Primary prevention of cardiovascular events and type 2 diabetes
Should we prioritize our interventions?

A Sultan, JF Thuan, A Avignon

SUMMARY
The diagnosis of type 2 diabetes is based on elevated blood glucose levels. However, in most individuals, metabolic abnormalities as well as cardiovascular risk factors co-exist with a significant proportion of patients presenting with elevated blood pressure, high triglycerides and decreased HDL-cholesterol in addition to hyperglycemia. The risk of cardiovascular disease in people with type 2 diabetes is very high as cardiovascular death represents the number 1 killer in this population. An integrated approach controlling all risk factors as well as blood glucose has been demonstrated to effectively reduce the risk of cardiovascular complications. However, this requires the administration of multiple medications and some patients will have difficulties adhering to the prescribed regimen, limiting the number of drugs the physician can prescribe.

In this review, we will summarize the efficacy of different approaches in primary prevention to help practitioners prioritize interventions in these situations.

Key-words: Type 2 diabetes · Cardiovascular risk factors · Cardiovascular complications · Primary prevention · Secondary prevention · Multifactorial intervention · Review.

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RéSUMÉ
Prévention primaire des événements cardiovasculaires et diabète de type 2 : quelle priorité pour nos interventions ?
Le diagnostic du diabète de type 2 repose sur une élévation de la glycémie. Il s’agit néanmoins d’une maladie très complexe qui associe des anomalies métaboliques multiples. Les individus atteints présentent également, à côté de l’hyperglycémie, une association de nombreux facteurs de risque cardiovasculaire comme une hypertension artérielle, une hypertriglycéridémie et une baisse du HDL-cholestérol. Par conséquent, les décès d’origine cardiovasculaire représentent la première cause de mortalité dans la population diabétique.

Une approche intégrée, prenant en compte l’ensemble des facteurs de risque cardiovasculaire, permet de réduire significativement le risque de ces patients. Cela nécessite cependant fréquemment l’administration de multiples traitements médicamenteux rendant difficile l’observance du patient et limitant ainsi le nombre de médicaments prescrits par les médecins.

Dans cette revue, nous évaluons l’efficacité des traitements préventifs dans la population diabétique de type 2 de façon à aider les praticiens à établir des priorités dans la prise en charge de leurs patients.

Mots-clés : Diabète de type 2 · Facteurs de risque cardiovasculaire · Complications cardiovasculaires · Prévention primaire · Prévention secondaire · Intervention multifactorielle · Revue générale.

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Preventing cardiovascular (CV) disease is the cornerstone of diabetes care, even before normalization of blood glucose. Risk factors (RFs) are commonly encountered in diabetic patients and are associated with a steeper increase in CVD mortality compared to non-diabetic patients [1]. Based on recent trials, it is suggested that treating RFs aggressively might significantly reduce the risk of heart disease, especially when integrated into a multifactorial approach including blood glucose control [2]. Successfully treating RFs requires considerable effort of physicians and patients as well as the administration of multiple medications. Still, a substantial proportion of patients may agree to take only a limited number of medications, driving physicians to prescribe those drugs that will be both accepted by patients and, hopefully, the most effective at reducing CV risk. In this review, we will briefly review the evidence in favor of blood pressure (BP) control, lipid control, aspirin therapy/antiplatelet agents, smoking cessation and blood glucose control in primary prevention to help practitioners prioritize interventions.

**Benefit of antihypertensive treatment**

**Blood pressure control**

Three randomized double-blind, placebo controlled trials studies (The Systolic Hypertension in the Elderly Program (SHEP)), the Systolic Hypertension in Europe (Syst-Eur) study and the normotensive Appropriate Blood Pressure Control in Diabetes (ABCD) have demonstrated the effectiveness of anti-hypertensive therapy for the prevention of CV diseases in diabetic patients (table I [3]). The 3 trials included a proportion of patients with a past history of CV diseases, and are not properly speaking primary prevention trials. The SHEP and the Syst-Eur study were carried out in a general hypertensive population aged >60 years and included sufficient patients with diabetes to allow subgroup analysis in this population. The SHEP study enrolled patients with isolated systolic hypertension [systolic blood pressure (SBP) >160 mmHg and diastolic blood pressure (DBP) <90 mmHg], including 583 patients with non-insulin treated diabetes who were randomly assigned to chlorthalidone plus atenolol or reserpine versus placebo and usual care. The intensive group had a 9.8/2.2 mmHg decrease in SBP and DBP which was accompanied by a significant reduction in CV events and in major coronary heart disease (CHD) in addition to a non-significant decrease in all cause mortality. No effect was noted on stroke. In a recently published long-term analysis of the results (mean follow-up of 14.3 years), diuretic treatment in subjects who had diabetes at baseline was strongly associated with lower long-term CV mortality rate and an almost significant decrease in total mortality rate [4].

The Syst-Eur study also addressed elderly patients with isolated systolic hypertension (SBP >160 mmHg and DBP <90 mmHg) who were randomly assigned to nitrendipine or placebo. The 492 diabetic patients who were included in the study were evaluated in a post-hoc analysis. The mean decreases in SBP and DBP were 8.6 and 3.9 mmHg in the intervention group compared with the placebo group. Nitrendipine treatment was strongly associated with lower CV mortality, CV events and strokes and a trend was noted for the decrease in total mortality rate.

The normotensive ABCD trial was carried out in 480 type 2 diabetic patients who were considered normotensive and/or moderately hypertensive (baseline DBP of 80 to 89 mmHg). Patients were randomized to moderate (diastolic blood pressure 80 to 89 mmHg, placebo group) versus intensive (diastolic decrease of 10 mmHg, intensive group) BP goals. Patients randomized to placebo had a mean BP of 137±0.7/81±0.3 mmHg over the last 4 years of treatment and those randomized to the intensive treatment had a mean 4-year BP of 128±0.8/75±0.3 mmHg (P<0.0001). The primary end point evaluated was the change in creatinine clearance with the incidence of CV diseases being a secondary endpoint. In addition to a significant effect on microvascular complications, the intensive BP control group experienced a lower incidence of strokes but no differences in non-stroke CV events as compared to the placebo group (table I).

**Blood pressure target**

Three trials, the U.K. Prospective Diabetes Study (UKPDS)–Hypertension in Diabetes Study (HDS), the ABCD hypertension trial and the Hypertension Optimal Treatment (HOT) trial compared different BP targets in a diabetic population (table I [3]). As with the placebo controlled trials, none of these trials were properly speaking primary prevention trials.

The UKPDS-HDS clearly demonstrated the beneficial effect of controlling BP in hypertensive diabetic patients (initial BP>160/90). The study included 1148 newly diagnosed type 2 diabetic subjects, most of whom were in primary prevention. 758 patients were allocated to what was designated to be a tight BP control group (goal: BP<150/85 mmHg), and 390 patients were allocated to a less tight control group (goal: BP<180/105 mmHg). The baseline BP level was 160/94 mmHg and patients were followed for a median of 8.4 years. BP was reduced to 144/82 mmHg in the tight control group and 154/87 mmHg in the less tight control group (P<0.0001). Primary end points were the occurrence of:

- a first clinical end point related to diabetes;
- death related to diabetes;
- death from all causes.

Secondary outcome analyses were carried out for MI and stroke. Tight blood pressure control reduced by 24% diabetes related end points (95% confidence interval CI, 8-38) and
Table I
Main clinical trials evaluating anti-hypertensive treatments in diabetic patients.

<table>
<thead>
<tr>
<th>N (% in secondary prevention)</th>
<th>Intervention</th>
<th>End Point</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Placebo-controlled trials</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SHEP (583)</td>
<td>thiazidic diuretic vs. placebo</td>
<td>Main outcome Major CV events, nonfatal plus fatal stroke, nonfatal MI and fatal CHD, major CHD events, and all-cause mortality.</td>
<td>0.66 (0.46 to 0.94)</td>
</tr>
<tr>
<td>SHEP (extended follow-up) (799*)</td>
<td>thiazidic diuretic vs. placebo</td>
<td>All cause mortality</td>
<td>0.82 (0.67 to 1.00)</td>
</tr>
<tr>
<td>Syst-Eur (492)</td>
<td>nitrendipine vs. placebo</td>
<td>Main outcome Stroke</td>
<td>0.31 (0.11 to 0.86)</td>
</tr>
<tr>
<td>Normotensive ABCD (480)</td>
<td>enalapril or nisoldipine vs. placebo</td>
<td>Secondary outcomes Stroke</td>
<td>0.30 (0.09 to 0.94)</td>
</tr>
<tr>
<td><strong>Trials comparing different blood pressure target</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>UKPDS (1148)</td>
<td>blood pressure &lt;180/105 vs. &lt;150/85</td>
<td>Main outcome Death related to diabetes</td>
<td>0.68 (0.49 to 0.94)</td>
</tr>
<tr>
<td>HOT (1501)</td>
<td>DBP &lt;80 vs. DBP &lt;90</td>
<td>Secondary outcomes Myocardial infarction Stroke</td>
<td>0.79 (0.59 to 1.07)</td>
</tr>
<tr>
<td>ABCD (470)</td>
<td>DBP &lt;75 vs. DBP 80-89</td>
<td>Secondary outcomes All cause mortality</td>
<td>0.49 (CI not given in the original publication, P=0.037)</td>
</tr>
</tbody>
</table>

*The number of diabetic patients at inclusion differs between the primary analysis of the SHEP results in which the old criteria for the definition of diabetes was used (serum glucose >140 mg/dl or 7.8 mmol/L) and the extended follow-up in which current criteria for the definition of diabetes was used (serum glucose >126 mg/dl or 7.0 mmol/L).

**The primary end point was the effect of intensive or moderate blood-pressure control on the change in the 24-hour creatinine clearance.
by 32% deaths related to diabetes (95% CI 6-51%, 2/3 of which were from CV diseases); strokes were reduced by 44% (95% CI 11-65%) whereas all cause mortality and MI were non significantly reduced.

The hypertensive ABCD trial randomized 470 hypertensive subjects (DBP >90 mmHg) to intensive BP control (DBP goal of 75 mmHg) versus moderate BP control (DBP goal of 80-89 mmHg). It evaluated CV events only as a secondary outcome, the primary outcome being microvascular complications; more than 50% of the patients had a past history of CVD. The patients randomized to intensive therapy had a lower incidence of all-cause mortality when compared to moderate therapy (5.5 vs. 10.7%, P=0.037). Subgroup analyses, however, did not reveal a statistically significant difference in MI, cerebrovascular events, or congestive heart failure to account for this difference in all-cause mortality.

The HOT trial included 18,790 patients with hypertension (baseline DBP between 100 and 115 mmHg), 1,501 of whom had diabetes with less than 10% of the patients being in secondary prevention. One-third of the patients were assigned to one of 3 different levels of pressure control, with treatment targets of DBP<90, <85, and <80 mmHg. The calcium channel blocker felodipine was used as initial treatment, followed by a five-step treatment to achieve the goal BPs. The subgroup of diabetic patients was the only one to experience a decline in major CV events in relation with the target BP. The group assigned to a target DBP <80 mmHg (achieved BP 81 mmHg) showed a marked reduction in major CV events and mortality as well as a trend for decrease in total mortality rate compared with those patients assigned to a target of <90 mmHg.

The Irbesartan Diabetic Nephropathy Trial (IDNT) aimed to evaluate the effect of different antihypertensive regimens on the progression of nephropathy in type 2 diabetic patients. The authors performed a post-hoc analysis to assess the impact of achieved systolic, diastolic, and pulse pressures on CV outcomes [5]. Patients (n=1990) were randomized to irbesartan, amlodipine, or placebo with other antihypertensive agents to a BP goal of <135/85 mmHg. Progressively lower achieved SBP to 120 mmHg predicted a decrease in CV mortality and heart failure but not MI. A SBP below this threshold was associated with increased risk for CV deaths and heart failure. Achieved DBP <85 mmHg was associated with a trend of increased all-cause mortality, significant increase in MI, but decreased risk for strokes. Increased pulse pressure predicted increased all-cause mortality, CV mortality, MI, and heart failure.

### Table II

Main clinical trials comparing different anti-hypertensive strategies in diabetic patients.

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug Comparison</th>
<th>Results on CV events</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPD5</td>
<td>ACEI vs. β-A</td>
<td>No difference</td>
</tr>
<tr>
<td>CAPP</td>
<td>ACEI vs diuretic + β-A</td>
<td>ACEI better</td>
</tr>
<tr>
<td>ABCD</td>
<td>ACEI vs. DCCB</td>
<td>ACEI better</td>
</tr>
<tr>
<td>FACTET</td>
<td>ACEI vs. DCCB</td>
<td>ACEI better</td>
</tr>
<tr>
<td>NORDIL</td>
<td>NDCCB vs. diuretic / β-A</td>
<td>No difference</td>
</tr>
<tr>
<td>INSIGHT</td>
<td>DCCB vs. diuretic</td>
<td>No difference</td>
</tr>
<tr>
<td>STOP-2</td>
<td>ACEI vs. DCCB vs. diuretic + β-</td>
<td>No difference in CV mortality, ACEI better than DCCB for myocardial infarction</td>
</tr>
<tr>
<td>ALLHAT</td>
<td>ACEI vs. diuretic vs. DCCB</td>
<td>No difference</td>
</tr>
<tr>
<td>LIFE</td>
<td>ARB vs. β-A</td>
<td>ARB better</td>
</tr>
<tr>
<td>ASCOT-BPLA</td>
<td>DCCB +/- ACEI vs. β- +/- diuretic</td>
<td>DCCB +/- ACEI better</td>
</tr>
</tbody>
</table>

A substantial number of studies solely in diabetic populations or including a sufficient number of diabetic patients for separate analysis have compared different antihypertensive regimens for CV prevention (table II [3]). As can be seen, no class of drug consistently showed any superiority in comparison to others.

Two additional studies, the Heart Outcomes Prevention Evaluation (HOPE) and the DIABHYCAR studies evaluated whether the angiotensin converting enzyme (ACE) inhibitor ramipril has protective effects on CV events independent of its BP lowering effect [6,7]. These were not hypertension trials, as a significant portion of the participants did not have hypertension and those who did were managed throughout the study with non–ACE inhibitor medications. In the HOPE study, a diabetic subgroup was pre-specified and 3,577 individuals with diabetes were randomized to receive either 10 mg of ramipril or placebo; a small proportion of patients had type 1 diabetes. DIABHYCAR included 4937 patients with high urinary albumin excretion who were randomized to receive either 1.25 mg of ramipril or placebo. The proportions of patients in secondary prevention in HOPE and DIABHYCAR were 68% and 22%, respectively. Thus DIABHYCAR is a more primary prevention trial and HOPE a secondary prevention trial. In HOPE, after 4.5 years of follow-up, the group of patients receiving ramipril had a significant 25% reduction of CV events; ramipril’s benefit was noted irrespective of whether participants had a history of CV events (p for interaction =0.91), but the study was not powered to detect different effects in the subgroups. The authors of the study suggested that the benefit in the ramipril group could be independent of its BP lowering effect, although this point is debated as some authors suggest that the small, non-significant difference in BP observed between the intervention and the control groups could be sufficient to explain the difference in CV outcome. In DIABHYCAR, 1.25 mg
ramipril did not prevent CV events although it slightly decreased BP.

Even though the overall data provide no clear evidence that one class of drug is better than another regarding CV complications, considerable data show that blockers of the renin angiotensin system are better than other classes of anti-hypertensive drugs in protecting against progressive renal damage and end-stage renal disease, leading the American Diabetes Association to recommend that all patients with diabetes and hypertension should be treated with a regimen that includes either an ACE inhibitor or an angiotensin II receptor blocker [8].

**Lipid lowering therapy**

**Statin trials**

Among 6 primary prevention studies (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT), Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT–LLA), Heart Protection Study (HPS), Pravastatin in elderly individuals at risk of vascular disease (PROSPER), the Collaborative Atorvastatin Diabetes Study (CARDS), Die Deutsche Diabetes Dialyze (4D) [9]) including more than 9000 diabetic patients, only the CARDS and the HPS reported an unequivocal and significant reduction in CV event rate in this specific population (table III). In the diabetic population of ASCOT-LLA, there was a reduction in the composite end-point including total CV events and procedure with 10 mg of atorvastatin but not of any of its individual components. Risk reduction in the primary end point of the trial (fatal CHD and nonfatal MI) was significant in the non-diabetic group (+4%) but not in the diabetic group (-16%).

Three other studies (ALLHAT-LLT, 4D and PROSPER) did not show any benefit of statin therapy in diabetic patients. The negative outcome in the ALLHAT-LLT study has been reported to likely be a result of a high rate of LDL cholesterol-lowering treatments in the usual care group, resulting in a small (11%) difference in LDL-cholesterol concentrations between the treated and usual care groups. The 4D trial enrolled patients with end-stage renal disease and failed to improve significantly CHD rate, suggesting either that statin treatment may need to be provided to patients with type 2 diabetes at an earlier stage of the disease or that CV events in patients with end-stage renal disease is not amenable to statin therapy. PROSPER evaluated the effect of 40 mg pravastatin in elderly subjects over 60 years of age. The number of diabetic patients was too small for valuable interpretation.

The recently published Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus (ASPEN) confirms that not all diabetic subjects in primary prevention benefit from statin

### Table III

<table>
<thead>
<tr>
<th>Number of patients with diabetes and in primary prevention</th>
<th>Intervention</th>
<th>End Point</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Statin Trials</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALLHAT-LLT</td>
<td>P40 vs. usual care</td>
<td>All cause mortality</td>
<td>1.03 (0.86 to 1.22)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CHD events</td>
<td>0.89 (0.71 to 1.10)</td>
</tr>
<tr>
<td>HPS</td>
<td>S40 vs. placebo</td>
<td>First major vascular event (ie, major coronary event, stroke or revascularisation)</td>
<td>0.67 (0.54 to 0.83)</td>
</tr>
<tr>
<td>PROSPER</td>
<td>P40 vs. placebo</td>
<td>CHD events + Stroke</td>
<td>1.23 (0.77 to 1.95)</td>
</tr>
<tr>
<td>ASCOT-LLA</td>
<td>A10 vs. placebo</td>
<td>CHD events</td>
<td>0.84 (0.55 to 1.29)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stroke</td>
<td>0.67 (0.41–1.09)</td>
</tr>
<tr>
<td>CARDS</td>
<td>A10 vs. placebo</td>
<td>All cause mortality</td>
<td>0.73 (0.52 to 1.01)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CHD events</td>
<td>0.67 (0.47 to 0.97)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stroke</td>
<td>0.52 (0.31 to 0.89)</td>
</tr>
<tr>
<td>4D</td>
<td>A20 vs. placebo</td>
<td>Cardiac death + non fatal MI + Stroke</td>
<td>0.92 (0.77 to 1.10)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>All cause mortality</td>
<td>0.93 (0.79 to 1.08)</td>
</tr>
<tr>
<td><strong>Fibrate Trials</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HHS</td>
<td>CHD events</td>
<td>0.32 (0.07 to 1.46)</td>
<td></td>
</tr>
<tr>
<td>FIELD</td>
<td>CHD events</td>
<td>0.81 (CI not given in the original publication, P=0.03)</td>
<td></td>
</tr>
</tbody>
</table>
therapy [10]. This study aimed to demonstrate that statin treatment might reduce the risk of CV events in individuals with LDL-cholesterol below contemporary guideline targets at the time of inclusion (1996 to 1999). It investigated the potential CV benefit of atorvastatin in a cohort of 2,410 type 2 diabetic subjects, including 1,905 in primary prevention with LDL cholesterol <160 mg/dl at inclusion. In the subjects in that latter group, the overall CV risk was low and no benefit was noted from 10 mg atorvastatin treatment.

Hence, by contrast to common belief, only 2 out of 7 trials show a clear benefit of statin therapy for primary prevention of CV diseases in diabetic patients, suggesting that all diabetic patients are not susceptible to benefit from statin therapy. Nevertheless, much care should be taken that such a conclusion does not lead to under-treat diabetic patients. Indeed, a recent meta-analysis shows that statins are effective drugs that can reduce major coronary events by 21% (95% CI 11-30%) and stroke by as much as 36% (95% CI 17-51%) in diabetic patients [11].

**Fibrate trials**

The Helsinki Heart Study (HHS) was a randomized, controlled primary prevention trial of gemfibrozil in patients with elevated non-HDL cholesterol levels (primarily triglyceride and LDL-cholesterol levels). A limited number of 135 patients with diabetes were enrolled in the study. Even though the incidence of CHD was 3.4% in the gemfibrozil group in comparison to 10.5% in the placebo group, the difference in risk did not reach the level of statistical significance [12].

Subsequently, the recently published Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) randomized 9,795 patients (7,664 in primary prevention), with type 2 diabetes to receive fenofibrate, 200 mg/d, or placebo. At inclusion, patients had neither elevated triglycerides (median value 152 mg/dl, range 118-202), nor decreased HDL-cholesterol levels (mean value ± standard deviation 43 ± 0.10 mg/dl). Fenofibrate did not produce a significant reduction in the primary outcome (coronary events) for the whole population when compared with placebo. A post-hoc subgroup analysis showed a significant, 19% event reduction in patients without previous CV events [13]. Even though this result is interesting and of the same magnitude of what is seen with statins in primary prevention, it is not sufficient to recommend fibrate therapy as a first line therapy in primary prevention in the diabetic population before statins. Unfortunately, the FIELD study does not give any answer to the key question regarding the preventive effect of fibrates in diabetic patients with elevated triglycerides and/or diminished HDL-cholesterol levels since these patients were not included in the study.

**Antiplatelet agents**

The American Diabetes Association recommends low-dose aspirin therapy as a secondary prevention strategy and as primary prevention strategy in adults with diabetes and who are at high risk for CV events [8]. These recommendations are based on the results of three studies: the Early Treatment Diabetic Retinopathy Study (ETDRS), the Physicians’ Health Study (PHS) and the HOT study [14-16].

The ETDRS was designed to evaluate the effect of photocoagulation and aspirin on ocular events [15]. It provided the opportunity to evaluate the daily administration of aspirin on mortality and CV events in the 3,711 diabetic patients with retinopathy who were included in the study. Mortality from all causes was not reduced by the administration of 650 mg aspirin per day for 5 years and the reduction in CV mortality did not reach the level of statistical significance either. Larger differences were noted in MI with a significant, 17% reduction in the group receiving aspirin (P=0.04). The PHS evaluated whether the administration of 325 mg aspirin every other day decreases CV mortality [16]. This study enrolled 22,071 participants, 533 of whom had diabetes. No reduction in all cause mortality was noted. However, there was a 44% reduction (95% CI 30 - 55%) in the risk of MI in the overall population and an 18% reduction (95% CI 4 - 30%) in important vascular events. Diabetes had no influence on the protective effect of aspirin on MI but its effect on other CV events was not reported. In the HOT study, 75 mg aspirin per day significantly reduced (P=0.03) major CV events by 15% (9% when silent MIs were included in the analysis) [14]. All MIs were 36% less frequent in the aspirin group (P=0.002). Inclusion of silent MI reduced the benefit of aspirin to 15%. There was no difference in stroke incidence. CV and total mortality were non-significantly reduced by aspirin. The relative benefit of aspirin on major CV events and all MIs was about the same in the groups of patients with diabetes as in the whole HOT population.

More recently, the Primary Prevention Project (PPP), an open-label study evaluated the effect of aspirin (100 mg/day) on CV events in 4,495 individuals with >1 RFs, including 1,031 with diabetes [17]. The trial demonstrated a significant benefit of aspirin in reducing the composite end point of CV deaths, stroke, or MI (RR 0.59, 95% CI 0.37–0.94). In the diabetic subgroup, there was no significant reduction in the risk for the combined vascular end point with aspirin. However, the substudy in diabetic patients was not adequately powered.

The meta-analysis of the Antithrombotic Trialists’ Collaboration published in 2002 [18] showed that aspirin therapy reduces the risk for coronary heart disease by 28% with no significant effects on total mortality and stroke in the overall population. The analysis showed a lack of evidence for the benefit for aspirin in patients randomized because of diabetes. Overall, among 4,961 patients with diabetes in nine trials, antiplatelet therapy was associated with only a moderate, non-significant 7% reduction in serious vascular events. Finally, the CHARISMA study showed that the addition of clopidogrel to a daily low-dose aspirin regimen is of no additional benefit at reducing the incidence of CV events among people with diabetes and should not be recommended [19].
Thus, the evidence favoring aspirin use in diabetic patients in primary prevention appears to be weak. In addition, the potential beneficial effects of aspirin must be balanced with its major side effect of bleeding with an increase in fatal or non-fatal haemorrhagic stroke (up to 22%) as well as an increase in major extracranial bleeds (Odd Ratio of 1.6, 95% CI 1.4-1.8) [18].

Taken together with side effects, these studies do not provide any clear evidence for a benefit of aspirin therapy in diabetic patients. However, once again, much care should be taken that this does not lead to the under treatment of diabetic patients since most of the results are based on subgroup analysis, the interpretation of which should always be taken with caution. Thus, the American diabetes association recommends aspirin therapy (75–162 mg/day) as a primary prevention strategy in patients with type 2 diabetes at increased CV risk, including those who are >40 years of age or who have additional risk factors [8]. The French diabetes and cardiology associations (ALFEDIAM and SFC) recommend low-dose aspirin therapy in diabetic patients with at least two additional risk factors [20].

**Smoking cessation interventions**

The evidence from studies of individuals with diabetes shows the strong influence of smoking on mortality. Cigarette smoking was shown to be a significant risk factor for death by coronary heart disease in type 2 diabetes in the Multiple Risk Factor Intervention Trial (MRFIT), the Finnish Prospective Study, and the Paris Prospective Study [21]. In addition, the combination of smoking and diabetes appears to heighten the development of macrovascular complications. Meigs et al [22] reported on 1,539 patients with type 2 diabetes and found, in addition to other factors such as sex and hypertension, former cigarette smokers were 1.54 times (95% CI 1.49–1.58) more likely to be diagnosed with coronary artery disease. Similar findings are reported by an international cohort study of 4,427 people with diabetes, reporting that mortality risks were associated with history and duration of smoking and quitting [23]. When compared with nonsmokers, mortality risk among individuals who had quit >10 years ago was increased by 25%, which was markedly lower than among those who had quit <9 years ago, suggesting the importance of quitting as early as possible in the course of diabetes. Thus, all health professionals should give simple, brief advice routinely to all smokers that they encounter as this has been reported to be one of the most cost effective interventions in medicine.

**Blood glucose control**

Epidemiological data suggest a role for plasma glucose in macrovascular complications in diabetic patients and post-prandial plasma glucose seems to be a particularly important player in this regard. A recent meta-analysis suggests that attempts to improve blood glucose control reduce macrovascular events both in type 1 and in type 2 diabetes. Effect was mainly due to reductions in stroke and peripheral vascular events in type 2 diabetes [24].

Analysis of data from the UKPDS suggests that more aggressive blood glucose lowering may be associated with reduced rates of CVD and that the maximal benefit from glucose lowering is realized as HbA1c levels approach 6% [25]. However, sulphonylureas or insulin had no significant effect on risk reduction of macrovascular disease beyond expected effects on glycaemic control whereas metformin was associated with significant reductions in MI [relative risk (RR) 0.81, 95% CI 0.41-0.81] and diabetes-related deaths (RR 0.64, 95% CI 0.45-0.91) in overweight and obese patients initially randomised to this treatment [26].

Even though epidemiological data highlight the role of post-prandial blood glucose in CV diseases and mortality in patients with type 2 diabetes, no study has demonstrated the beneficial effect of drugs targeting post-prandial plasma glucose on CV complications specifically. The STOP-NIDDM trial has shown that patients with impaired glucose tolerance treated with the alpha-glucosidase inhibitor acarbose had a significant reduction in the risk of CV diseases [27]. However, this study has raised a number of methodological questions and meta-analysis of the studies performed with acarbose does not seem to confirm any beneficial effect on CV complications in diabetic patients [28].

Two additional recent publications require our attention even though they are not directly dealing with primary prevention and type 2 diabetes. The first one is the PROActive study, which is a secondary prevention trial evaluating the impact of pioglitazone on CV events [29]. In this study, pioglitazone did not significantly reduce the primary composite endpoint in the high-risk population of the study. The reduction of the main secondary endpoint (the composite of all-cause mortality, non-fatal MI, and stroke) was significant but modest (RR 16%, P=0.027). Further analysis of the results must be awaited before definitive conclusions can be drawn regarding the effectiveness of glitazones in secondary prevention. However, these results are not sufficient to influence our attitude regarding the use of glitazones for primary prevention of CV events in type 2 diabetes. The second publication is the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study research group showing that the previous degree and duration of glycaemic exposure are important determinants of risk of developing macrovascular diabetic complications [30]. In that study, intensive therapy for diabetes for a limited period of 6.5 years reduced the risk of CV events by 42%. Even though this study concerns type 1 diabetic patients, it highlights the importance of blood glucose control.
Summary: establishing priorities of care for primary cardiovascular prevention of type 2 diabetic patients

The selection of initial therapy for type 2 diabetic patients is based on a clinical and biochemical assessment of the patient, taking safety into consideration. The majority of patients are middle aged and overweight or obese at diagnosis and have blood pressure and blood lipids above the currently recommended targets. Most of them will not be able to achieve or sustain those targets without multiple drugs.

In these patients, we would recommend the following strategy:
– advise smoking cessation in patients who smoke (most cost effective);
– initiate treatment with metformin and increase dose up to 2550 mg/day (only antidiabetic drug with demonstrated effects on CV events beyond blood glucose control);
– add 10 mg atorvastatin when patients are ready to intensify their treatment instead of adding new classes of blood glucose lowering drugs, even if patients do not reach the targeted HbA1c and increase progressively the dose to obtain a 40% reduction in LDL-cholesterol (patients who have the highest risk seem to benefit the most from statin therapy; these patients include those who have LDL-cholesterol values >160 mg/dl or with additional RFs such as hypertension and smoking);
– initiate treatment with 2.5 mg ramipril and increase progressively to 10 mg;
– if necessary, add additional anti-hypertensive classes to achieve target BP (control of blood pressure is certainly critical for the prevention of renal failure; however, the evidence in favour of anti-hypertensive therapy for the prevention of CV events in younger patients with moderately elevated blood pressure remains scarce);
– add aspirin (lowest level of evidence; optimal dose in diabetic patients remains a matter of debate).

Establishing priorities, we should keep in mind that the level of risk is closely associated to the level of a given risk factor and that the order of priorities must be pondered according to the imbalance of these factors. BP>160/90 mmHg would require earlier introduction of antihypertensive treatments as would an HbA1c value >8%, due to their additional protective effect on microvascular complications. If LDL-cholesterol value is >160 mg/dl, statin therapy becomes the #1 priority.

To conclude, we would like to remind that intensive target-driven, multifactorial approach to management of type 2 diabetes is very effective to reduce the risk of both micro- and macrovascular complications in high-risk patients [2]. Thus, when feasible, optimal prevention in high risk type 2 diabetic patients is based on a multifactorial approach including the management of all RFs to recommended targets.

References

11. Costa J, Borges M, David C, Vaz Carneiro A. Efficacy of lipid lowering drugs, even if patients do not reach the recommended targets. Most of them will not be able to achieve or sustain those targets without multiple drugs.

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Cardiovascular prevention and type 2 diabetes


