EDITORIAL

Glycaemic control and cardiovascular risk in diabetes: lessons from recent trials

Diabetes is associated with increased mortality and morbidity due to its chronic microvascular and macrovascular complications.[1] These complications are major causes of blindness, renal failure, amputations, stroke, and coronary heart diseases (CHD) in the Asian-Pacific region, where an epidemic of type 2 diabetes is evident and major cities now exhibit a prevalence of 10% or over.[2,3] In the study by Au et al in this issue,[4] diabetes was present in 42% of the 904 consecutive patients having coronary artery bypass graft surgery for severe CHD, clearly illustrating the importance of diabetes as a key risk factor of this condition in Hong Kong. The characteristics of the patients with diabetic foot problems in the study by Leung et al reported in this issue[5] also reflect the high prevalence of microangiopathic complications in patients with prolonged diabetes and poor glycaemic control.

Multi-centre randomised controlled trials in recent decades have established the benefit of intensive glycaemic control, represented by HbA_{1c} lowering, on diabetes-related microvasuclar diseases, including retinopathy, nephropathy, and neuropathy. In the Diabetes Control and Complications Trial (DCCT),[6] intensive glycaemic control for 6.5 years in young patients with type 1 diabetes resulted in a mean HbA_{1c} of 7%, versus 9% in the group on standard treatment, and a 60% reduction in the development or progression of diabetic retinopathy, nephropathy, and neuropathy. Similar findings were reported for patients with newly diagnosed type 2 diabetes assigned to intensive glycaemic control in the UK Prospective Diabetes Study[7] (UKPDS) who achieved a mean HbA_{1c} of 7% over 10 years. Compared to the conventionally treated group with a mean HbA_{1c} of 7.9%, a 25% reduction in microvascular complications was observed. In both studies, a continuous curvilinear relationship was seen between glycaemic control and the rate of microvasuclar complications, with no glycaemic threshold. On the other hand, in both studies the relationship between glycaemic control and cardiovascular risk was less convincing. Notably, intensive glycaemic control did not result in significant benefit with respect to the development of macrovascular diseases (peripheral vascular disease, CHD, and stroke) during the interventional periods.

In the last year, three long-term randomised controlled trials involving large cohorts (10 251, 11 140, and 1791 patients with long-standing type 2 diabetes and established atherosclerotic disease or high cardiovascular risk) have been published.[8-10] These studies reported no significant benefit from intensive HbA_{1c} lowering in terms of cardiovascular outcomes. The mean age of the patients in these trials ranged from 60 to 66 years and the average duration of diabetes at the start of these studies ranged from 8 to 11.5 years. The first trial, Action to Control Cardiovascular Risk in Diabetes (ACCORD)—which tested a target HbA_{1c} of lower than 6% in the intensively treated group—was terminated at 3.5 years, because of increased mortality in the latter patients compared to those on standard care.[8] The median HbA_{1c} levels achieved in the respective groups were 6.4% and 7.5%. In the second trial,[9] the Action in Diabetes and Vascular Disease–Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE), the target HbA_{1c} was lower than 6.5%, and the median HbA_{1c} levels achieved over 5 years were 6.4% and 7% in the intensive-therapy and standard-care groups, respectively. With regard to microvascular complications, in the former group only the incidence of nephropathy showed a significant reduction of 21%. In the third trial,[10] the Veterans Affairs Diabetes Trial (VADT), patients with a baseline HbA_{1c} of 9.4% or more, achieved median HbA_{1c} levels of 6.9% and 8.4% over 5.6 years in the intensive-therapy and standard-care groups, respectively. A nominal reduction (P=0.05) for any worsening of albuminuria was conferred by intensive glycaemic control even in these subjects with long diabetes duration (mean, 11.5 years) and advanced disease (52% being in receipt of insulin at baseline).

Interestingly, despite the similar HbA_{1c} levels achieved in ACCORD and ADVANCE,[8,9] intensive glycaemic control did not result in excess mortality in the latter study. It should be noted, however, that compared to the ACCORD patients, those in ADVANCE had shorter disease durations (8 vs 10 years on average), lower baseline HbA_{1c} levels (median, 7.2 vs 8.1%), and less advanced disease as indicated by insulin treatment at baseline (1.55 vs 35%). Furthermore, the intensively treated subjects in ADVANCE achieved their HbA_{1c} level reductions much more gradually, and experienced far less weight gain and episodes of severe hypoglycaemia. Indeed subgroup analysis in ACCORD showed that intensive glycaemic control led to fewer cardiovascular complications in those with no antecedent cardiovascular events or baseline HbA_{1c} levels of less than 8%. These findings indicated a more favourable risk-benefit ratio from intensive glycaemic control in diabetic subjects with shorter disease durations before significant atherosclerotic disease was established. Similarly, only in subjects with a low baseline coronary artery calcium score in the VADT study, was there a significant benefit in terms of primary cardiovascular outcome.[11] The cardiovascular benefit of intensive glycaemic control in subjects with shorter diabetes duration and no pre-existing cardiovascular disease was also supported by the

follow-up of DCCT and UKPDS patients.[12,13] Despite similar HbA_{1c} levels as in the standard-care group 1 year after the end of the trials, DCCT and UKPDS patients who had been intensively treated enjoyed a 42% and 15% lower cardiovascular event rate, respectively, over 9 to 10 years after study completion. These findings provide further support for the benefit of early implementation of aggressive glycaemic control, aiming at HbA_{1c} levels of lower than 7%, in terms of reducing cardiovascular risk in patients with diabetes. Findings from ADVANCE and VADT suggest that lower HbA_{1c} goals may provide additional benefits for nephropathy progression and may be considered in younger patients with short diabetes durations and no significant cardiovascular disease. On the other hand, less stringent glycaemic goals may be more appropriate in those with advanced chronic diabetic complications and limited life expectancy, especially if they have a history of severe hypoglycaemia.

In ADVANCE, the annual rate of cardiovascular events of 2.2% in the standard-care group was lower than the expected rate of 3% based on previous studies in type 2 diabetes, possibly due to greater use of statins, blood pressure–lowering drugs and anti-platelet agents. Furthermore, even the standard-care group achieved a median HbA_{1c} of 7%. In type 2 diabetes, long-term data from the Steno-2 study[14] also support the benefit of a multifactorial approach in reducing both microvascular and macrovascular complications, as well as long-term mortality. Apart from early implementation of intensive glycaemic control, there should be an emphasis on the management of related cardiometabolic risk factors, which include the treatment of hypertension and dyslipidaemia, as well as the optimal use of anti-platelet agents, and renin-angiotensin blockade. Whilst hypertension is present in over half of the patients with type 2 diabetes,[15] an optimal low-density lipoprotein (LDL)–cholesterol level should be maintained, even in the absence of overt cardiovascular diseases.[16] Unfortunately, even in the United States, the combined therapeutic target of HbA_{1c} <7%, blood pressure <130/80 mm Hg, and LDL-cholesterol <2.6 mmol/L was only achieved by 12.2% of diabetic patients in the latest nation-wide survey.[17] More effort is required on the part of diabetic patients and their health care providers, so as to achieve the optimal control of hyperglycaemia and its related cardiometabolic risk factors, with a view to reducing the health care burden of chronic diabetic complications.

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