Original Article

Intensive Glucose Control and Cardiovascular Outcomes in Type 2 Diabetes

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Numerous observational studies have clearly shown a relationship between hyperglycaemia and cardiovascular (CV) disease. However, the United Kingdom Prospective Diabetes Study (UKPDS), which involved subjects with newly diagnosed type 2 diabetes, just failed to show that intensive glucose control significantly reduces CV events. The results of three subsequent large randomised controlled trials, the Action to Control Cardiovascular Risk in Diabetes (ACCORD), Action in Diabetes and Vascular Disease Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) and the Veterans Administration Diabetes Trial (VADT), that involved approximately 25,000 subjects with established type 2 diabetes also failed to show that intensive glucose control, aiming for a glycated haemoglobin (HbA_{1c}) level < 7%, significantly reduces CV events. The ACCORD trial even suggested that under certain circumstances, intensive glucose control is associated with an increased risk for CV and all-cause mortality. Although the exact mechanisms responsible for an increase in mortality in the ACCORD trial remain unknown, there was an association between increased rates of mortality with higher rates of severe hypoglycaemia in the intensive glucose control group. In contrast, a 10-year post-randomisation follow-up study of the tight glucose intervention arm of the UKPDS showed that intensive glucose control was associated with a significant reduction in the risk for myocardial infarction (MI), diabetes-related deaths and all-cause mortality. This suggests that early strict glucose control generates a legacy effect that is eventually translated into protection from CV events. Recent meta-analyses of the above randomised trails have also shown that intensive glucose control is associated with a reduced risk of MI, without a clear benefit on other CV diseases such as stroke. Furthermore, these analyses have also shown that intensive glucose control is associated with increased rates of severe hypoglycaemia but not increased rates of CV or all-cause mortality. Aiming for HbA_{1c} levels of <7.0% still remains the general target for good glucose control. Under certain circumstances, aiming for lower HbA_{1c} levels may be appropriate. This applies in the setting of newly diagnosed diabetes in relatively young individuals without significant co-morbidities and in patients treated with agents that minimise the risk of severe hypoglycaemia such as metformin. Whether this also applies to newer glucose-lowering agents that target the incretin system will depend on CV outcomes of long-term studies which are in progress.

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Introduction

The incidence of diabetes is increasing worldwide mainly though an increase in the prevalence of type 2 diabetes which accounts for >90% of all diagnosed cases. An Australian community based study estimated the prevalence of diabetes at 7.6% in 2000 with a predicted increase to 11.4% by 2025 if current trends continue [1]. In the United States, the prevalence of diabetes based on the 2005–2006 National Health and Nutrition Examination Survey (NHANES) was estimated at 12.9% [2].

The major causes of morbidity and mortality in subjects with diabetes are related to the development of cardiovascular (CV) disease, especially coronary heart disease (CHD). It is well established that subjects with type 2 diabetes are at a two- to four-fold increased risk of CV disease compared to people without diabetes. This risk persists even after accounting for traditional CV risk factors such as smoking, hypertension and dyslipidaemia. Indeed, in the Australian Diabetes, Obesity, and Lifestyle Study (AusDiab), known diabetes (hazard ratio 2.6, 95% CI: 1.4–4.7) and even impaired fasting glucose (hazard ratio 2.5, 95% CI: 1.2–5.1) were independent predictors for CV mortality after adjustment for age, sex, and other traditional CV risk factors [3]. Such a finding suggests that this residual increased risk for vascular disease could be ascribed directly or indirectly to elevated glucose levels. Although cholesterol and blood pressure lowering trials have demonstrated a CV benefit in subjects with type 2

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diabetes, the effects of intensive glucose control, aimed at achieving glucose levels close to those of euglycaemia, remain uncertain.

In this article we focus on the results of recent trials that have examined the relationship between intensive glucose control and CV outcomes in ambulatory subjects with type 2 diabetes.

Results from Observational Studies

Observational studies have generally shown a linear relationship between elevated glucose levels and increased CV mortality. However, for levels of glycaemia near or below the threshold for diabetes, the relationship has been described as continuous [4], a threshold [5] or "J-shaped" [6] depending on the measure of glycaemia used.

For approximately 10,000 individuals without diagnosed diabetes, the AusDiab Study reported a continuous increased risk for CV mortality with increasing two-hour glucose levels after an oral glucose tolerance test and also with increasing HbA_{1c} levels. However, a "J-shaped" relationship between CV mortality and fasting glucose levels was also found [7]. In another large community based study involving subjects free from diagnosed diabetes at the start of follow-up, there was no association between HbA_{1c} levels < 5.0% and fatal and non-fatal CHD. However, higher HbA_{1c} levels were associated with an increased hazard ratio for CHD events of 1.38 (95% CI: 1.22–1.56) when compared with a reference range HbA_{1c} 5.0–5.5%.

For subjects with diabetes, some studies have reported that the relationship between hyperglycaemia and CV mortality is a continuum that starts for glucose levels below the threshold used to diagnose diabetes. An observational analysis of the United Kingdom Prospective Diabetes Study (UKPDS), a study of subjects with newly diagnosed type 2 diabetes, has suggested that a 1% decrease in HbA_{1c} levels should be associated with a 14% (95% CI: 8–21%) decrease in the relative risk for myocardial infarction (MI) [8]. In comparison, results from a large cohort of elderly patients (approximately 28,000) with diabetes generated from the UK General Practice Research Database has suggested that there is a "U-shaped" association between HbA_{1c} levels and CV events with the lowest hazard ratio at an HbA_{1c} level of approximately 7.5% [9].

As discussed below, these theoretical relationships between glycaemia and CV outcomes have been recently tested in interventional trials of intensive glucose control that have been published over the last two years.

The United Kingdom Prospective Diabetes Study (UKPDS) Glucose Interventional Study

In the glucose interventional arm of the UKPDS, 3867 newly diagnosed subjects with type 2 diabetes were randomised to an intensive glucose control policy involving the use of sulfonylureas or insulin and a conventional policy based on lifestyle management. Over the 10-year period of the trial, intensively treated patients achieved a mean HbA_{1c} of 7.0% compared with conventionally treated patients, who only achieved a mean HbA_{1c} level of 7.9%. This degree of intensive glucose control was associated with an approximate 1% decrease in HbA_{1c} and a 16% (relative risk 0.84, 95% CI: 0.71–1.0) reduction in the risk of myocardial infarction compared to conventional glucose control which just failed to reach statistical significance ($p = 0.052$). There were no effects of intensive glucose control on any other CV disease outcomes. However, intensive glucose control reduced the risk of microvascular complications by 25% (95% CI: 7–14, $p = 0.01$). There was also a non-significant (6%) relative reduction in all-cause mortality associated with intensive glucose control [10].

A group of overweight subjects in the UKPDS was included in a sub-study that compared intensive glucose control with metformin ($n = 343$) against conventional therapy ($n = 411$) based on lifestyle modification [11]. Despite there being no significant difference in HbA_{1c} levels between subjects treated with metformin or conventionally treated subjects, the use of metformin was associated with a 39% relative reduction in the risk for myocardial infarction ($p = 0.01$) and a 36% relative reduction in all-cause mortality ($p = 0.01$) without any effect on microvascular complications. These results have been widely interpreted to mean that metformin has beneficial effects on reducing CV events that are to some extent independent of glucose control.

Recent Intensive Glucose Control Trials

As most patients without diabetes have an HbA_{1c} level below 6.5%, the question remained after the completion of the UKPDS in 1997 as to whether targeting HbA_{1c} levels close to the non-diabetic range might still result in a significant reduction in CV events. Therefore, given the uncertainty as to whether intensive glucose control could reduce the risk of CV outcomes in subjects with type 2 diabetes, three large interventional trials were started to compare the effects of intensive versus standard glucose control. The main features and results of these trials, together with those of the UKPDS are shown in Table 1. The results of these three trials were released in rapid succession in mid 2008 and are also summarised in Table 1 i.e. the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial [12], the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) [13] and the Veterans Administration Diabetes Trial (VADT) [14].

The ACCORD Study

In the ACCORD trial, 10,251 patients with established type 2 diabetes and at high risk of CV events were randomised to receive intensive glucose control (targeting an HbA_{1c} < 6.0% and achieving a level of 6.4%) or standard therapy (targeting an HbA_{1c} 7.0–7.9% and achieving a level of 7.5%). Numerous glucose-lowering therapies from a variety of drug classes were sequentially added in an attempt to achieve intensive glucose control. The unexpected finding of a higher CV mortality rate (hazard ratio 1.35, 95% CI: 1.04–1.76 $p = 0.02$) and higher all-cause mortality (hazard ratio 1.22, 95% CI, 1.01–1.46, $p = 0.04$) in the