Editorial

Multifactorial Intervention for the Prevention of Vascular Complications of Type 2 Diabetes

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Type 2 diabetes mellitus (T2DM) is one of the leading causes of morbidity and mortality worldwide.[1] T2DM increases the risk for development of blindness, end-stage renal disease, non-traumatic lower limb amputations and cardiovascular disease (CVD).[1] Patients with T2DM are at 2-4 times higher risk for CVD events and death compared with non-diabetics[2] and approximately two thirds of people with T2DM die from coronary artery disease (CAD) or stroke.[1] Recent data report a 60% increase in the frequency of T2DM (from 17.4 to 28.0%) among patients with CAD in just over a decade.[3] The HELlenic Infarction Observation Study (HELIOS) reported similar findings; 31% of Greek patients with CAD have T2DM.[4] These data suggest a substantial rise in T2DM incidence in the community and an increase in the incidence of myocardial infarction (MI) in patients with T2DM.

During the last 2 decades, a decline in mortality rates was observed in patients with and without T2DM in the US, but all-cause mortality did not fall in diabetic women.[5] Moreover, the MONICA study from Sweden reported favourable trends in the incidence and outcome of MI in non-diabetic subjects but not in diabetic patients.[6] Likewise, the outcome of acute coronary syndromes (ACS) in patients with T2DM is worse (higher in-hospital, 30-day and 6-month mortality).[4] Coronary angioplasty is associated with a greater risk of complications in T2DM (even when drug-eluting stents are used) and diabetic patients undergoing coronary artery bypass graft surgery (CABG) have worse survival rates than non-diabetics.[7] Therefore, it is important to manage effectively the increased vascular risk of diabetic patients. A number of recent studies addressed this issue.

The United Kingdom Prospective Diabetes Study (UKPDS) was the first study to investigate the relation between glycaemic control and the incidence of micro- and macrovascular complications in T2DM.[8] In this study, tight glucose control significantly reduced micro-vascular complications but had a marginally non-significant effect (-16%, p=0.052) on the risk of MI.[8] However, in a subgroup of overweight patients in UKPDS, treatment with metformin decreased the risk of MI by 39% (p=0.01) and the risk of death from any cause by 36% (p=0.01) after a median follow up of 10.7 years.[9] In addition, a recent UKPDS post-trial analysis showed that 10 years after the end of the trial (20 years after patient recruitment) the risk of MI and all cause mortality was reduced in all treatment groups (MI -33%, p=0.005, and death from any cause -27%, p=0.002).[10] In the metformin

group, the benefits in terms of macrovascular complications were sustained.[10] This risk reduction occurred even though previous glycaemic control was not maintained after the completion of UKPDS; the differences in glycosylated haemoglobin (HbA1c) levels between the study groups were non-significant 1 year after the completion of the study.[10] These data suggest that tight glycaemic control early in the course of T2DM may have a beneficial effect on both micro- and macrovascular complications in the long run.

More recently, the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial investigated the effect of tight glycaemic control (HbA1c level to a target of 6.5% or less) on vascular outcomes in 11,140 patients with T2DM during a median 5-year follow-up.[11,12] The effect of blood pressure (BP) lowering was also evaluated.[11,12] Compared with standard control, intensive control resulted in a significant reduction in the incidence of combined major macro- and microvascular events by 10% (p=0.01). This was attributed mainly to a reduction in the risk of microvascular events by 14% (p=0.01), primarily nephropathy relative risk reduction (RRR 21%; p=0.006). In contrast, the incidence of major macrovascular events did not differ significantly between the study groups (RRR 6%; p=0.32).[11,12]

In contrast to the findings of the ADVANCE trial, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, which was also designed to investigate the effects of intensive glycaemic control on CVD events in 10,251 patients with T2DM, was prematurely terminated (at 3.4 years of follow up), because of higher mortality rates in the intensive glycaemic control group.[13] The very high incidence of severe hypoglycaemic episodes (10% in intensive care vs. 3.5% in standard care), the substantial weight gain in the intensive glucose lowering group (mean 3.6 kg) and the wide use of thiazolidinediones (almost exclusively rosiglitazone) to achieve tight glycaemic control (92% in the intensive glucose lowering group vs. 58% in the standard-therapy group) might partly explain this unexpected finding.[13-17] Thiazolidinediones were administered to a minority of patients in the ADVANCE trial (16.7% in the intensive glucose lowering group vs. 10.9% in the standard control group).[11,12]

Recently published analyses of the ADVANCE trial showed that additional BP lowering of 5.6/2.2 mmHg in the combination group (intensive BP and glycaemic control) reduced the incidence of combined major macro- and microvascular events by 9% (p=0.041), CVD death by 18% (p=0.027), total mortality by 14% (p=0.025), and total renal events by 21% (p<0.01) compared with placebo.[18,19] In addition, combination treatment reduced the risk of new or worsening nephropathy by 33% (p=0.005), new onset macro-albuminuria by 54% (p<0.0001) and new onset micro-albuminuria by 26% (p<0.001).[19] Therefore, combined BP lowering and intensive glucose control reduced both CVD and all-cause mortality and also improved renal outcomes (a CAD risk factor).[18] This finding supports the importance of multifactorial intervention in patients with T2DM. It is also in accordance with the findings of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), which compared the effects of two antihypertensive treatment strategies in the prevention of CVD and included a large subgroup of diabetic patients (n=5137).[20] Patients were randomised to receive treatment with amlodipine-perindopril or atenolol-thiazide diuretic. The trial was terminated early due to a significant reduction in the incidence of total CVD events, which was similar in diabetic patients and in the total study population (by 14% and 16%, respectively).[20] In the amlodipine-perindopril arm, there were also significant reductions in fatal and non-fatal strokes (by 25%, p=0.0017), peripheral arterial disease (by 48%, p=0.004) and non-coronary revascularisation (by 57%, p<0.001).[20]

Besides glycaemic and BP control, lipid-lowering treatment with statins is another important component of the multifactorial management of diabetic patients.[21] In the placebo-controlled Collaborative Atorvastatin Diabetes Study (CARDS),[22] atorvastatin 10 mg/d reduced the composite endpoint (death and non-fatal MI) by 37% (p=0.001), ACS by 36%, coronary revascularisations by 31% and stroke by 48% in patients with T2DM without overt CVD at baseline.[22] A subgroup analysis of the GREek Atorvastatin and Coronary heart disease Evaluation (GREACE) study[23] assessed the effects of atorvastatin (24 mg/day) in patients with CAD who also had T2DM. Treatment with atorvastatin reduced the composite primary endpoint (all vascular events plus death) by 59% (p<0.0001) compared with "usual care".[23] In a pre-specified subgroup analysis of 1501 patients with T2DM and CAD included in the Treating to New Targets (TNT) trial, high dose atorvastatin (80 mg/d) reduced CVD events compared with low dose atorvastatin (10 mg/d).[24] The reduction was greater in patients with HbA1c ≤7% than in those with HbA1c >7% (43% and 23%, respectively), suggesting a synergy between tight glycaemic control and aggressive lipid-lowering treatment.[24] How-

ever, statins are under-prescribed in diabetic patients, even in clinical trials; in the ADVANCE and ASCOT studies, less than half and only one quarter of patients, respectively, were given statins.[11,12]

The findings of the Steno study further support the importance of multifactorial intervention in diabetic patients.[25,26] In this study, tight glycaemic, BP and lipid control combined with aspirin reduced both microvascular complications (nephropathy, end-stage renal disease, micro-albuminuria, retinopathy and autonomic neuropathy) and macrovascular events (non-fatal CVD events as well as CVD and all-cause deaths).[25,26] The recently published Swedish National Diabetes Register (NDR) trial also suggests that multi-targeted treatment reduces vascular risk in patients with T2DM.[27] This was an observational study in 4753 patients with T2DM, with or without tight glycaemic and BP control, who were followed up for a mean of 5.7 years. A median difference of HbA1c/BP 1.6%/25/5 mmHg between tight and suboptimal BP and glycaemic control reduced the risk of non-fatal MI (by 28%, $p=0.01$), CAD (by 31%, $p<0.001$) and stroke (by 38%, $p=0.002$).

In conclusion, intensive multifactorial management, aiming at tight control of glycaemia, BP and lipid levels, should be implemented in patients with T2DM to reduce both micro- and macrovascular complications. Long-term adherence to this intervention should also be actively pursued.

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