Letter from North America

GLYCAEMIC CONTROL AND MACROVASCULAR DISEASE IN PEOPLE WITH DIABETES MELLITUS

Observational studies have shown an association between levels of glycaemia and micro- and macrovascular disease in people with diabetes.[1] Clinical trials have confirmed that lowering glycated haemoglobin (HbA_1c) levels to a target of 7% can substantially reduce the risk of microvascular complications in both type 1 and type 2 diabetes.[2,3] Although the association between elevated HbA_1c and cardiovascular disease (CVD) events has been demonstrated,[4] no clinical trial thus far has confirmed the benefit of sustained glucose control on macrovascular events. Several reports from large randomized controlled trials and long term follow up studies have emerged in 2008. We aim to provide perspective and greater clarity on the clinical and population-level importance of these findings.

The Veterans Affairs Diabetes Trial (VADT),[5] Action to Control Cardiovascular Risk in Diabetes (ACCORD)[6] study, and Action in Diabetes and Vascular Disease (ADVANCE)[7] trial are large, multicentre clinical trials that aimed to test whether intensive glucose control reduces the progression to CVD. The most recently completed trial was the VADT which reported results after a median follow up of 5.6 years in 1791 veteran diabetes patients with long standing disease (mean duration 11.5 years) and poor response to maximal doses of therapy. Participants were randomized to intensive or standard glucose control, with both arms receiving identical treatment for co-morbid CVD risk factors, including aggressive prescription of aspirin and statins to all study subjects. From a baseline HbA_1c level of 9.4%, median HbA_1c levels were achieved rapidly and were 6.9% and 8.4%, respectively in the two groups. Although there were 29 less events in the intensive therapy arm, there was no significant between-group difference (hazard ratio [HR] in the intensive group 0.88; 95% CI: 0.75–1.05; p=0.14) in the primary outcome of time to CVD events (composite of myocardial infarction [MI], stroke, death from CVD, congestive heart failure [CHF], vascular intervention or amputation), nor in the number of new, or progression of, microvascular complications.

The ACCORD and ADVANCE studies randomized 10 251 and 11 140 patients with type 2 diabetes, respectively, a third of whom had a previous history of CVD events and the remainder had at least one coexisting CVD risk factor, to intensive (aiming for bold, near-normal glycaemic targets) or conventional therapy, using different treatment regimens (e.g. ADVANCE stipulated use of modified-release gliclazide). In ACCORD, stable median HbA_1c levels of 6.4% (intensive) and 7.5% (standard) were achieved within a year. However, the trial was discontinued prematurely after a mean follow up of 3.5 years due to higher all-cause mortality (54 excess deaths) in the intensive-therapy group (HR 1.22; 95% CI: 1.01–1.46; p=0.04). There was also no difference in the primary outcome (composite of non-fatal MI, non-fatal stroke, or death from CVD causes) between the groups (352 *v.* 371; HR 0.90; 95% CI: 0.78–1.04; p=0.16). The ADVANCE trial achieved a 0.8% relative difference in median HbA_1c between participants treated intensively (6.5%) and those treated conventionally (7.3%) over a follow up of 5 years. With regard to the primary outcome (a composite of major micro- and macrovascular events), those treated intensively had a 10% relative reduction in incidence of the composite outcome (HR 0.90; 95% CI: 0.82–0.98; p=0.01), which included a 21% reduction in nephropathy (HR 0.79; 95% CI: 0.66–0.93; p=0.006). After adjustment for this reduction in renal dysfunction, the difference between intensive and standard glycaemic control was attenuated for major macrovascular events (HR 0.94; 95% CI: 0.84–1.06; p=0.32), death from CVD (HR 0.88; 95% CI: 0.74–1.04; p=0.12), or death from any cause (HR 0.93; 95% CI 0.83–1.06; p=0.28).

Notably, among all these trials, episodes of hypoglycaemia requiring assistance and weight gain were more frequent in the intensive therapy groups, although less pronounced in the ADVANCE trial due to the gradual course of lowering glucose.

The results of these 3 well-randomized, multicentre studies have brought about uncertainty among clinicians and scientists, prompting the American Diabetes Association, American College of Cardiology and American Heart Association to assimilate the current evidence base and issue an appropriate statement.[8] Several considerations need to be borne in mind with regard to the interpretation of these trial results.

First, all participants were at high risk (32%–40% had previous CVD events; average duration of diabetes was 8–11.5 years; and subjects had poor baseline control with high pre-existing use of insulin [35%–52%], especially in ACCORD and VADT), suggesting that there was established atherosclerosis. Subset analyses in these trials did demonstrate that intensive treatment was beneficial in those with shorter duration of diabetes, lower HbA_1c levels at entry, and absence of pre-existing CVD.

Second, the methods, intensity and speed of glucose-lowering resulted in more adverse effects (hypoglycaemia and weight gain) when aggressive (e.g. ACCORD and VADT permitted any drug combination with rapid glucose-lowering) than measured (e.g. ADVANCE used sulphonylureas with gradual between-group differences in glycaemia).

Third, it has been shown that CVD risk reduction in these patients requires a comprehensive approach, and that by aggressively managing all modifiable risk factors (blood pressure and lipid control)[9–11] and implementing evidence-based guidelines (e.g. aspirin therapy),[12,13] vascular events and mortality can be reduced by about 50%.[14,15] In these trials, targeted, rigorous treatment of co-morbid risk factors did result in lower-than-expected event rates, and may have resulted in the relative impact of controlling glucose on macrovascular disease outcomes becoming less remarkable.

In addition, despite the null findings of VADT (probably due to the large proportion of participants [62%] that had pre-existing microvascular diseases), the evidence supporting glycaemic control in patients with diabetes to prevent microvascular complications remains overwhelming.[2,3] Also, the follow up results of the Diabetes Control and Complications Trial (DCCT)[16] and United Kingdom Prospective Diabetes Study (UKPDS)[17] have both demonstrated delayed beneficial effects of previous glycaemic control on macrovascular outcomes, a 'metabolic memory' of sorts. These studies reinforce the importance of earlier intervention in those with less advanced disease.

The important lessons that have emerged from the recent literature on the role of glycaemic control in macrovascular risk and mortality are:

1. Glucose control is very important in averting disabling microvascular complications in people with diabetes, and the current target recommendation of HbA_1c <7% should be continued.
2. There is good evidence for strict glycaemic control in patients with type 1 diabetes, as they have lower rates of co-morbid conditions and glycaemia is therefore the main mediator of micro- and macrovascular risk.
3. a. In patients with type 2 diabetes, comprehensive, multi-factorial risk management is necessary and beneficial in reducing events and mortality.
   b. However, glycaemic control may need to be individualized for patients based on the duration of diabetes, baseline level of control, history of hypoglycaemia and general health. While intensive treatment and stricter targets may be appropriate for those at low risk with shorter duration of disease, highly vigilant care with less aggressive targets may be appropriate for older, frail people and those at higher risk and with long-standing disease.

Taken together, the evidence presented suggests that there are sizeable benefits in applying all currently proven interventions early, intensively and extensively in all newly diagnosed and low risk patients, with more attentive, gradual care for those at high risk of morbidity and mortality. Yet, despite US$ 116 billion being spent each year on the direct medical care of people with diabetes,[18] implementation of proven interventions remain grossly suboptimal even in the USA.[19,20] The challenge of translating existing evidence (e.g. control of glucose, blood pressure, lipids, use of aspirin and angiotensin-converting enzyme inhibitors [ACE-I] or angiotensin-II receptor blockers [ARB], and regular examination of the eyes, feet and urine) into clinical practice and quality of care improvement must therefore be at the forefront in the minds of those who care for people with diabetes.

REFERENCES

1 Laakso M. Cardiovascular disease in type 2 diabetes: Challenge for treatment and prevention. *J Intern Med* 2001;**249:**225–35.
2 The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *N Engl J Med* 1993;**329:**977–86.
3 Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;**352:**837–53.
4 Selvin E, Marinopoulos S, Berkenblit G, Rami T, Brancati FL, Powe NR, *et al*. Meta-analysis: Glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. *Ann Intern Med* 2004;**141:**421–31.
5 Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, *et al*. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med* 2009;**360:**129–39.
6 Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, Buse JB, *et al.* Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008;**358:**2545–59.
7 Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, *et al.* Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008;**358:**2560–72.
8 Skyler JS, Bergenstal R, Bonow RO, Buse J, Deedwania P, Gale EA, *et al*. Intensive glycemic control and the prevention of cardiovascular events: Implications of the ACCORD, ADVANCE, and VA diabetes trials. A position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association. *Diabetes Care* 2009;**32:**187–92.
9 Vijan S, Hayward RA. Treatment of hypertension in type 2 diabetes mellitus: Blood pressure goals, choice of agents, and setting priorities in diabetes care. *Ann Intern Med* 2003;**138:**593–602.
10 Collins R, Armitage J, Parish S, Sleigh P, Peto R. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: A randomised placebo-controlled trial. *Lancet* 2003;**361:**2005–16.
11 Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, *et al.* Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): Multicentre randomised placebo-controlled trial. *Lancet* 2004;**364:**685–96.
12 Antithrombotic Trialists Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;**324:**71–86.
13 American Diabetes Association. Standards of medical care in diabetes—2008. *Diabetes Care* 2008;**31** (Suppl 1):S12–S54.
14 Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* 2003;**348:**383–93.
15 Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med* 2008;**358:**580–91.
16 Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ, *et al*. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* 2005;**353:**2643–53.
17 Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008;**359:**1577–89.
18 American Diabetes A. Economic costs of diabetes in the U.S. in 2007. *Diabetes Care* 2008;**31:**596–615.
19 Saaddine JB, Engelgau MM, Beckles GL, Gregg EW, Thompson TJ, Narayan KM. A diabetes report card for the United States: Quality of care in the 1990s. *Ann Intern Med* 2002;**136:**565–74.
20 Saydah SH, Fradkin J, Cowie CC. Poor control of risk factors for vascular disease among adults with previously diagnosed diabetes. *JAMA* 2004;**291:**335–42.

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Letter from Glasgow

THE HEAT TARGETS

First, let me get the news out of the way. I have moved to a new post as Director of Public Health and Health Policy at NHS Lanarkshire. Lanarkshire lies just to the south and east of Glasgow in Scotland. Like the rest of Scotland it has health problems of coronary heart disease, stroke, cancer and mental health including others. Lanarkshire health lags behind the Scottish average and one of the reasons for this is the nature of the population and the legacy it carries. Lanarkshire was part of the industrial heartland of Scotland with extensive employment in coal mining and heavy industry. That