Aspirin in the prevention of cardiovascular disease in type 2 diabetes

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Pharmacological strategies to reduce cardiovascular risk in type 2 diabetes mellitus

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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. In this article, we provide a review on current insights in treatment of hyperglycaemia, hypertension, dyslipidemia and platelet aggregation in the type 2 diabetic subject, focussing on information provided by recent trials.

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 dyslipidemia significantly reduce cardiovascular risk. Meticulous control of blood pressure to a level ≤130/80 mmHg, preferably using RAS-modulating agents is of proven value. Use of statins as LDL-cholesterol-lowering therapy, initiated at a level of ≥2.60 mmol/L is firmly established. Recent trials lend support to lower the target level for LDL-cholesterol-lowering therapy to LDL-cholesterol of ≤1.81 mmol/L. Mainly based on risk analogy, international guidelines advocate the use of aspirin in primary prevention of CVD in 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 the patient with type 2 diabetes, stratified to individual patients, is necessary to reduce the excess in cardiovascular burden these patients suffer from.

Introduction

Type 2 diabetes mellitus is a common disorder, defined by the presence of elevated blood glucose and characterized 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 mellitus is increasing, mostly due to obesity and a sedentary lifestyle. As estimated worldwide prevalence is expected to increase from 2.8% in 2000 to 4.4% in 2030, one could easily speak of an upcoming pandemic (1). In industrialized countries, prevalence rates are even higher. In 2001, 7.9% of adults in the United States were having type 2 diabetes mellitus (2).

Approximately 65% of patients with type 2 diabetes mellitus die as a result of a cardiovascular event (3). Patients with type 2 diabetes mellitus have a 2-4 fold increased relative risk for developing myocardial infarction (MI), peripheral arterial disease and stroke (4). Moreover, in diabetic patients cardiovascular disease (CVD) follows a more detrimental course and prognosis is worse compared with their non-diabetic counterparts. In the report of the Minnesota Heart Survey, diabetic individuals had an odds ratio of in-hospital death after a MI 1.5 times that of non-diabetic individuals (5). Although certain interventions have significantly improved CVD mortality in the general population, diabetic subjects did not benefit in the same extent. In the Prevention of RESstenosis with Tranilast and its Outcomes (PRESTO) trial, diabetes was independently associated with death compared with the non-diabetic subjects, RR 1.87 (6). In an impressive study stressing the impact of diabetes as cardiovascular risk factor on mortality, the seven-year incidence on myocardial infarction in a Finnish population was compared between 1378 non-diabetic subjects and 1059 subjects with type 2 diabetes (7). Subjects with diabetes but without a prior MI had similar event rates as subjects with prior MI but without diabetes. This suggestion has remained somewhat controversial, especially for patients at younger age. However, a recent large nationwide population-based study in Denmark corroborated the findings of Haffner, providing definitive evidence that patients with diabetes mellitus requiring glucose-lowering therapy have a cardiovascular risk comparable to non-diabetics with a prior myocardial infarction (8).

Various metabolic factors in the diabetic patient contribute to the accelerated atherosclerotic process. Hyperglycaemia, high levels of circulating free fatty acids and insulin resistance result in altered function of endothelial cells lining the vessel wall (9). 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 (10). This contributes to a more unstable atherosclerotic plaque, i.e. prone to thrombosis resulting in acute occlusion. Most of these alterations in vascular homeostasis are already present years before diabetes is diagnosed (11).

This early and accelerated form of atherosclerosis in type 2 diabetes mellitus, leading to high morbidity and mortality, necessitates a shift in medical care. Whereas traditional therapeutic approaches have emphasized glycaemic control, international guidelines on care for the diabetic patient nowadays ask for an aggressive multifactorial CVD risk factor reduction strategy (12). Such an intensified approach is beneficial, as shown in the Steno-2 trial (13). In this study, an intensified, targeted, multifactorial intervention comprising behaviour modification and polypharmacologic 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. Patients in the intensive treatment group had a lower risk of death (hazard ratio 0.54, 95% confidence interval (CI) 0.32 to 0.89) and reduced risk of both micro- and macrovascular complications.

In recent years, several important large trials on treatment of hypertension, dyslipidemia, glycemic control and antiplatelet therapy in patients with type 2 diabetes have been published. In this article, we will review current insights in pharmacological strategies to reduce the high rate of cardiovascular disease in these patients.

Treatment of hyperglycaemia

As the cardinal feature of diabetes mellitus 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 (14). This increased oxidative stress impairs both endothelial function and function of the insulin producing β-cell, worsening insulin resistance (15,16). Numerous epidemiological studies confirmed the relationship between blood glucose level and CVD risk. The concentration of glycated haemoglobin (HbA1c) correlated with increased risk of death in a prospective population study. An increase of 1% in HbA1c was independently associated with a 28% increased risk of death (17). 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 CV event was found, even at glucose levels clearly below the diabetic threshold (18).

Though the link between hyperglycemia and cardiovascular risk seems clear, there is surprisingly less evidence that improved glycaemic control is associated with a decrease in risk. In the 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 (19). After 10 years, the obtained HbA1c in the intensive group was 7.0% versus 7.9% in the conventional group. This 0.9% difference in HbA1c was associated with a 16% decreased risk for myocardial infarction. This strong trend in reduction in macrovascular events did however not 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 attained HbA1c.

It might be possible that the choice of hypoglycaemic agent is a factor of importance. In a posthoc analysis of the subgroup of overweight participants treated with metformin, a relative risk of 0.61 (95% CI 0.41-0.89) for myocardial infarction was found (20). Diabetes related death and all-cause mortality were significantly

reduced as well in this subgroup. The median HbA1c after 10 years was 7.4% in the metformin group and 8.0% in the conventional group. Much debate surrounds the use of a new class of oral bloodglucose lowering agents: the thiazolidinediones (TZD). The TZDs 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 (21, 22). The PROactive study (PROspective pioglitazone clinical trial in macrovascular events) was specifically designed to assess reduction in cardiovascular endpoints in high-risk patients with type 2 diabetes (23). In this study, 5238 patients were randomized to placebo or pioglitazon and after a mean follow-up of nearly 3 years a non-significant reduction was noted in the combined primary endpoint of cardiovascular, cerebrovascular and peripheral vascular outcomes. However, pioglitazone reduced by 16% a prespecified secondary endpoint including death, nonfatal myocardial infarction and stroke. Of note, the beneficial effects of TZD are not a class effect. Use of another available TZD rosiglitazon is associated with an increase in risk for myocardial infarction (24). For both TZD, the risk of heart failure is significantly increased.

Mainly based on the results of both UKPDS trials, guidelines from the American Diabetes Association (ADA) advise a target HbA1c of ≤7.0% (25). Increased efforts to improve glycaemic regulation to target HbA1c at near-normal levels of 6.0 to 6.5% did not prove to be of benefit. Both the ACCORD (Action to control cardiovascular risk in diabetes) and ADVANCE (Action in diabetes and vascular disease: preterax and diamicron modified release controlled examination) trial compared standard and intensive glucose-lowering strategies in type 2 diabetes (26, 27). Median HbA1c levels at the end of the follow-up period in both studies were 6.4% in the intensive group versus 7.0 to 7.5% in the standard care group. Much to a surprise, in the preliminary terminated ACCORD trial, the intensive strategy was associated with an increase in mortality (HR 1.22, 95% CI 1.01 to 1.46) without a reduction in cardiovascular events (26). The ADVANCE trial came to slightly different conclusions: use of an intensive strategy that lowered the level of HbA1c to 6.5% did not reduce risk of death or macrovascular events (27). However, incidence of major microvascular events was significantly reduced by 14% (95% CI 3 to 23%). On the basis of the aforementioned data, the advice in current guidelines to target HbA1c to an level of approximately 7.0% is still valid.

Treatment of hypertension

Hypertension is highly prevalent in patients with type 2 diabetes. About 75% of diabetic subjects have a blood pressure ≥130/80 mmHg or use any antihypertensive medication (28). The frequent coexistence of hypertension and diabetes mellitus is in particular a risk factor for the development of end-stage renal failure (29). In addition to the risk associated with the presence of diabetes, cardiovascular mortality is increased in diabetic patients with high blood pressure levels (30).

Treatment of hypertension has proven to be of great value. In the Systolic Hypertension in the Elderly Program (SHEP) 4736 subjects aged 60 years or more with isolated systolic hypertension (systolic blood pressure ≥160 mmHg, diastolic <90 mmHg) were randomised between active treatment and placebo (31). 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. Another study compared active treatment of hypertension with placebo. In the Systolic Hypertension in Europe (Syst-Eur) study, patients were randomly assigned to active treatment beginning with the calcium channel blocker (CCB) nitrendipine or placebo (32). In the diabetic subgroup, the net differences in systolic and diastolic pressure between the placebo and active treatment groups were 8.6 and 3.9 mmHg respectively. This resulted in a reduction of the rate of all CVD events by 69% in the diabetic patients but by only 26% in the patients without diabetes.

As blood pressure reduction has a distinct effect on the incidence of CVD in the diabetic subject, the next question to be answered would be what target level of blood pressure one should aim for. Several studies addressed this question specifically. In a study embedded in the United Kingdom Prospective Diabetes Study (UKPDS), tight blood pressure regulation with captopril or atenolol, aiming at a blood pressure level of <150/85 mmHg, was compared with less tight control aiming at a level of <180/105 mmHg (33). After a mean follow-up of 8.4 years a net decrease of systolic 10 mmHg and diastolic 5 mmHg was achieved by tight control. Lower blood pressure was associated with a non-significant reduction of 21% of myocardial infarction and a significant 44% reduction of fatal or non-fatal 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 two years later showed that each 10 mmHg reduction in systolic blood pressure was associated with a 12% decrease in the risk of any end point 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 (34).

The Hypertension Optimal Treatment (HOT) trial was specifically designed to examine whether reduction of blood pressure to a normotensive range would reduce cardiovascular risk in patients with hypertension (35). A total of 18790 patients with a diastolic blood pressure between 100 and 115 mmHg were randomised to three target groups, aiming at a diastolic blood pressure of ≤90 mmHg, ≤85 mmHg or ≤80 mmHg. Diastolic blood pressure was reduced from 105 mmHg at baseline to 85.2 mmHg, 83.2 mmHg and 81.1 mmHg respectively. In the subgroup of 1501 diabetic patients, the number of all major cardiovascular events / 1000 patient years dropped from 24.4 to 11.9 in the group with a target diastolic blood pressure of ≤80 mmHg compared with the target group ≤90 mmHg. When both groups were compared, cardiovascular mortality was significantly reduced but total mortality did not change (36). Primarily based on these results, guidelines issued by the Joint National Committee on the prevention, detection, evaluation and treatment of high blood pressure (JNC-7), the American Diabetes Association and European society of hypertension (ESH) all recommend a target blood pressure of ≤130/80 mmHg (25, 37, 38). Interestingly, in a study among 499 American-Indians with type 2 diabetes, a combined approach to lower bloodpressure beyond the recommended target to a level of 115 mmHg systolic and to further lower LDL-cholesterol levels below 1.8 mmol/l resulted in regression of carotid IMT and a greater decrease in left ventricular mass, suggesting the possibility of incremental cardiovascular risk reduction with more aggressive targets of treatment in blood pressure (39).

Which agent should be used as first-line agent in the treatment of hypertension in the diabetic subject? Discussion on this topic has become rather hypothetical, as the average patient needs more than two different agents to achieve adequate blood pressure control (40). The JNC-7 report advises to start immediately with at least two agents when blood pressure is 20/10 mmHg above target level in diabetic subjects

(38). ESH guidelines state that most often combination therapy is required (37). Numerous studies have compared the effects of different classes of antihypertensive agents in the management of hypertension in patients with diabetes. As the results of these trials sometimes are in conflict, it is difficult to identify a single class of agents with superior benefit. On the basis of selected studies, it is often claimed that 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 accomplished independent of the blood pressure lowering effect. Furthermore, the formation of NADPH-dependent reactive oxygen species is diminished by RAS inhibiton. Oxidative stress plays a pivotal role in endothelial dysfunction, inflammation and generation of advanced glycation end products. Inhibition of the RAS with both angiotensin converting enzyme (ACE) inhibitors and angiotensin-II receptor blockers (ARB's) is associated with a reduced formation and accumulation of advanced glycation end products. The Heart Outcomes Prevention Evaluation (HOPE) study and the MICRO-HOPE substudy, focussing on renal endpoints, studied the effects of the addition of the ACE inhibitor ramipril to current medical regime in high-risk patients on cardiovascular endpoints (36). A total of 3577 patients with diabetes and at least one additional risk factor was included, 60% had a history of coronary artery disease. The rate of the combined primary outcome of myocardial infarction, stroke, or cardiovascular death was significantly 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 2.2 mmHg in systolic and 1.4 mmHg 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).

The ARB losartan was compared to atenolol in the Losartan Intervention For Endpoint reduction (LIFE) study. In a prespecified subgroup analysis of all 1195 hypertensive diabetic patients with left ventricular hypertrophy on electrocardiography, after a mean follow-up of 4.7 years, the difference in blood pressure was 2/0 mmHg in atenolol vs. losartan group (41). The primary composite endpoint of cardiovascular death, all myocardial infarction and all stroke was reached by 39.2% in the losartan

group and by 53.6% in the atenolol group. This resulted in an adjusted risk ratio of 0.76 (95% CI 0.58-0.98). Interestingly, both in the HOPE and in the LIFE study, participants treated with an inhibitor of the RAS were less likely to develop type 2 diabetes in the course of the study. Both animal and human studies have shown improvement in insulin resistance by inhibiting angiotensin-II (42, 43). In contrast, both diuretics and β-blockers may exert detrimental metabolic effects, leading to an increase in incidence of type 2 diabetes (44). In a large trial among 25577 patients with high cardiovascular risk, among which a large proportion of patients with diabetes mellitus, use of the ARB telmisartan was not inferior to ramipril in prevention of a combined endpoint consisting of death, nonfatal myocardial infarction or stroke and hospitalisation for heart failure (45). Comparison of results within the diabetes subgroup (n=6365) showed similar results for the ramipril and telmisartan group. Combination of ramipril with telmisartan did not result in an increase in benefit.

Several trials have unequivocally demonstrated a beneficial effect of ARB's on renal endpoints in type 2 diabetes. Rate of progression of nephropathy was clearly slowed down in type 2 diabetic subjects with signs of early or overt nephropathy using irbesartan (46, 47) and losartan (48). Yet, addition of an ARB did not reduce secondary cardiovascular endpoints in these trials.
In contrast with the above mentioned evidence from trials supporting the concept that an ACE inhibitor or ARB offers cardiovascular protection, are the results from the Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial (ALLHAT) (49). Although much criticised because of flaws in design and comparability of groups, in ALLHAT no difference in CVD event rate was found between groups assigned to an ACE inhibitor, a CCB and a thiazide diuretic. In their prospectively designed overview of randomized trials, the blood pressure lowering treatment trialists' collaboration concluded that total major cardiovascular events were reduced to a comparable extent in patients with and without diabetes by regimens based on ACE inhibitor, ARB, calcium antagonists and diuretics/β-blockers (50).

In summary, all available evidence underlines the large benefits of aggressive blood pressure lowering in type 2 diabetes, both on micro- and on macrovascular endpoints. In order to attain recommended target levels, combination therapy of 2 or 3 agents is necessary. Weighing individual risk profile and possible metabolic side effects (51, 52), a choice can be made between diuretics, ACE inhibitors, ARB's, CCB's and β-blockers. All agents have proven to be effective in reducing blood pressure. Based on present evidence, the choice for a combination of a low-dose thiazide diuretic and an ARB or ACE inhibitor as first-line therapy in the hypertensive diabetic patient may be considered rational.

Treatment of dyslipidemia

An elevated level of low-density lipoprotein (LDL)-cholesterol was the most powerful predictor of coronary heart disease 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 coronary heart disease 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 (53). In the Multiple Risk Factor Intervention Trial (MRFIT), a decrease of LDL-cholesterol of 1 mmol/L was associated with a 50% lower coronary heart disease risk, again regardless baseline LDL-cholesterol levels (30). 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 to nondiabetic subjects. Increased flux of free fatty acids (FFA) from adipocytes accounts for increased very low-density lipoprotein (VLDL) production in the liver. Furthermore, uptake of FFA in peripheral tissue is impaired due to 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 (54).

The hydroxymethylglutarylcoenzyme-A (HMG-CoA) reductase inhibitors or statins are currently the class of drugs that have shown most convincing data on reduction

of LDL-cholesterol and cardiovascular protection (55). 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.

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 Heart Protection Study (HPS) 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 (56). 5963 patients with diabetes along with 14573 patients without diabetes but with a history of CVD were randomised between simvastatin 40 mg daily and placebo. Mean LDL-cholesterol at entry was 3.2 mmol/L. Mean duration of follow-up was 4.8 years. Among those allocated 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 vs. 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 or usual care (57). In the subgroup of 3638 patients with hypertension and diabetes relative risk for any CVD event was 0.89 (95% CI 0.71-1.10). The net difference in attained LDL-cholesterol reduction between both groups was much smaller than in other studies (0.6 mmol/L), mostly because of large use of non-trial 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 Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm (ASCOT-LLA) failed as well to demonstrate a significant relative risk reduction in the diabetic subgroup of patients randomised to atorvastatin 10 mg or placebo (58). CVD event rate in the total diabetic population was however surprisingly small, 3.6% in the control group. In a comparison between pravastatin 40 mg and atorvastatin 80 mg in patients with acute coronary syndrome, among them 18% patients with

diabetes, more intensive LDL-cholesterol lowering by atorvastatin to an attained level of 1.61 mmol/L resulted in a 16% reduction of a composite CVD endpoint (59). In 2004, the results from the Collaborative Atorvastatin Diabetes Study (CARDS) were published. Atorvastatin 10 mg was compared with placebo in 2838 patients with type 2 diabetes and a maximal LDL-cholesterol of 4.14 mmol/L (60). Use of a statin reduced baseline LDL-cholesterol of 3.04 mmol/L with 40%. Treatment with atorvastatin 10 mg was associated with a 37% reduction in the primary composite CVD event rate (61). On contrast, in a study with a rather similar design, Knopp et al. found no significant cardiovascular benefit among users of atorvastatin 10 mg versus placebo (62).

The results of these recent trials, mandated an update of the National Cholesterol Education Program Adult Treatment Panel III (NCEP – ATP III) guidelines on management of high LDL-cholesterol. In the updated report it is emphasized that in individuals with diabetes the appropriate threshold for initiation of LDL-cholesterol lowering 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 (63). Recognizing 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. In their large meta-analysis on all subjects with diabetes included in large randomized trials with statins, the cholesterol treatment trialists' collaborators found after a mean follow-up of 4.3 years a significant 21% reduction in major vascular events (95% CI 4 to 28%), irrespective of prior history of vascular disease or baseline LDL-cholesterol level (64). Therefore, authors argue that a statin should be prescribed to all patients with diabetes, without any LDL-cholesterol threshold.

In order to achieve such a strict target level, ezetimibe, a cholesterol absorption inhibitor, could be co-administered to a statin. In a study in high risk individuals, the additional use of ezetimibe resulted in an incremental 15%-20% reduction of LDL-cholesterol (65). However, no long-term outcomes are available for ezetimibe and evidence of beneficial effects in type 2 diabetic subjects is lacking.

Fibric acid derivatives target specifically the typical pattern of diabetic dyslipidemia 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 (66) and the Veteran Affairs HDL intervention Trial (VA-HIT) respectively (67). 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 daily. Increase of 6% in HDL-cholesterol and decrease of 20% in level of triglycerides resulted in 24% reduction of all myocardial infarction. The Diabetes Atherosclerosis Intervention Study (DIAS) addressed specifically the treatment of the diabetic dyslipidemia with a fibrate (68). 418 type 2 diabetic subjects were randomised between micronised fenofibrate (200 mg / day) and placebo. 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. An adequately powered trial to investigate the hypothesis that treatment with fenofibrate 200 mg reduces cardiovascular risk in patients with type 2 diabetes with baseline total cholesterol < 6.5 mmol/L was recently reported (69). Fenofibrate did not reduce the risk of a primary combined cardiovascular outcome parameter. The inability to demonstrate any benefit might be explained by a high rate of statin-use among patients allocated placebo.
Because of an increased risk of statin-associated myopathy and rhabdomyolysis when combined with statins, fibrates should be used with care.

Use of Antiplatelet therapy

Cardiovascular events precipitated by occlusion of the vessel are caused by disruption of the atherosclerotic plaque, platelet activation and aggregation. This results in intravascular thrombosis. As the haemostatic balance in the diabetic patient favours thrombosis, therapies directed towards correction of this prothrombotic tendency are rational (70). Aspirin causes an irreversible inhibition of cyclooxygenase, 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 doubtlessly demonstrates that aspirin reduces the risk of any vascular event in patients with prior myocardial infarction, coronary bypass surgery, coronary angioplasty and stroke with about 25% (71). Evidence for the effectiveness of aspirin in a primary prevention setting is less abundant. In the published primary prevention trials, mostly small subgroups of diabetic patients were included.

The Early Treatment Diabetic Retinopathy Study (ETDRS) is a mixed primary and secondary prevention study in both type 1 and type 2 diabetics (72). Treatment with 650 mg aspirin daily resulted in a relative risk of 0.72 (95% CI 0.55-0.95) for myocardial infarction. In the US Physician's health study a small proportion of participants had diabetes (2.0%). Aspirin 325 mg every other day was compared with placebo. In the diabetic subgroup, there was a relative risk of 0.39 for myocardial infarction (73). In addition to assignment to different treatment groups in hypertension, participants in the HOT study were also randomised to aspirin 75 mg daily or placebo (35). 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. An Italian primary prevention trial with aspirin (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 (74). Relative risk for the composite endpoint of cardiovascular death, myocardial infarction 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 non-diabetes group. Recently, two interesting studies on primary prevention with antiplatelet therapy have been published, both in a specific subgroup of diabetic patients. In a population of 1276 adult patients with type 1 or type 2 diabetes and asymptomatic peripheral vascular disease, as defined by an ankle brachial pressure index of <1.0, aspirin 100 mg daily did not reduce a composite primary endpoint of death, nonfatal myocardial infarction and stroke compared with placebo (HR 0.98, 95% CI 0.76-1.26) (75). A study by Ogawa et al for the Japanese primary prevention of atherosclerosis with aspirin for diabetes (JPAD) investigators reached the same conclusion (76). Among a cohort of 2539 patients with type 2 diabetes without a history of cardiovascular disease, aspirin failed to

reduce combined incidence of atherosclerotic events (HR 0.80, 95% CI 0.58-1.10). Of note, the study was underpowered due to a less than expected rate of events. Several large trials are currently ongoing.
The ADP-receptor blocker clopidogrel could be considered an alternative in a secondary prevention setting. In diabetic patients, clopidogrel was shown to produce additional risk reduction as was demonstrated in a subgroup analysis of the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study (77). A total of 19185 patients with prior CVD were randomised to clopidogrel 75 mg once daily versus aspirin 325 mg once daily. In the subgroup of diabetic patients treated with clopidogrel, 15.6% reached the primary composite endpoint (CV death, non-fatal MI, non-fatal stroke) versus 17.7% in the aspirin group.

Although the ADA advocates the use of aspirin (75 mg–162 mg daily) as a primary prevention strategy in every patient with type 2 diabetes older than 40 years or in presence of an additional CV risk factor, which would concern 99% of all patients with type 2 diabetes, evidence is poor (78, 79). As the use of aspirin is associated with an increased relative risk for major gastrointestinal bleeding or hemorrhagic stroke of 1.7, until further evidence changes the net balance of risk and benefit dramatically, in patients with type 2 diabetes aspirin should be prescribed only in patients with symptomatic cardiovascular disease.

Conclusion

The burden of CVD morbidity and mortality in type 2 diabetes imposes a great challenge to both 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. Next to these modifications, powerful pharmacological strategies are available to further reduce cardiovascular disease risk. Meticulous control of blood pressure to well-defined target levels of ≤130/80 mmHg offers clear benefits on macro- and microvascular endpoints. Aggressive lipid lowering to LDL-cholesterol levels ≤2.6 mmol/L and in high-risk patients probably even lower 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 as well. Antiplatelet therapy with aspirin as a primary prevention strategy should not be considered in the diabetic patient without any cardiovascular disease.

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 inability to reach the defined targets (80, 81). 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 cardiovascular disease in type 2 diabetes mellitus.

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