Treating diabetes in the elderly: what is the impact for cardiovascular health?

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‘There is clear evidence that use of aspirin, a statin, and the targeted lowering of blood pressure are each associated with substantial reductions in cardiovascular risk in patients with diabetes.’

The risk of cardiovascular disease (CVD) is greatly increased in patients with diabetes, and this risk doubles for elderly individuals [1]. Coexisting cardiovascular risk factors warrant aggressive management, including a change of diet, increased exercise and usually several pharmacological therapies.

Benefits of reducing blood pressure & lipid interventions

Blood pressure reduction trials

Data from a number of studies support the advantages of lowering blood pressure in older adults with diabetes [2], reporting significant reductions in major cardiovascular events: 34% with thiazide diuretics in the Systolic Hypertension in the Elderly Program (SHEP); 62% with a calcium-channel blocker in the Systolic Hypertension in Europe trial (Syst-EUR); 25% with an angiotensin-converting enzyme (ACE) inhibitor in the Heart Outcomes and Prevention Evaluation Study (HOPE); 10% in the Reduction in Endpoints with the Angiotensin Antagonist Losartan (RENAAL) study; 34% with captopril or atenolol in the United Kingdom Prospective Diabetes Study (UKPDS); and 51% with multiple agents in the Hypertension Optimal Treatment (HOT) study.

Lipid-lowering trials

A meta-analysis of both primary (22% reduction) and secondary (24% reduction) prevention trials supports the use of lipid-lowering agents in older adults with diabetes. Treating 34.5 patients over 4.3 years (for primary prevention) or 13.8 patients over 4.8 years (for secondary prevention) will prevent one major cardiovascular event in these patients [3].

Treatment of hyperglycemia: results from recent major trials

The relative increase in events for each percentage increase in glycated hemoglobin (A1c) is modest [4]. Although there is a link between hyperglycemia and cardiovascular risk, the evidence is less clear that glucose lowering is associated with reduction in risk. Patients with newly diagnosed Type 2 diabetes, aged 25 to 65 years at baseline, whose A1c was reduced from 7.9 to 7% in the UKPDS, did not exhibit a reduction in cardiovascular events, although a subgroup of patients treated with metformin showed a trend to a lower incidence of events [5].

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Recent trials in patients with Type 2 diabetes have assessed the effect of lowering blood glucose to near-normal levels on cardiovascular risk in the aging population.

ACCORD

Patients in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial (n = 10,251) had a mean age of 62.2 years at entry and 10 years of diabetes duration. Of these patients, 62% were men and 30% had prior macrovascular disease and a baseline median A1c level of 8.1% [6]. Study patients were assigned to receive intensive therapy (median A1c level achieved of 6.4%, interquartile range of 6.1 to 7%) or standard therapy (median A1c level achieved of 7.5%, interquartile range of 7 to 8.1%). After a median follow-up of 3.4 years, compared with the standard-therapy group, those in the intensive-therapy group had higher overall mortality (4 vs 5%) and cardiovascular mortality (1.8 vs 2.6%) and more major hypoglycemic events (1 vs 3.1%).

ADVANCE

Patients in the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE)

study ($n = 11,140$) had a mean age of 66 years at entry and 8 years of diabetes duration. Of these patients, 57% were men and 32% had prior macrovascular disease and a baseline median A1c level of 7.2% [7]. Study patients were assigned to receive intensive therapy (median A1c level achieved of 6.4%, interquartile range of 6.0 to 6.8%) or standard therapy (median A1c level achieved of 7%, interquartile range of 6.5 to 7.9%). After a median follow-up of 5 years, compared with the standard therapy group, those in the intensive therapy group achieved a reduction in the incidence of nephropathy (4.1 vs 5.2%), although severe hypoglycemia was more common (1.5 vs 2.7%). There were no differences in overall mortality (9.6 vs 8.9%), cardiovascular mortality (5.2 vs 4.5%) or major macrovascular events (10.6 vs 10%).

VADT

Patients in the Veterans Affairs Diabetes Trial (VADT; $n = 1792$) had a mean age of 60.4 years at entry and 11.5 years of diabetes duration. Of these patients, 97% were men and 40% had prior macrovascular events and a baseline mean A1c level of 9.4% [8]. As recently presented in the American Diabetes Association scientific sessions [101], they were assigned to receive intensive therapy (median A1c level achieved of 6.9%, interquartile range of 6.5 to 7.4) or standard therapy (median A1c level achieved of 8.4%, interquartile range of 7.6 to 9.1). After a median follow-up of 6 years there was no significant difference in the rate of the composite primary end point (myocardial infarction, congestive heart failure, invasive revascularization, inoperable coronary artery disease, amputation for ischemia, stroke or cardiovascular death) between the intensive and the standard therapy groups (25.9 vs 29.3%; $p = 0.12$). Fewer cardiovascular events than expected were observed in both groups, in part owing to the aggressive management of blood pressure (reduction from 131/77 mmHg to 127/70 mmHg) and lipids (LDL-cholesterol and triglycerides fell from 106 and 157 mg/dl to 78 and 135 mg/dl, respectively, while HDL rose from 34 to 40 mg/dl) as well as lifestyle changes (40–57% exercised regularly, 60–68% adhered to diet and cigarette smoking was reduced from 16 to 10%) and the increased use of antiplatelet/anticoagulants (from 76% at entry to 92% at the end of the study). Intensive therapy was associated with a lower risk of the

primary end point only in those who had diabetes for less than 15 years and those that had low arterial calcium (AC) scores ($AC < 100$). Severe hypoglycemia requiring medical assistance was higher than expected and more frequent in the intensive than in the standard group (21.1 vs 9.7%; $p < 0.01$). In fact, hypoglycemic events that led to impaired or loss of consciousness were independent predictors of major cardiovascular events and cardiovascular and total mortality.

These three studies have several features in common: they all compared intensive and standard glucose-lowering targets in Type 2 diabetes, and study patients received drugs of a variety of classes, with or without insulin. However, the studies also differed in several aspects: the ACCORD and ADVANCE trials used a factorial design to test additional and different treatment interventions in their study participants. It is expected that longer-term cardiovascular risk reductions may be studied in subgroups of patients most likely to benefit. In the ACCORD trial, there were significant reductions in fatal and nonfatal cardiovascular events in patients who did not have known cardiovascular disease at study entry.

Conclusion & future perspective

Tight glycemic control may not lead to a reduction of cardiovascular morbidity and mortality in those with longer diabetes duration, but may still benefit those treated early in the natural history of their disease. Older patients with diabetes require an individualized plan for A1c control based on their functional status, comorbidities and life expectancy. In general, glycemic control should be kept low enough to reduce microvascular complications whilst avoiding significant hypoglycemia. Lowering both lipids and blood pressure is beneficial among those who are 65 years of age or older. There is clear evidence that use of aspirin, a statin, and the targeted lowering of blood pressure are each associated with substantial reductions in cardiovascular risk in patients with diabetes; there may be even greater benefit when these reductions are achieved together [9,10]. Since life expectancy at 65 years of age is between 15 and 20 years in most Western countries, appropriate management of cardiovascular risk factors may increase quality of life and preserve independence and functionality even if mortality is not delayed.

Prevention of cardiovascular complications in older adults with diabetes is very much needed, along with efforts to raise awareness, including screening, education and targeted intervention.

Financial & competing interests disclosure

Hermes Florez and Jennifer Marks are Co-PI and PI of the VADT at the Miami VA Healthcare System. Carlos Abaira is National Co-Chairman of the VADT. The authors have no other relevant affiliations or financial involvement with

any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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