Should We Prescribe Statin and Aspirin for Every Diabetic Patient?

Is it time for a polypill?

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There is clear evidence that diabetic patients constitute a group at high cardiovascular risk. Epidemiologic data show that with the aging of the European population, the percentage of diabetic patients will increase in the upcoming years, with important consequences for cardiovascular mortality. Therefore, the question arises, "How aggressive should prevention with statins and aspirin in diabetic patients be?"

As several studies have demonstrated, cardiovascular mortality of diabetic patients is as high as in nondiabetic patients with known coronary artery disease (1–3); thus, the term "coronary artery disease risk equivalent" has been introduced.

A coronary artery disease risk equivalent implicates the need for stronger treatment goals of secondary prevention for cardiovascular risk factors. A further debate is whether medical treatment provided to patients with coronary heart disease should also be given to diabetic patients without known coronary heart disease.

ASPIRIN — Aspirin administration as secondary prevention in coronary heart disease is well established. The beneficial effect of aspirin therapy in secondary prevention of coronary heart disease has been demonstrated by the meta-analysis of the Antithrombotic Trialist' Collaboration in 2002, with a total relative risk reduction of 15% for cardiovascular death and of 28% for nonfatal re-infarction (4) (Fig. 1).

Regarding primary prevention, Ridker et al. (5) showed a risk reduction by aspirin of 26% for a first cardiovascular event in women ≥65 years of age. In a meta-analysis of primary prevention, Patrono et al. (6) demonstrated that with increasing cardiovascular risk, the benefit of aspirin therapy increases without an increase of bleeding complications; the benefit-risk profile of aspirin becomes more beneficial with increasing cardiovascular risk, for instance in diabetic patients.

Side effects of aspirin remain constant with increasing risk of coronary heart disease, whereas the protective effects increase (Table 1). For these reasons, the German recommendations of primary prevention of coronary heart disease (7) advocate the use of aspirin, if the annual risk of coronary heart disease is ≥1.5%. Treatment with aspirin should be considered if the annual risk of coronary heart disease is 0.7–1.4%. Aspirin is not recommended if the annual risk of coronary artery disease is ≤0.6%. Because diabetic patients have a high annual risk of coronary heart disease >1.5%, these guidelines recommend treatment with aspirin for diabetic patients.

There are several ongoing trials concerning primary prevention with aspirin, such as the POPADAD study (Prevention of Progression of Asymptomatic Diabetic Arterial Disease) or the ASCEND study (A Study of Cardiovascular Events In Diabetes). The results of these studies may possibly influence the current recommendations regarding aspirin treatment in the upcoming years.

STATINS — Statin therapy in cardiovascular prevention and target levels of lipid-lowering therapy are currently under debate and may be modified when results of recent and ongoing studies are made available. The National Cholesterol Education Program/Adult Treatment Panel III guidelines, based on recent trials until 2004, recommended an LDL cholesterol treatment goal of <100 mg/dl in high-risk patients, including patients with diabetes. However, when the risk was very high, an LDL cholesterol goal of <70 mg/dl was considered optional (8).

Routine statin treatment in every diabetic patient is controversial. In the recently published joint guidelines of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD) (9) on diabetes, pre-diabetes, and cardiovascular disease, a summary of different subgroup analyses, comprising more than 5,000 patients with diabetes included in the major statin trials on secondary prevention, demonstrated the evidence of cardiovascular risk reduction by statin therapy in diabetic patients. Data from the Scandinavian Simvastatin Survival Study (4S) (10,12), Lescol Intervention Prevention Study (LIPS) (12), Heart Protection Study (HPS) (13), Cholesterol and Recurrent Events (CARE) trial (14), Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) study (15), and the Greek Atorvastatin and CHO Evaluation Study (GREACE) (16) demonstrated that patients with diabetes showed similar relative risk reductions compared with those without diabetes ranging from 19 to 58%, dependent on the study population and the statin used. Given the higher risk in patients with diabetes, the number needed to treat to prevent any cardiovascular event is even lower (Table 2).

The Heart Protection Study (13) provided direct evidence that cholesterol-

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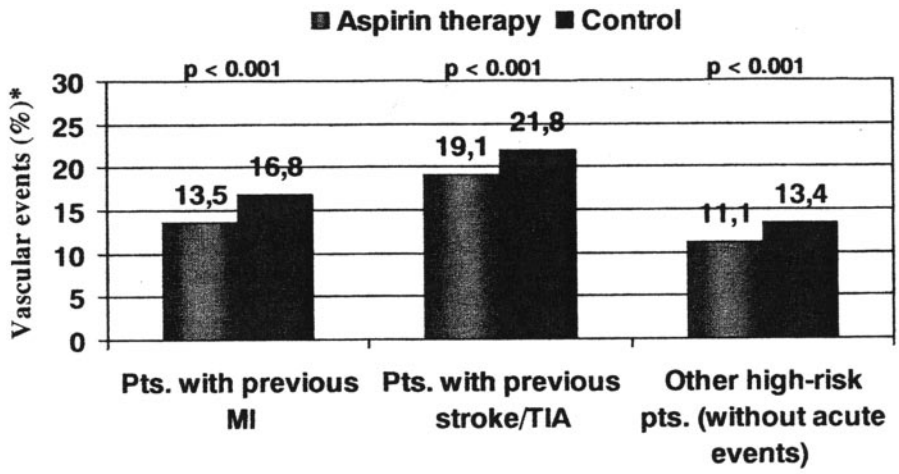

Figure 1—*Beneficial effect of aspirin in secondary coronary prevention. Adapted from Antithrombotic Trialists' Collaboration (4). *Vascular events: death from vascular causes, nonfatal myocardial infarction, and nonfatal stroke. MI, myocardial infarction; pts., patients; TIA, transient ischemic attack.*

lowering treatment with 40 mg simvastatin daily was beneficial for diabetic patients, even without coronary artery disease or high cholesterol levels.

Costa et al. (17) performed a meta-analysis of randomized controlled trials evaluating lipid-lowering therapy. Strong evidence of a reduced cardiovascular risk by lipid-lowering therapy with statins in diabetic and nondiabetic patients was found. The data suggested that after adjustment for baseline characteristics, diabetic patients benefit even more from lipid-lowering therapy in both primary and secondary prevention.

In the Collaborative Atorvastatin Diabetes Study (CARDS) trial (18), statins for primary prevention of cardiovascular disease were investigated in patients with type 2 diabetes without high LDL cholesterol. Atorvastatin, 10 mg daily, was safe and efficacious in reducing the risk of first cardiovascular disease events. During a follow-up of 3.9 years, a significant reduction of 37% of major cardiovascular events including stroke was found. Even in diabetic patients with a baseline LDL cholesterol of <3 mmol/l, the treatment with atorvastatin, 10 mg once daily, led to a relative 37% risk reduction in the first occurrence of acute coronary heart disease events, coronary revascularization, or stroke.

The authors of the Collaborative Atorvastatin Diabetes Study trial even suggested that the debate about whether all patients with type 2 diabetes warrant statin treatment should now focus on whether any patients can reliably be identified as being at sufficiently low risk for statin treatment to be withheld (18).

Following the new European Society of Cardiology guidelines on diabetes, pre-diabetes, and cardiovascular disease (10), the goals for therapy given for diabetic patients for primary prevention are similar to that given for patients with symptomatic disease: cholesterol <174 mg/dl (4.5 mmol/l) and LDL <97 mg/dl (2.5 mmol/l).

The decision whether statin therapy should be started in patients whose LDL cholesterol is already <100 mg/dl (2.6 mmol/l) is left to individual clinical judgment (10).

Another important point to consider is cost-effectiveness. The new European Society of Cardiology/European Association for the Study of Diabetes guidelines on diabetes, pre-diabetes, and cardiovascular disease (10) also discuss that lipid-lowering provides a cost-effective way of preventing complications of diabetes. In a subgroup analysis of the Scandinavian Simvastatin Survival Study (4S) trial (19), cost-effectiveness ratios of treating diabetic patients with 20–40 mg simvastatin were found to be well below the levels that are usually considered cost-effective. Data of the Heart Protection Study confirm these results of acceptable cost-effectiveness ratios for patients with this risk level (20).

In conclusion, there is sufficient evidence of an effective and economic reduction of cardiovascular events by secondary and primary prevention with statins in the high-risk group of diabetic patients.

Table 1—*Benefit of primary coronary prevention with aspirin*

Risk of myocardial infarction per year (%)	NNT to prevent one myocardial infarction	NNT to prevent one myocardial infarction without a major bleeding episode
0.5	133	256
1.0	67	88
1.5	44	53

NNT, number needed to treat for 5 years. Adapted from Kubler and Darius (7).

COMBINATION OF DRUGS

Co-administration of aspirin and statins shows additional effects in reducing cardiovascular mortality. An analysis of individual randomized trials and meta-analyses by Hennekens et al. (21) showed that aspirin therapy provided an additive effect of 24% relative risk reduction of cardiovascular events in addition to statin monotherapy. Statin therapy provided an additional 13% relative risk reduction to aspirin monotherapy.

Treatment and prevention of coronary heart disease has evolved into combination therapy. The rate of combination therapy for secondary prevention has increased within the past few years, and combination therapy has been found to be associated with a significant reduction of mortality.

Data of the German MITRA PLUS registry, including >35,000 consecutive patients with ST-elevation myocardial infarction (STEMI), showed that between 1994 and 2002 the number of administered medications significantly increased, including anti-platelet treatment with aspirin and/or clopidogrel, β-blockers, ACE inhibitors, and statins. There was a significant reduction of mortality of STEMI in clinical practice associated with this improved implementation of practice guidelines (22). This finding was recently confirmed by an analysis of the worldwide Global Registry of Acute Coronary Events (GRACE) registry on acute coronary syndromes (23). Between 1999 and 2006, GRACE documented an improvement in the management of patients with acute coronary syndromes, which was associated with a significant reduction in cardiovascular complications including

Table 2—*Relative risk reduction in the primary end point by statin treatment in diabetic subjects*

	n	End point	Relative risk reduction (%)
CARE (14)	586	Death, MI	25
GREACE (16)	313	Death, MI, unstable angina pectoris, heart failure, stroke, revascularization	58
HPS (13)	3,050	Major coronary event, stroke, revascularization	18
LIPID (15)	782	Death, MI, revascularization	19
LIPS (9)	202	Death, MI, revascularization	47
4S (11)	202	Death, MI	55
4S (12)	483	Death, MI	42

MI, myocardial infarction.

death, stroke, myocardial infarction, and heart failure at 6 months (23).

CONCLUSIONS — An analysis of medical treatment of consecutive patients with acute coronary syndromes of the MITRA PLUS registry (Germany 2000–2002) showed that only 28% of the patients with coronary artery disease risk equivalent such as diabetes received statin therapy. Data from several large registrations support the disappointing implementation of treatment guidelines in actual clinical practice, showing that we are far away from overtreatment of patients at cardiovascular risk.

Aspirin as well as statins are drugs with strong evidence of their beneficial effects, with a significant reduction of cardiovascular events and a low rate of side effects. Therefore in our opinion, a broad use of aspirin and statin treatment in diabetic patients is recommended.

Based on this evidence for the benefit of aspirin as well as of statins in primary and secondary prevention in diabetic patients and decreasing compliance with an increasing number of medications, it might be time again to discuss the concept of a polypill (24), starting with a simple composition of drugs with standard dosages, especially in the setting of diabetes.

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