Good diabetes control prevents heart attacks and saves lives

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For years we have known that blood glucose control in Type 1 and Type 2 diabetes with target HbA1c of 7% reduces microvascular complications. However, blood pressure lowering, statins or multifactorial intervention was needed to reduce macrovascular complications, primarily cardiovascular disease. Recently, extended follow-up of randomised trials in patients with Type 1 and Type 2 diabetes shows that an earlier period of intensive blood glucose control will reduce the incidence of cardiovascular events many years later. Newer trials in patients with Type 2 diabetes indicate that aggressive therapy aiming for HbA1c of <6% may be harmful in some patients, but achieving HbA1c of 6.5% is feasible and may offer incremental reduction in risk of nephropathy. Patients should be advised that good blood glucose control with a target HbA1c of 7% can prevent heart attacks and save lives over time.

Overview

Type 1 diabetes is characterised by autoimmune destruction of pancreatic β-cells resulting in absolute insulin deficiency, typically affecting children and younger adults but also older persons. Treatment requires attention to healthy lifestyle and eating, blood glucose monitoring and insulin replacement therapy via multiple subcutaneous injections or continuous subcutaneous infusion.

Type 2 diabetes combines insulin resistance and impaired pancreatic β-cell function. In overweight persons with Type 2 diabetes, weight loss via diet and exercise reduces insulin resistance. With preserved endogenous insulin production, oral treatment options include metformin, sulphonylureas or glitazones. Exenatide and sitagliptin are additional newer therapies. With progressive β-cell dysfunction insulin replacement is often required, in combination with metformin as an insulin sensitiser.

Treatment of diabetes aims to achieve close to normal blood glucose levels reflected in an HbA1c of 7% or less, while minimising occurrence of hypoglycaemia, thus allowing pursuit of normal activities of living and reducing the risk of diabetes-related complications.

Blood glucose control reduces microvascular complications

The landmark Diabetes Care and Complications Trial (DCCT, 1993) involving 1,441 patients with Type 1 diabetes demonstrated that intensive glycaemic control achieving HbA1c of 7.2 vs 9.1% over 6.5 years resulted in ~50% reduction in the incidence of microvascular complications of retinopathy, nephropathy (albuminuria) and neuropathy.

The UK Prospective Diabetes Study (UKPDS, 1998) of 3,867 patients with newly diagnosed Type 2 diabetes showed that intensive glycaemic control over 10 years, achieving HbA1c of 7.0 vs 7.9%, reduced the incidence of predominantly microvascular complications. Only in the subset of overweight patients treated initially with metformin (HbA1c 7.4 vs 8%) was there a reduction in mortality.

These studies led to "intensive" glycaemic control – HbA1c 7% becoming the standard for patients with Type 1 and Type 2 diabetes, with metformin the preferred initial treatment in Type 2 diabetes. However, prevention of macrovascular complications, specifically cardiovascular disease, needed to be addressed by careful blood pressure control, statin therapy and multifactorial intervention encompassing lifestyle, aspirin, blockade of the renin-angiotensin system and lipid-lowering therapy in addition to blood glucose control.

Blood glucose control reduces cardiovascular events

Extended post-trial follow up of the DCCT and UKPDS study cohorts yielded interesting results. After completion of the DCCT study, glycaemic control in participants from the control arm improved and HbA1c in both arms became similar. The 17 year follow-up was published in 2005 – 11 years after the trial finished, it became clear that intensive control for the 6.5 years of intervention reduced subsequent macrovascular events, with a ~50% reduction in the incidence of myocardial infarction, stroke or death from cardiovascular disease. Thus good diabetes control in persons with Type 1 diabetes protects against cardiovascular disease many years later.

This was followed in 2008 by publication of the follow-up from UKPDS. Ten years after the 10-year interventional study finished, intensive blood glucose control had reduced the incidence of death (26.8 vs 30.3%) and myocardial infarction (16.8 vs 19.6%).

Finally, the extended follow-up of the Steno-2 study showed 5.5 years after the completion of the original 7.8-year study, multifactorial intervention reduced overall mortality as well as cardiovascular events.

Results from ACCORD, ADVANCE and VADT

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study involved 10,251 patients with Type 2 diabetes of average 10 years duration who had cardiovascular disease or were at higher risk. Mean age of these patients was 62 years, BMI 32 kg/m2, waist 107 cm and baseline HbA1c 8.1%. Participants randomised to intensive glycaemic control received multiple glucose-lowering therapies aiming to lower HbA1c to <6% compared with control (7-7.9%). However, the glycaemic control arm of ACCORD was terminated prematurely after a median of 3.5 years follow-up, with final HbA1c in the intensive arm of 6.4 vs 7.5%. Intensively treated patients had more hypos, gained more weight (>10 kg weight gain in 27.8 vs 14.1%), and experienced higher overall mortality (5 vs 4%, hazard ratio [HR] 1.22, p=0.04) and more cardiovascular deaths (2.6 vs 1.8%, HR 1.35, p=0.02). There was a reduction in non-fatal myocardial infarction and no difference in the primary outcome of myocardial infarction, stroke or cardiovascular death. These results questioned the advisability of setting the target HbA1c as low as 6%, and highlighted the risk of harm with aggressive multi-agent therapy.

In contrast, the ADVANCE study – Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation – involved 11,140 patients with Type 2 diabetes of average duration 8 years, age 66 years with BMI 28 kg/m2, waist 99 cm and baseline HbA1c 7.5%. Patients in the intensive arm of ADVANCE received gliclazide MR and titration of therapy aiming for HbA1c ≤6.5%. After a median 5 years follow-up final HbA1c was 6.5 vs 7.3%. Intensively treated patients had more major hypos (2.7 vs 1.5%) and a reduction in the combined endpoint of macro- and microvascular events (18.1 vs 20.0%, HR 0.90, p=0.01), driven primarily by a reduction in microvascular events particularly new or worsening nephropathy (4.1 vs 5.2%, HR 0.79, p=0.006). Therefore, ADVANCE demonstrated that the target HbA1c of 6.5% was achievable, but while there was no excess of mortality there was no reduction in macrovascular events.

The Veterans Affairs Diabetes Trial (VADT) study involved 1,791 patients with Type 2 diabetes average duration 11.5 years, age 60.4 years, of whom 40% had had a cardiovascular event. Mean BMI was 31 kg/m^2 and baseline HbA1c 9.4%. After 5.6 years of follow-up, final HbA1c in the intensive arm was 6.9 vs 8.4%. Intensively treated patients experienced more hypos with blood glucose <2.8 mmol/L (2.0 vs 0.5/patient-yr) but there was no difference in the occurrence of major cardiovascular events (234 vs 264, HR 0.88, p=0.14) or all-cause mortality (HR 1.07, p=0.62).

Conclusions

Extended follow-up of the DCCT study in patients with Type 1 diabetes and UKPDS in patients with Type 2 diabetes shows that an earlier period of intensive blood glucose control will reduce the incidence of cardiovascular events many years later. However, the ACCORD study found that aggressive glucose-lowering therapy aiming for HbA1c of <6% may be harmful in patients with established Type 2 diabetes at higher risk of cardiovascular disease. The ADVANCE study found that HbA1c of 6.5% is feasible and may offer incremental reduction in risk of nephropathy in patients with Type 2 diabetes. Patients with either Type 1 or Type 2 diabetes should be advised that good blood glucose control with a target HbA1c of 7% can prevent heart attacks and save lives over time. ■

References available on request.