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Pharmacological Strategies to Reduce Cardiovascular Risk in Type 2 Diabetes Mellitus

An Update

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Abstract

Morbidity and mortality in patients with type 2 diabetes mellitus is largely dominated by the occurrence of cardiovascular disease (CVD). Treatment of known risk factors of CVD has proven to be beneficial in terms of reduction in risk of major CVD events in the general population. Recent trials have provided information on the treatment of hyperglycaemia, hypertension, dyslipidaemia and platelet aggregation in the patient with type 2 diabetes.

Strict glycaemic control is not associated with a significant reduction in CVD risk, although new hypoglycaemic agents may offer additional benefits. In contrast, it has been demonstrated that treatment of hypertension and dyslipidaemia significantly reduce cardiovascular risk. Meticulous control of blood pressure to a level ≤130/80mm Hg, preferably using renin-angiotensin system-modulating agents, is of proven value. Use of HMG-CoA reductase inhibitors (statins) as low-density lipoprotein (LDL)-cholesterol-lowering therapy, initiated at a level of ≥2.60 mmol/L is firmly established. Recent trials lend support to lowering the target level for LDL-cholesterol-lowering therapy to ≤1.81 mmol/L. Mainly based on risk analogy, international guidelines advocate the use of aspirin (acetylsalicylic acid) in the primary prevention of CVD in patients with type 2 diabetes. However, there is no support from large trials that the estimated 25% risk reduction in primary prevention in a high-risk population is the same in the subgroup with diabetes.

An intensified approach in order to identify and treat cardiovascular risk factors in patients with type 2 diabetes, stratified to individual patients, is necessary to reduce the excess cardiovascular burden of these patients.

Type 2 diabetes mellitus is a common disorder, defined by the presence of elevated blood glucose and characterised by insulin resistance and other metabolic disturbances. Morbidity and mortality in the diabetic patient are related to the development of micro- and macrovascular complications. The prevalence of type 2 diabetes is increasing, mostly as a result of obesity and a sedentary lifestyle. As estimated worldwide prevalence of diabetes is expected to increase from 2.8% in 2000 to 4.4% in 2030, one could easily expect an upcoming pandemic.[1] In industrialised countries, prevalence rates are even

higher. In 2001, 7.9% of adults in the US had type 2 diabetes.[2]

Approximately 65% of patients with type 2 diabetes die as a result of a cardiovascular event.[3] Patients with type 2 diabetes have a 2- to 4-fold increased relative risk for developing myocardial infarction (MI), peripheral arterial disease and stroke.[4] Moreover, cardiovascular disease (CVD) follows a more detrimental course in diabetic patients and prognosis is worse compared with their nondiabetic counterparts.[5] In the report of the Minnesota Heart Survey,[5] diabetic individuals had an odds ratio of in-hospital death after an MI 1.5 times that of nondiabetic individuals. Although certain interventions have significantly improved CVD mortality in the general population, individuals with diabetes did not benefit in the same extent.[6] In the PRESTO (Prevention of RESstenosis with Tranilast and its Outcomes) trial, diabetes was independently associated with death compared with the nondiabetic subjects (relative risk 1.87).[7] In an impressive study stressing the impact of diabetes as a cardiovascular risk factor on mortality, the 7-year incidence on MI in a Finnish population was compared between 1378 nondiabetic patients and 1059 patients with type 2 diabetes. Patients with diabetes but without a prior MI had a similar 7-year incidence rate on MI (20.2%) to those with prior MI but without diabetes (18.8%).[8] However, this statement remains controversial as these results were not confirmed by other population-based studies.[9,10]

Various metabolic factors in the diabetic patient contribute to the accelerated atherosclerotic process. Hyperglycaemia, high levels of circulating free fatty acids (FFAs) and insulin resistance result in altered function of endothelial cells lining the vessel wall.[11] Endothelial dysfunction and, subsequently, an upregulated inflammatory pathway and impaired vascular smooth muscle function all accelerate the progression of atherosclerotic lesions. Furthermore, platelet function is altered, resulting in hypersensitivity for aggregatory stimuli and decreased sensitivity for antiaggregatory mechanisms.[12] This contributes to a more unstable atherosclerotic plaque that is prone to thrombosis resulting in acute occlusion. Most of these alterations in vascular homeostasis are already present years before diabetes is diagnosed.[13]

This early and accelerated form of atherosclerosis in type 2 diabetes, leading to high morbidity and mortality, necessitates a shift in medical care. Whereas traditional therapeutic approaches have emphasised glycaemic control, international guidelines on care for the diabetic patient ask for an aggressive multifactorial CVD risk factor reduction strategy.[14] Such an intensified approach is beneficial, as shown in the Steno-2 trial.[15] In this study, an intensified, targeted, multifactorial intervention comprising behaviour modification and polypharmacological therapy aimed at several modifiable risk factors in patients with type 2 diabetes and microalbuminuria was compared with a conventional intervention involving multiple risk factors. This resulted in long-term risk reduction of both microvascular endpoints and CVD of 50%.

Since the last publication in *Drugs* on this topic in 2000,[16] several important trials on treatment of hypertension, dyslipidaemia and antiplatelet therapy in diabetic subjects have been published. In this article, we review current insights in specific pharmacological strategies on cardiovascular risk reduction in type 2 diabetes.

1. Treatment of Hyperglycaemia

As the cardinal feature of diabetes is a high blood glucose level, reducing hyperglycaemia seems like a logical first step in the treatment of cardiovascular risk factors in type 2 diabetes. Hyperglycaemia increases intracellular production of reactive oxygen species.[17] This increased oxidative stress impairs both endothelial function and function of the insulin-producing β cell, worsening insulin resistance.[18,19] Numerous epidemiological studies have confirmed the relationship between blood glucose level and CVD risk. The concentration of glycosylated haemoglobin (HbA_{1c}) correlated with increased risk of death in a prospective population study. An increase of 1% in HbA_{1c} was independently associated with a 28% increased risk of death.[20] In a meta-regression analysis of published

data from 20 prospective studies of CVD risk according to baseline glucose levels, a graded relationship between fasting blood glucose levels and occurrence of a cardiovascular event was found, even at glucose levels clearly below the diabetic threshold.[21]

It has now become clear that improved glycaemic control does not significantly decrease the risk for macrovascular events. In the UKPDS (United Kingdom Prospective Diabetes Study), 3867 newly diagnosed patients with type 2 diabetes were randomised between intensive treatment of hyperglycaemia with a sulphonylurea or insulin and conventional treatment primarily with diet.[22] After 10 years, the obtained HbA_{1c} in the intensive group was 7.0% versus 7.9% in the conventional group. This 0.9% difference in HbA_{1c} was associated with a 16% decreased risk for MI. This strong trend in reduction in macrovascular events did not, however, fully reach statistical significance at the 5% level. Microvascular endpoints (as defined by the presence of retinopathy, vitreous haemorrhage or renal failure) were significantly reduced by 25%. Risk of diabetes related death or all-cause mortality was not changed. The lack of benefit of improved glycaemic control on macrovascular endpoints may have resulted from a low difference in the attained HbA_{1c}.

It might be possible that the choice of antihyperglycaemic agent is a factor of importance. In a *post hoc* analysis of the subgroup of overweight participants treated with metformin, a relative risk of 0.61 (95% CI 0.41, 0.89) for MI was found.[23] Diabetes-related death and all-cause mortality were also significantly reduced in this subgroup. The median HbA_{1c} after 10 years was 7.4% in the metformin group and 8.0% in the conventional group. A new class of antihyperglycaemic agents, the thiazolidinediones, improve insulin sensitivity by activating the intracellular peroxisome proliferator activated receptor-γ. Activation of this receptor improves a range of metabolic derangements in the insulin resistant state.[24,25] Thiazolidinediones have shown to improve endothelial function in patients with type 2 diabetes.[26] Use of a thiazolidinedione as first-line oral antihyperglycaemic agent has been associated with a decrease of carotid arterial wall thickness, an intermediate endpoint of CVD risk.[27] Further evaluation of the role of this class of drugs in treatment of type 2 diabetes and associated atherosclerosis is needed. Intervention studies with pioglitazone and rosiglitazone using clinical endpoints in both type 2 diabetic patients with and without CVD are ongoing.[28]

Mainly based on the results of both UKPDS trials, guidelines from the American Diabetes Association (ADA) advise a target HbA_{1c} of ≤7.0%.[14] A new trial, ACCORD (Action to Control Cardiovascular risk in Diabetes), is currently being conducted, in which 10 000 patients with type 2 diabetes will be primarily randomised between targeted glycaemic control with HbA_{1c} ≤6.0% and HbA_{1c} 7.0–7.9%, in combination with interventions concerning blood pressure and dyslipidaemia.[29] Primary endpoints are CVD event rate and mortality. The study is expected to finish in 2009. In contrast to the established role for strict glycaemic control in the treatment of microvascular complications, the protective effect of strict glycaemic control for reducing cardiovascular events is still unclear.

2. Treatment of Hypertension

Hypertension is highly prevalent in patients with type 2 diabetes. About 75% of diabetic patients have a blood pressure ≥130/80mm Hg or use any antihypertensive medication.[30] The frequent coexistence of hypertension and diabetes, in particular, is a risk factor for the development of end-stage renal failure.[31] In addition to the risk associated with the presence of diabetes, cardiovascular mortality is increased in diabetic patients with high blood pressure levels.[32]

Treatment of hypertension has proven to be of great value. In the SHEP (Systolic Hypertension in the Elderly Program) 4736 individuals aged ≥60 years with isolated systolic hypertension (systolic blood pressure ≥160mm Hg, diastolic blood pressure <90mm Hg) were randomised between active treatment and placebo. A subgroup of 583 participants with type 2 diabetes showed the same 34% reduction in 5-year CVD event rate as was seen in

the total group.[33] Another study compared active treatment of hypertension with placebo. In the Syst-Eur (Systolic Hypertension in Europe) study, patients were randomly assigned to active treatment with the calcium channel antagonist nitrendipine or placebo. In the diabetic subgroup, the net differences in systolic and diastolic pressure between the placebo and active treatment groups were 8.6 and 3.9mm Hg, respectively. This resulted in a reduction of the rate of all CVD events by 69% in the diabetic patients, but only by 26% in the patients without diabetes.[34]

As blood pressure reduction has a distinct effect on the incidence of CVD in the diabetic patient, the next question to be answered would be what target level of blood pressure should be aimed for. Several studies addressed this question specifically. In a study embedded within the UKPDS, tight blood pressure regulation with captopril or atenolol, aiming for a blood pressure level of <150/85mm Hg, was compared with less tight control aiming for a blood pressure level of <180/105mm Hg.[35] After a mean follow-up of 8.4 years a net decrease of 10 and 5mm Hg was achieved in systolic and diastolic blood pressure, respectively, by tight control. Lower blood pressure was associated with a nonsignificant reduction of 21% of MI and a significant 44% reduction of fatal or nonfatal stroke. Combining all macrovascular endpoints, risk was significantly reduced by 34% compared with the group assigned to less tight control. Risk of microvascular disease was significantly decreased by 25%. An observational analysis of the same set of data, published 2 years later showed that each 10mm Hg reduction in systolic blood pressure was associated with a 12% decrease in the risk of any endpoint related to diabetes and a 15% reduction in the risk of death related to diabetes. No lower threshold of benefit was seen, suggesting that systolic blood pressure should be targeted as low as possible.[36]

The HOT (Hypertension Optimal Treatment) trial was specifically designed to examine whether reduction of blood pressure to a normotensive range would reduce cardiovascular risk in patients with hypertension.[37] A total of 18 790 patients with a diastolic blood pressure between 100 and 115mm Hg were randomised to three target groups, aiming at a diastolic blood pressure of ≤90, ≤85 or ≤80mm Hg. Diastolic blood pressure was reduced from 105mm Hg at baseline to 85.2, 83.2 and 81.1mm Hg, respectively. In the subgroup of 1501 diabetic patients, the number of all major cardiovascular events per 1000 patient-years dropped from 24.4 to 11.9 in the group with a target diastolic blood pressure of ≤80mm Hg compared with the group with target diastolic blood pressure of ≤90mm Hg. Cardiovascular mortality was significantly reduced but total mortality did not change when both groups were compared.[38] Primarily on the basis of these results, guidelines issued by the Joint National Committee on the Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC-7), the ADA and European Society of Hypertension (ESH) all recommend a target blood pressure of ≤130/80mm Hg.[14,39,40]

Discussion regarding which agent should be used as the first-line agent in the treatment of hypertension in the diabetic patient has become rather hypothetical, as the average patient needs more than two different agents to achieve adequate blood pressure control.[41] The JNC-7 report advises to start immediately with at least two agents when blood pressure is 20/10mm Hg above target level in patients with diabetes. ESH guidelines state that combination therapy is required most often.[40]

Numerous studies have compared the effects of different classes of antihypertensive agents in the management of hypertension in patients with diabetes. Table I summarises the main results of recent trials comparing two different agents in large study populations with patients with type 2 diabetes. As the results of these trials are sometimes conflicting, it is difficult to identify a single class of agents with superior benefit. Nevertheless, weighing up the currently available evidence, agents that inhibit the renin-angiotensin system (RAS) may add extra value in reducing cardiovascular and renal risk. By inhibiting the production of angiotensin II, a potent vasoconstrictor also involved in vascular remodelling, reduction of cardiovascular events may be ac-

Table I. Trials comparing antihypertensive agents in type 2 diabetes mellitus

Trial	Comparison	No. of patients with diabetes	Difference in attained reduction of BP	Effect on CV disease endpoints	
				endpoint	relative risk (95% CI)[a]
ACE inhibitor vs calcium channel antagonist					
ABCD[44]	Enalapril vs nisoldipine	470	No difference	Death from CV cause	0.50 (0.16, 1.43)
FACET[45]	Fosinopril vs amlodipine	380	Higher BP with fosinopril	All CV events	0.49 (0.26, 0.95)
ACE inhibitor vs β-adrenoceptor antagonists (β-blockers)					
CAPPP[46]	Captopril vs diuretic or β-adrenoceptor antagonist	572	Higher BP with captopril	All CV events	0.59 (0.38, 0.91)
UKPDS[47]	Captopril vs atenolol	1148	No difference	Myocardial infarction	1.20 (0.82, 1.76)
Angiotensin II receptor antagonists vs β-adrenoceptor antagonist					
LIFE[48]	Losartan vs atenolol	1195	Higher BP with losartan	All CV events	0.76 (0.58, 0.98)
Calcium channel antagonist vs other					
NORDIL[49]	Diltiazem vs diuretic or β-adrenoceptor antagonist	727	No difference	All CV events	1.01 (0.66, 1.53)
INSIGHT[50]	Nifedipine vs co-amilozide (hydrochlorothiazide 25mg plus amiloride 2.5mg)	1302	No difference	All CV events	1.11 (0.90, 1.36)
Multiple comparisons					
ALLHAT[51]	Lisinopril vs chlortalidone	16 063	Higher systolic BP with lisinopril	All CV events	1.08 (1.00, 1.17)
	Amlodipine vs chlortalidone		No difference	All CV events	1.06 (0.98, 1.15)
STOP-2[52]	ACE inhibitor vs diuretic or β-adrenoceptor antagonist	719	No difference	All CV events	0.85 (0.62, 1.18)
	ACE inhibitor vs calcium channel antagonist		No difference	All CV events	0.94 (0.67, 1.32)
	Calcium channel antagonist vs diuretic or β-adrenoceptor antagonist		No difference	All CV events	0.91 (0.66, 1.26)

a Relative risk <1 favours first listed agent in the comparison.

ABCD = Appropriate Blood Pressure Control in Diabetes; **ALLHAT** = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; **BP** = blood pressure; **CAPPP** = Captopril Prevention Project; **CV** = cardiovascular; **FACET** = Fosinopril versus Amlodipine Cardiovascular Events Trial; **INSIGHT** = International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment; **LIFE** = Losartan Intervention For Endpoint reduction; **NORDIL** = Nordic Diltiazem study; **STOP-2** = Swedish Trial in Old Patients with Hypertension-2; **UKPDS** = United Kingdom Prospective Diabetes Study.

complished independent of the blood pressure-lowering effect. Furthermore, the formation of reduced nicotinamide adenine dinucleotide phosphate-dependent reactive oxygen species is diminished by RAS inhibition.[42] Oxidative stress plays a pivotal role in endothelial dysfunction, inflammation and generation of advanced glycation end products. Inhibition of the RAS with both ACE inhibitors and angiotensin II receptor antagonists is associated with a reduced formation and accumulation of advanced glycation end products.[43] The HOPE (Heart Outcomes Prevention Evaluation) study and the MICRO-HOPE (Microalbuminuria Cardiovascular Renal Outcomes-HOPE) substudy, focussing on renal endpoints, studied the effects of the addition of the ACE inhibitor ramipril to current medical regimens in high-risk patients on cardiovascular endpoints.[38] A total of 3577 patients with diabetes and at least one additional risk factor were included; 60% of patients had a history of coronary artery disease. The rate of the combined primary outcome of MI, stroke or cardiovascular death was signifi-

cantly lower in the ramipril group than in the placebo group, with a relative risk reduction of 25% (95% CI 12, 36). This protective effect persisted after correction for the difference in blood pressure (decrease of 2.2mm Hg in systolic and 1.4mm Hg in diastolic blood pressure in the ramipril group compared with placebo). On combined microvascular endpoints, ramipril reduced the risk by 16% (95% CI 1, 29).[38]

The angiotensin II receptor antagonist losartan was compared with atenolol in the LIFE (Losartan Intervention For Endpoint reduction) study.[48] In a prespecified subgroup analysis of all 1195 hypertensive diabetic patients with left ventricular hypertrophy on ECG, after a mean follow-up of 4.7 years, the difference in mean blood pressure was 2 and 0mm Hg in the atenolol and the losartan group, respectively. The primary composite endpoint of cardiovascular death, all MI and all stroke occurred in 39.2 per 1000 patient-years in the losartan group and in 53.6 per 1000 patient-years in the atenolol group. This resulted in an adjusted risk ratio of 0.76 (95% CI 0.58, 0.98).[48] Interestingly, in both the HOPE and the LIFE studies, participants treated with an inhibitor of the RAS were less likely to develop type 2 diabetes over the course of the study. Both animal and human studies have shown improvement in insulin resistance by inhibiting angiotensin II.[53,54] In contrast, both diuretics and β-adrenoceptor antagonists (β-blockers) may exert detrimental metabolic effects, leading to an increase in the incidence of type 2 diabetes.[55]

Several trials have unequivocally demonstrated a beneficial effect of angiotensin II receptor antagonists on renal endpoints in type 2 diabetes. The rate of progression of nephropathy was clearly slowed down in type 2 diabetic patients with signs of early or overt nephropathy using irbesartan[56,57] and losartan.[58] However, addition of an angiotensin II receptor antagonist did not reduce secondary cardiovascular endpoints in these trials.

In contrast with this evidence from trials supporting the concept that an ACE inhibitor or angiotensin II receptor antagonist offers cardiovascular protection are the results from the ALLHAT (Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial).[51] Although much criticised because of flaws in design and comparability of groups, no difference in the CVD event rate was found between groups assigned to an ACE inhibitor, a calcium channel antagonist and a thiazide diuretic in ALLHAT. In patients with diabetes, the ACE inhibitor group even showed a trend towards elevated risk for CVD compared with the diuretic group (relative risk 1.08, 95% CI 1.0, 1.17).

In summary, all available evidence underlines the large benefits of aggressive blood pressure lowering in type 2 diabetes, both on micro- and macrovascular endpoints. In order to attain recommended target levels, combination therapy of two or three agents is necessary. Weighing individual risk profile and possible metabolic adverse effects,[59,60] a choice can be made between diuretics, ACE inhibitors, angiotensin II receptor antagonists, calcium channel antagonists and β-adrenoceptor antagonists. All agents have proven to be effective in reducing blood pressure. On the basis of present evidence, the choice for a combination of a low-dose thiazide diuretic and an angiotensin II receptor antagonist or ACE inhibitor as first-line therapy in the hypertensive diabetic patient may be considered rational.

3. Treatment of Dyslipidaemia

An elevated level of low-density lipoprotein (LDL)-cholesterol was the most powerful predictor of coronary heart disease (CHD) in the UKPDS. In diabetic patients without a history of CVD, patients with a LDL-cholesterol in the highest tertile (>3.89 mmol/L) had an adjusted estimated hazard ratio for CHD of 2.26. An increment of 1 mmol/L was associated with an increased risk of 1.57 in a wide range of LDL-cholesterol levels.[61] In the MRFIT (Multiple Risk Factor Intervention Trial), a decrease of LDL-cholesterol of 1 mmol/L was associated with a 50% lower CHD risk, again regardless of baseline LDL-cholesterol levels.[32] The characteristic abnormalities of the lipid profile in insulin resistance and type 2 diabetes include elevated triglyceride levels, decreased high-density lipoprotein (HDL)-cholesterol levels and a LDL-cholesterol

level comparable with nondiabetic individuals. Increased flux of FFAs from adipocytes accounts for increased very low-density lipoprotein (VLDL) production in the liver. Furthermore, uptake of FFA in peripheral tissue is impaired because of insulin resistance. In addition to these alterations, there is an abnormal transfer of cholesterol and triglycerides between VLDL and LDL. LDL particles derived from this excess of VLDL are typically smaller and denser, which makes them even more atherogenic as they enter the endothelium easily.[62]

The HMG-CoA reductase inhibitors (statins) are currently the class of drugs that have shown most convincing data on reduction of LDL-cholesterol and cardiovascular protection. Next to their direct LDL-cholesterol-lowering effects, statins have anti-inflammatory properties and improve endothelial dysfunction, which may add to their net protective function.[63] Early statin trials included *post hoc* analysis of relatively small diabetic subpopulations. For example, the 4S (Scandinavian Simvastatin Survival Study), one of the first large statin trials, enrolled 202 diabetic patients (of 4444 participants) with a history of CHD.[64] LDL-cholesterol was lowered to 3.03 mmol/L in the simvastatin group and 4.81 mmol/L in the placebo group. The relative risk for any CVD event in the statin allocated group was 0.63 (95% CI 0.43, 0.92). The relative risk reduction was similar to the nondiabetic group. A meta-analysis of other lipid-lowering intervention studies in diabetic patients support the conclusion that use of statins is associated with a similar reduction in both cholesterol and CVD endpoints in the diabetic subgroup compared with the total study population.[65-67] In secondary prevention, calculated using pooled data, a number needed to treat for benefit of 14 was found.[67]

Until recently, there was a gap between the epidemiological evidence suggesting that lowering LDL-cholesterol is advantageous, irrespective of baseline LDL-cholesterol, and clinical trials confirming this statement. The HPS (Heart Protection Study) provided conclusive evidence that cholesterol lowering produces substantial reductions in CVD event rates in diabetic patients, even in primary prevention setting and at relatively low LDL-cholesterol levels.[68] 5963 patients with diabetes and 14 573 patients without diabetes but with a history of CVD were randomised between simvastatin 40 mg/day and placebo. Mean LDL-cholesterol at entry was 3.2 mmol/L. Mean duration of follow-up was 4.8 years. Among those allocated to placebo, an average of 17% were taking non-study statin therapy during the study. The use of simvastatin resulted in an average difference in LDL-cholesterol of 1.0 mmol/L. There was a significant reduction in numbers of patients having a major vascular event: 25.1% in placebo group versus 20.2% in the statin group. This 24% reduction was similar to the reduction in other high-risk individuals. Pre-treatment LDL-cholesterol levels did not influence outcome. Even among the subgroup of diabetic patients without history of CVD and a pre-treatment LDL-cholesterol level of <3.0 mmol/L, there was a reduction in first major vascular event, albeit marginally significant.

In the lipid lowering arm of the ALLHAT study (ALLHAT-LLT), patients with hypertension were randomised to open-label pravastatin 40 mg/day or usual care.[69] In the subgroup of 3638 patients with hypertension and diabetes the relative risk for any CVD event was 0.89 (95% CI 0.71, 1.10). The net difference in LDL-cholesterol reduction between both groups was much smaller than in other studies (0.6 mmol/L), mostly because of the large use of non-study statins in the usual care group. These findings support the concept that adequate LDL-cholesterol lowering is needed to obtain significant CVD risk reduction. The ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm) also failed to demonstrate a significant relative risk reduction in the diabetic subgroup of patients randomised to atorvastatin 10 mg/day or placebo.[70] However, the CVD event rate in the total diabetic population was surprisingly small: 3.6% in the control group. In a comparison between pravastatin 40 mg/day and atorvastatin 80 mg/day in patients with acute coronary syndrome, among them 18% being patients with diabetes, more intensive LDL-cholesterol lowering by atorvastatin to an at-

Table II. Large placebo-controlled trials with HMG-CoA reductase inhibitors (statins) for primary prevention of cardiovascular (CV) disease in type 2 diabetes mellitus

Trial	Statin/dosage (mg/day)	Patients with diabetes	Baseline LDL-cholesterol (% reduction in statin group) [mmol/L]	Effect on CV disease endpoints	
				endpoint	relative risk (95% CI)[a]
HPS[68]	Simvastatin 40	2912	3.20 (−28)	First major CV event	0.67 (0.54, 0.83)
ALLHAT-LLT[2,6]	Pravastatin 40	3638	3.77 (−28)	Any CV event	0.89 (0.71, 1.10)
ASCOT-LLA[70]	Atorvastatin 10	2532	3.44 (−35)	Fatal and nonfatal coronary heart disease	0.84 (0.55, 1.29)
CARDS[72]	Atorvastatin 10	2838	3.04 (−40)	First major CV event	0.63 (0.48, 0.83)

a Relative risk <1 favours statin.

ALLHAT-LLT = Lipid lowering arm of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; **ASCOT-LLA** = Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm; **CARDS** = Collaborative Atorvastatin Diabetes Study; **HPS** = Heart Protection Study; **LDL** = low-density lipoprotein.

tained level of 1.61 mmol/L resulted in a 16% reduction of a composite CVD endpoint.[71] Recently, the results from the CARDS (Collaborative Atorvastatin Diabetes Study) were published.[72] Atorvastatin 10 mg/day was compared with placebo in 2838 patients with type 2 diabetes and a maximal LDL-cholesterol of 4.14 mmol/L. The statin reduced baseline LDL-cholesterol of 3.04 mmol/L by 40%. Treatment with atorvastatin 10 mg/day was associated with a 37% reduction in the primary composite CVD event rate.[72]

The results of these recent trials, summarised in table II, mandated an update of the National Cholesterol Education Program – Adult Treatment Panel III (NCEP-ATP III) guidelines on management of high LDL-cholesterol. It is emphasised in the updated report that the appropriate threshold for initiation of LDL-cholesterol lowering in individuals with diabetes is 2.60 mmol/L, while opening up the option to target at LDL-cholesterol levels of ≤1.81 mmol/L for the very high-risk individual.[73] Recognising the subset of younger diabetic patients without additional risk factors who have a moderately high CVD risk (10-year risk of 10–20%), a possibility was created for LDL-cholesterol threshold of 3.37 mmol/L. Results from future trials may add extra evidence to these recommendations. In order to achieve such a strict target level, ezetimibe, a cholesterol absorption inhibitor, could be coadministered with a statin. In a study in high-risk individuals, this additional use of ezetimibe resulted in an incremental 15–20% reduction of LDL-cholesterol.[74] However, no long-term outcomes are available for ezetimibe and evidence of beneficial effects in patients with type 2 diabetes is lacking.

Fibric acid derivatives specifically target the typical pattern of diabetic dyslipidaemia of high triglyceride levels and low HDL-cholesterol levels. Gemfibrozil has proven to be effective for primary and secondary CVD prevention, as documented in the Helsinki Heart Study[75] and the VA-HIT (Veteran Affairs HDL Intervention Trial),[76] respectively. In the latter trial a large subgroup of diabetic patients with prior CVD and low HDL-cholesterol, high triglycerides and a normal LDL-cholesterol level were treated with gemfibrozil 1200 mg/day. An increase of 6% in HDL-cholesterol and a decrease of 20% in the level of triglycerides resulted in a 24% reduction of all MIs. The DAIS (Diabetes Atherosclerosis Intervention Study) specifically addressed the treatment of the diabetic dyslipidaemia with a fibric acid derivative.[77] 418 type 2 diabetic patients were randomised between micronised fenofibrate (200 mg/day) and placebo. The primary endpoint was angiographic progression of coronary artery disease. Fenofibrate mainly reduced triglycerides by 28%. Compared with placebo, the use of fenofibrate was associated with a reduced rate of progression of angiographically confirmed coronary artery lesions. The trial was not powered to assess clinical parameters. A large trial in diabetic patients is currently ongoing (FIELD [Fenofibrate Intervention and Event Lowering in Diabetes] trial), examining effects of fenofibrate on CVD events.[28] Because of

an increased risk of statin-associated myopathy and rhabdomyolysis when combined with statins, fibric acid derivatives should be used with care.

4. Antiplatelet Therapy

Cardiovascular events precipitated by occlusion of the vessel are caused by disruption of the atherosclerotic plaque, platelet activation and aggregation, resulting in intravascular thrombosis. As the haemostatic balance in the diabetic patient favours thrombosis, therapies directed towards correction of this prothrombotic tendency are rational. Aspirin (acetylsalicylic acid) causes an irreversible inhibition of cyclo-oxygenase, an essential enzyme for the production of thromboxane A2 in the platelet. Thromboxane A2 is a powerful stimulant of platelet aggregation, and use of aspirin results in effective inactivation of the platelet.

A large collaborative meta-analysis of 195 randomised trials of antiplatelet therapy demonstrates that aspirin reduces the risk of any vascular event in patients with prior MI, coronary bypass surgery, coronary angioplasty and stroke by about 25%.[78] Evidence for the effectiveness of aspirin in a primary prevention setting is less abundant. In the published primary prevention trials, only small subgroups of diabetic patients were included.

The ETDRS (Early Treatment Diabetic Retinopathy Study) is a mixed primary and secondary prevention study in both type 1 and 2 diabetic patients.[79] Treatment with aspirin 650 mg/day resulted in a relative risk of 0.72 (95% CI 0.55, 0.95) for MI. In the US Physician's Health Study a small proportion of participants had diabetes (2.0%). Aspirin 325mg every other day was compared with placebo. In the diabetic subgroup, there was a relative risk of 0.39 for MI.[80] In addition to assignment to different treatment groups in hypertension, participants in the HOT study were also randomised to aspirin 75 mg/day or placebo.[37] Use of aspirin was associated with a relative risk of 0.85 (95% CI 0.73, 0.99) for major CVD events. In the 8% of the population with diabetes, the relative benefit was reported to be roughly the same. The most recent primary prevention trial with aspirin (the Primary Prevention Project) intended to include 4000 participants with diabetes but was prematurely stopped because of a strong reduction of the primary composite endpoint in the total population. *Post hoc* analysis of the 1031 diabetic individuals compared with their 3753 nondiabetic counterparts failed to show a similar reduction.[81] Relative risk for the composite endpoint of cardiovascular death, MI and stroke was 0.90 (95% CI 0.50, 1.62) in the diabetes group compared with 0.59 (95% CI 0.37, 0.94) in the nondiabetes group.

The adenosine diphosphate receptor antagonist clopidogrel could be considered an alternative in a secondary prevention setting. Clopidogrel was shown to produce additional risk reduction in diabetic patients, as was demonstrated in a subgroup analysis of the CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events) study.[82] A total of 19 185 patients with prior CVD were randomised to clopidogrel 75mg once daily versus aspirin 325mg once daily. In the subgroup of diabetic patients treated with clopidogrel, 15.6% reached the primary composite endpoint (cardiovascular death, nonfatal MI, nonfatal stroke) versus 17.7% in the aspirin group.

Although the ADA advocates the use of aspirin (75–162 mg/day) as a primary prevention strategy in every patient with type 2 diabetes >40 years old or in the presence of an additional cardiovascular risk factor, which would include 99% of all patients with type 2 diabetes, evidence is poor.[83,84] As the use of aspirin is associated with an increased relative risk for major gastrointestinal bleeding or haemorrhagic stroke of 1.7, the decision to initiate antiplatelet therapy requires an individualised estimation of the risks and benefits.[85]

5. Conclusion

The burden of CVD morbidity and mortality in type 2 diabetes imposes a great challenge to both the patient and healthcare provider. However, several opportunities to stem the diabetic tide are feasible. Compliance with comprehensive lifestyle modifications is of paramount importance to the patient. Powerful pharmacological strategies are available to

further reduce CVD risk. Meticulous control of blood pressure to well defined target levels of ≤130/80mm Hg offers clear benefits on macro- and microvascular endpoints. Aggressive lipid lowering to LDL-cholesterol levels ≤2.60 mmol/L, and probably even lower in high-risk patients, has proven to be of great value in the diabetic patient. Considering present evidence, the role of improved glycaemic control is less clear but is likely to be protective. Antiplatelet therapy with aspirin as a primary prevention strategy should be considered in the high-risk patient with diabetes.

Notwithstanding the present evidence, there are some questions that remain unanswered. Is there a difference in the class of drugs used to attain goals for glycaemic control and blood pressure? How low should the targeted level of LDL-cholesterol be in the diabetic patient? Should every patient with type 2 diabetes receive aspirin? Large-scale randomised clinical trials addressing these questions and including a significant proportion of diabetic individuals are necessary. Furthermore, recognising the fact that there are subsets of patients with type 2 diabetes with a lower CVD risk, there is a need to test strategies incorporating CVD risk stratification.

It is indeed a challenging task for both patient and doctor to achieve defined goals of therapy. Several surveys unequivocally report a poor adherence to guidelines and an inability to reach the defined targets.[86,87] Nonetheless, the use of a comprehensive multifactorial CVD risk approach tailored to expected risks and benefits in the individual patient is bound to reduce the risk for CVD in type 2 diabetes.

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