as retinopathy and nephropathy can be reduced by tight glycaemic control.\(^4,5\) In type 2 diabetes, the United Kingdom Prospective Diabetes Study (UKPDS) reported in those with tight glycaemic compared with less tight control with a median difference of glycated haemoglobin (HbA1c) of 0.9% over 10 years, a reduced risk of retinopathy progression by 21% (\(P=0.015\)) and need for laser photocoagulation treatment.\(^4\)

However, the impact of tight glycaemic control on cardiovascular disease in type 2 diabetes remains unclear. In the UKPDS, in which those with tight glycaemic control, there was a 16% non-significant relative reduction risk of myocardial infarction (\(P=0.052\)).\(^5\) A number of recently completed multi-centre clinical trials have attempted to answer the question as to whether good glycaemic control in those with type 2 diabetes can reduce the incidence of cardiovascular disease. These will now be discussed in detail.

Action to Control Cardiovascular Risk in Diabetes

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial was a randomized controlled, non-blinded study in those with type 2 diabetes and glycated haemoglobin (HbA1c) >7.5% with either cardiovascular disease or at least one other risk factor for cardiovascular disease.\(^6\) The 10,251 participants were randomized to intensive or standard blood glucose control. The medication prescribed was at the physician’s discretion and any

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A hypoglycaemic agent could be used including insulin. The target HbA1c level was <6.0% in the intensive group and between 7.0% and 7.5% in the less intensive arm. The mean duration of follow-up was 3.5 years, terminated early because of higher mortality in intensive arm. The mean HbA1c achieved was 6.7% in intensive compared with 7.5% in standard group (Table 1). The primary outcome was first occurrence of non-fatal myocardial infarction (MI), non-fatal stroke or death from cardiovascular causes. The primary outcome was no different between the intensive and less intensive groups (6.9% vs. 8.4%, \( P = 0.16 \)). There was a higher rate of death in the intensive group \( 5.0\% \text{ vs.} \ 4.0\% \), \( P = 0.04 \). The death rate was independent of type of drug usage or confounding differences in the groups. There were inconsistencies in the trial results, a lower incidence of non-fatal myocardial infarction occurred in the intensive compared with less intensive arm (3.6% vs. 4.6%, \( P = 0.004 \), Table 1). The intensive group also had a higher frequency of usage of insulin and thiazolidinediones. Consequently, both weight gain and hypoglycaemia were significantly greater in the intensive arm. A net gain of 3.5 kg occurred in the intensive group compared to 0.4 kg in the less intensive group.

**Table 1** Comparison of data from the ACCORD, ADVANCE, VADT and UKPDS studies

<table>
<thead>
<tr>
<th>Name of trial</th>
<th>ACCORD</th>
<th>ADVANCE</th>
<th>VADT</th>
<th>UKPDS (Follow-up)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>10 251</td>
<td>11 140</td>
<td>1 791</td>
<td>3 277</td>
</tr>
<tr>
<td>Mean age (year)</td>
<td>62</td>
<td>66</td>
<td>60</td>
<td>53</td>
</tr>
<tr>
<td>Mean duration of Diabetes (year)</td>
<td>10</td>
<td>8</td>
<td>12</td>
<td>0 (newly diagnosed)</td>
</tr>
<tr>
<td>Median HbA1c at entry (%)</td>
<td>8.1</td>
<td>7.2</td>
<td>9.5(^a)</td>
<td>7.0</td>
</tr>
<tr>
<td>Macrovascular disease at entry (%)</td>
<td>35</td>
<td>32</td>
<td>40</td>
<td>NA</td>
</tr>
<tr>
<td>Median duration of trial (year)</td>
<td>3.4</td>
<td>5.0</td>
<td>6.2</td>
<td>16.8–17.7</td>
</tr>
<tr>
<td>Major endpoints/data (Intensive vs. less intensive)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median HbA1c (at study end) (%)</td>
<td>6.4 vs. 7.5(^*)</td>
<td>6.4 vs. 7.0(^*)</td>
<td>6.9 vs. 8.4(^*)</td>
<td>7.0 vs. 7.9(^{ab})</td>
</tr>
<tr>
<td>Any death (%)</td>
<td>5.0 vs. 4.0(^*)</td>
<td>8.9 vs. 9.6</td>
<td>NA</td>
<td>26.8 vs. 30.8(^{abc})</td>
</tr>
<tr>
<td>Cardiovascular death (%)</td>
<td>2.6 vs. 1.8(^*)</td>
<td>4.5 vs. 5.2</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Non-fatal myocardial infarction (%)</td>
<td>3.6 vs. 4.6(^**)</td>
<td>2.7 vs. 2.8</td>
<td>NA</td>
<td>16.8 vs. 19.6(^{abc})</td>
</tr>
<tr>
<td>Non-fatal stroke (%)</td>
<td>1.3 vs. 1.2</td>
<td>3.8 vs. 3.8</td>
<td>NA</td>
<td>14.8 vs. 21.1(^{abcd})</td>
</tr>
<tr>
<td>Heart failure (%)</td>
<td>3.0 vs. 2.4</td>
<td>3.9 vs. 4.1</td>
<td>NA</td>
<td>6.3 vs. 6.9(^c)</td>
</tr>
<tr>
<td>Severe hypoglycaemia (%)</td>
<td>10.5 vs. 3.5(^**)</td>
<td>2.7 vs. 1.5(^**)</td>
<td>NA</td>
<td>6.0 vs. 6.8(^d)</td>
</tr>
</tbody>
</table>

\(^a\)Mean value reported; NA: No data available.
\(^b\)During 1st 10 years, HbA1c difference between groups was significant. The difference post-trial was not significant.
\(^c\)Intensive sulphonylurea/insulin vs. less intensive.
\(^d\)Intensive metformin vs. less intensive.

Significance difference (\( *P < 0.05; **P ≤ 0.01 \)) of intensive compared with less intensive group.

**The Action in Diabetes and Vascular Disease Study**

The Action in Diabetes and Vascular Disease Study (ADVANCE) trial was aimed to determine whether intensive glucose lowering, using initially a sulphonylurea drug, would reduce the risk of microvascular and macrovascular events in individuals with type 2 diabetes and vascular risk factors compared with standard conventional control.\(^7\) The study population was considered to be at high risk with one-third having had a cardiovascular event. The target HbA1c was 6.5% or lower in the intensive group with the standard group targeting HbA1c according to local policy. The primary endpoint was a composite of major macrovascular events and major microvascular events. The median duration of follow-up was 5.0 years (Table 1). Mean HbA1c achieved was 6.5% or lower in the intensive group targeting HbA1c according to local policy. The primary endpoint was a composite of major macrovascular events and major microvascular events. The median duration of follow-up was 5.0 years. The primary outcome was no different between the intensive and less intensive groups (6.9% vs. 8.4%, \( P = 0.16 \)). There was a higher rate of death in the intensive group \( 5.0\% \text{ vs.} \ 4.0\% \), \( P = 0.04 \). The death rate was independent of type of drug usage or confounding differences in the groups. There were inconsistencies in the trial results, a lower incidence of non-fatal myocardial infarction occurred in the intensive compared with less intensive arm (3.6% vs. 4.6%, \( P = 0.004 \), Table 1). The intensive group also had a higher frequency of usage of insulin and thiazolidinediones. Consequently, both weight gain and hypoglycaemia were significantly greater in the intensive arm. A net gain of 3.5 kg occurred in the intensive group compared to 0.4 kg in the less intensive group.
particular, there were no differences in deaths from all causes or in cardiovascular events (Table 1).

**Veterans Affair Diabetes Trial**

The Veterans Affair Diabetes Trial (VADT) was a prospective, randomized, two-arm clinical trial designed to assess the impact of glycaemic control on major cardiovascular events in 1791 patients with type 2 diabetes. This has been reported in abstract form to date. The population was at high cardiovascular risk as 40% had a prior event with the majority of participant’s hypertensive. The entry HbA1c was 9.4% with a mean age of 60 years, mean follow-up was 6.5 years (Table 1). The HbA1c at follow-up was 6.9% in intensive arm compared with 8.5% in the less intensive arm. By the end of the study, 90% needed insulin in the intensive group compared to 70% in less intensive group. There was no difference in cardiovascular events or death in the two groups, although the intensive group had a favourable non-significant trend to fewer cardiovascular events. Severe hypoglycaemia was more frequent in the intensive arm compared to less intensive.

**United Kingdom Prospective Diabetes Study post-trial study**

The original United Kingdom Prospective Diabetes Study (UKPDS) examined a cohort of 3867 newly diagnosed patients with type 2 diabetes, with intensive compared with less intensive control. After a median follow-up of 10 years, the intensive group compared with less intensive had a reduction in the incidence of myocardial infarction that was of borderline significance in \( P = 0.052 \), although no differences were found in death rates. More recently Holman et al. examined the UKPDS post-trial with an average additional follow-up of 8.5 years. A significant relative risk reduction of both myocardial infarction of 15% \( P = 0.01 \) and overall death rate of 13% \( P = 0.007 \) began to emerge post-trial in those with tight glycaemic control compared with less tight control. This despite the differences in glycated haemoglobin disappearing soon after the trial had ended.

**Commentary**

The ACCORD and ADVANCE studies both contained large numbers of participants with a median follow-up of 3.5–5.0 years. The prior duration of diabetes was 8–10 years at recruitment into the studies. The lack of a benefit of tight glycaemic control for cardiovascular events in these trials may have been due to the short duration of study follow-up and perhaps a longer follow-up is needed before any observed benefits would have become apparent. The significant benefits of both cardiovascular events and overall death rate in the UKPDS follow-up study, (newly diagnosed at trial entry), were only borne out with extended post-trial follow-up. The UKPDS data suggest that the benefits of intensive glycaemic control on cardiovascular disease are seen only after a long duration in newly diagnosed younger patients with type 2 diabetes. In those older patients with type 2 diabetes with longer disease duration, atherosclerotic disease may already have been established and therefore intensive glucose control may have had little benefit.

Thus possible, prolonged, prior poor glycaemic control, longer duration of disease and the presence of cardiovascular risk factors or established cardiovascular disease in the ACCORD, ADVANCE and VADT cohorts may have reduced the benefits of glycaemic control in this high-risk population compared with the low-risk population in the UKPDS cohort of whom only a minority had prior cardiovascular disease.

It is also possible that the widespread use of aspirin, statin therapy and optimal blood pressure control in the ACCORD, ADVANCE and VADT trials may have diminished the effects of intensive glucose control by reducing the frequency of cardiovascular event rates and hence the power of these studies.

The occurrence of hypoglycaemia requiring medical assistance was significantly greater in the ACCORD intensive arm compared with the less intensive group 10.5% vs. 3.5%, \( P < 0.001 \). It is possible that the stress of acute hypoglycaemia may have provoked myocardial ischaemia or infarction. This is supported by the Veterans Affairs Co-operative study that reported a non-significant increased frequency of cardiac events after strict glycaemic control. It is possible that cardiac arrhythmias may be precipitated by the adrenergic response to hypoglycaemia although the direct evidence in support of this hypothesis is lacking.

Overall the ACCORD trial suggests that less intensive glycaemic targets may be appropriate for high-risk patients with multiple cardiovascular risk factors or those with existing cardiovascular disease. This is particularly so in those with frequent or severe hypoglycaemia. The UKPDS data support at least for newly diagnosed, younger type 2 diabetes patients without cardiovascular risk factors or established cardiovascular disease, targeting for tight glucose control is appropriate for the benefits.
of protection of both microvascular and macrovascular complications. Furthermore, there appears to be a beneficial ‘legacy effect’ or ‘glycaemic memory effect’ following a period of intensive glucose control that has also been observed in other studies.\(^5\)

Recent NICE 2008 guidelines from England, UK recommend targets of HbA1c to \(\leq 6.5\%\);\(^\text{14}\) and also endorse avoiding intensive management to lower glycaemic targets for those at risk of hypoglycaemia. These recent trial data support these guidelines with targeted HbA1c appropriate to individuals but a greater emphasis should be positioned to avoid tight control in those with established cardiovascular disease.

Conflict of interest: None declared.

References