Prevention of Cardiovascular Risk in Diabetic Patients – An Update

a report by
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DOI:10.17925/EE.2007.00.02.66

Patients with type 2 diabetes have a well-documented increased risk of cardiovascular disease (CVD) that is more than two to three times higher than the risk seen in non-diabetic subjects.[1] In spite of modern methods to treat diabetes and its complications, the increased risk is still substantial even if data on risk factor controls in national surveys have shown improving trends for blood pressure and lipid control, for example from Sweden.[2] The most important CVD risk factors to detect, treat and make follow-up visits for are elevated blood-pressure levels, dyslipidaemia and elevated low-density lipoprotein (LDL) cholesterol, as well as hyperglycaemia and smoking. In addition, chronic inflammation, defects in fibrinolytic function and adverse psychosocial conditions could all contribute to this risk, besides the impact of background factors that it is not possible to change such as age, gender and diabetes duration.

For a number of years data have been accumulating on treatment benefits of risk-factor control based on reports from large-scale clinical trials involving patients with type 1 diabetes – i.e. Diabetes Control and Complications Trial (DCCT) – or type 2 diabetes – i.e. UK Prospective Diabetes Study (UKPDS), Heart Protection Study (HPS), Reduction of Endpoints in NIDDM [non-insulin-dependent diabetes mellitus] with the Angiotensin II Antagonist Losartan (RENAAL), Irbesartan Diabetic Nephropathy Trial (IDNT), Collaborative Atorvastatin Diabetes Study (CARDS), Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) and Anglo–Scandinavian Cardiac Outcomes Trial (ASCOT). Therefore, we have so far had strong support for some, but not all, of the goals for risk factor control stated in contemporary guidelines for treatment of patients with diabetes, from both the joint American Diabetes Association (ADA) and American Heart Association (AHA) guidelines[3] and the corresponding joint European Society of Cardiology (ESC) and European Association for the Study of Diabetes (EASD) guidelines.[4] For example, the recommended goal of blood-pressure control in patients with diabetes and hypertension (<130/80mmHg)[3,4] was not based on solid evidence from intervention studies, but from observational studies, most notably from the observational arm of UKPDS where a linear association between systolic blood pressure and risk of coronary artery disease (CAD) was noticed.[5]

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Lessons From a New Large Intervention Trial of Blood-pressure Control

Recently, however, new evidence has been published based on data from another large-scale intervention study – Action in Diabetes and Vascular Disease (ADVANCE) – aiming at controlling blood pressure in patients with type 2 diabetes.[6] This multicentre, international study assessed the effects of the routine administration of a fixed angiotensin-converting enzyme (ACE) inhibitor–diuretic combination on serious vascular events in patients with diabetes, irrespective of initial blood pressure levels or the use of other blood-pressure-lowering drugs. The trial was performed by 215 collaborating centres in 20 countries. After a six-week active run-in period, 11,140 patients with type 2 diabetes were randomised to treatment with a fixed combination of perindopril and indapamide or matching placebo, in addition to current therapy for CVD risk-factor control. The primary end-points were composites of major macrovascular and microvascular events, defined as death from CVD, non-fatal stroke or non-fatal myocardial infarction, and new or worsening renal or diabetic eye disease.

All analyses were made by intention-to-treat. The macrovascular and microvascular composites were analysed both jointly and separately. After a mean of 4.3 years of follow-up, 73% of those assigned to active treatment and 74% of those assigned to the control (placebo) treatment remained on randomised treatment. Compared with patients assigned to placebo, those assigned to active therapy had a mean reduction in blood pressure of 5.6/2.2mmHg. The relative risk of a major macrovascular or microvascular event was reduced by 9% – 861 (15.5%) active versus 938 (16.8%) placebo (hazard ratio (HR) 0.91, 95% confidence interval (CI) 0.83–1.00; p=0.04) (see *Figure 1*). The separate reductions in macrovascular and microvascular events were similar, but were not independently significant (macrovascular: HR 0.92, 95% CI 0.81–1.04; p=0.16; microvascular: HR 0.91; 95% CI 0.80–1.04; p=0.16). The relative risk of death from cardiovascular disease was reduced by 18% – 211 (3.8%) active versus 257 (4.6%) placebo (HR 0.82, 95% CI 0.68–0.98; p=0.03) – and all-cause mortality was reduced by 14% – 408 (7.3%) active versus 471 (8.5%) placebo (HR 0.86, 95% CI 0.75–0.98; p=0.03). There was no evidence that the effects of the study treatment were influenced by initial blood pressure level or concomitant use of other treatments at baseline.[6]

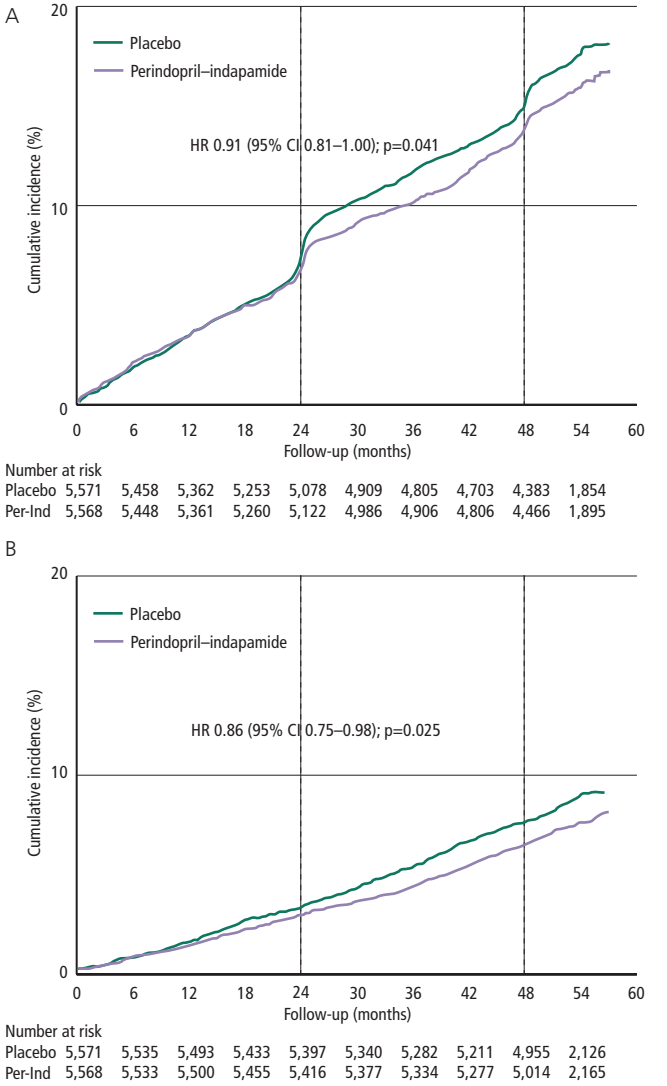
Therefore, the authors concluded that the routine administration of a fixed combination of perindopril and indapamide to patients with type 2

diabetes was well tolerated and reduced the risks of major vascular events, including death. Although the confidence limits were wide, the results suggest that over five years one death due to any cause would be averted among every 79 patients assigned to active therapy. However, in an accompanying editorial by Kaplan,[7] it was mentioned that other combinations of antihypertensive drugs would probably be able to achieve the same clinical benefits, as the blood-pressure reduction *per se* seems to be most important, not the way in which it is achieved. Another critical question is why no preventative effect on cerebrovascular events (stroke) was noticed. This may be due to the fact that a large proportion of the patients were already on statin therapy or received it during the study (45% at follow-up) as background medication, and it has been shown that statins contribute to stroke prevention. It could be hypothesised that in the lower blood-pressure interval, as found in the ADVANCE trial, the preventative effect of statins could over-ride the impact of blood-pressure lowering by antihypertensive drugs.

The Important Role of Smoking Cessation

Another important aspect of CVD prevention in patients with diabetes is smoking cessation, as a large minority of these patients use tobacco products on a daily or regular basis. In the INTERHEART Study it was shown that a linear association exists between the number of cigarettes smoked daily and the risk of myocardial infarction.[8] In Sweden, data from the National Diabetes Register (NDR) show that even in a country with relatively low rates of smoking, middle-aged subjects with diabetes in particular continue to smoke at the same level as seen in the non-diabetic general population (see *Table 1*).[9] What can be done to stop this extremely dangerous habit in patients already at high risk? So far, many interventions to achieve smoking cessation in diabetics have proved less successful, but in recent years some more positive findings have been published from Spain[10] and from Sweden.[11] This has mainly been achieved by combining professional advice to patients to stop smoking with both individual counselling and group support sessions. Pharmacological therapy has so far included mainly nicotine replacement therapy (NRT) in various preparations and bupropion, an atypical antidepressant drug, but recently this pharmacological arsenal has been complemented by a very effective new drug (varenicline) that is a partial nicotine receptor agonist. Vareniclin has been shown to be effective not only for smoking cessation, but also for so-called relapse prevention. In diabetics who smoke, all of these remedies should be tried, and the goal of zero tobacco consumption reached according to recommendations.[3,4]

Figure 1: Main Results from the Action in Diabetes and Vascular Disease Intervention Trial



Trial in 11,140 patients with diabetes and blood-pressure control.
A: Combined primary outcome; B: All-cause mortality.
CI = confidence interval; HR = hazard ratio.

Important Data Expected from Ongoing Trials

Finally, three ongoing trials are of great importance in further expanding the evidence base for prevention of CVD in diabetes: the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET),[12] Action to Control Cardiovascular Risk in Diabetes (ACCORD)[13] and Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD)[14] trials. In the first trial, ONTARGET, high-risk patients with hypertension are randomised to receive treatment with either the well-proven ACE-inhibitor ramipril,[12] documented in high-risk patients with diabetes in the Heart Outcomes Prevention Evaluation (HOPE) trial,[15] or the angiotensin-2 receptor blocker telmisartan, or to the combination of both agents. As almost the same proportion of patients has diabetes in ONTARGET (37.3%) as in the previous HOPE trial (38.3%), the results will be applicable to most high-risk diabetics with hypertension. The trial is planned to report data in March 2008 at the American College of Cardiology (ACC) meeting; the results are awaited with great interest as they may influence the revision of current guidelines for the treatment of hypertension and other associated risk factors.[16]

The second study of importance is the ACCORD trial, which is more or less UKPDS the American way, with a factorial design of randomisation of patients with type 2 diabetes to strict glycaemic control, strict blood pressure control or strict lipid control by use of alternative drug treatment options.[13] This study is ongoing and expected to deliver final results a few years from now. Interestingly, even tighter goals for risk factor control than were used in the UKPDS have been applied in the ACCORD trial; for example, there is an ambitious blood pressure goal of <125/80mmHg in the tight control arm versus conventional treatment (<140/90mmHg). It is still an open question whether this is feasible or not, but according to recent results from the ADVANCE trial[6] no substantial increase of adverse effects was noted in the actively treated arm (perindopril–indapamide fixed combination). However, it should be kept in mind that all patients first received a run-in period of active treatment and only patients tolerant to the drug combination were allowed to continue in the trial for more than a mean of four years of follow-up.

Table 1: Age, Sex and Various Clinical Characteristics Among Smokers and Non-smokers in Type 1 and Type 2 Diabetes Patients (2001)

	Smokers	Non-smokers	n
Type 1 diabetes			
Frequency (%)	14.3 ***	85.7	11,513
Male/female	47/53 ***	55/45	11,513
Age (years)	41.3 (11.9)	40.8 (13.4)	11,513
Diabetes duration (years)	25.3 (12.7)	25.3 (14.0)	11,513
HbA_{1c} (%)	7.67 (1.44) ***	7.21 (1.34)	11,340
HbA_{1c} >6.5 (%)	82.6 ***	71.6	11,340
BMI (kg/m^2)	24.6 (3.8) ***	25.3 (3,7)	10,892
BMI >25kg/m^2 (%)	40.8 ***	47.3	10,892
Systolic BP (mmHg)	130.0 (17.9)	129.3 (16.7)	11,259
Diastolic BP (mmHg)	73.5 (8.7) *	74.1 (8.9)	11,259
Antihypertensives (%)	36.4 **	33.1	11,484
Lipid-lowering drugs (%)	19.9 ***	16.2	11,328
Microalbuminuria (%)	18.4 ***	14.1	11,204
Type 2 diabetes			
Frequency (%)	11.1 ***	88.9	40,648
Male/female	61/39 ***	53/47	40,648
Age (years)	61.1 (10.4) ***	68.4 (12.2)	40,648
Diabetes duration (years)	7.5 (6.5) ***	9.1 (7.6)	32,810
HbA_{1c} (%)	6.65 (1.50) ***	6.44 (1.39)	37,764
HbA_{1c} >6.5 (%)	49.5 ***	44.0	37.764
BMI (kg/m^2)	28.5 (5.3) ***	28.9 (5.0)	31,546
BMI >25kg/m^2 (%)	73.6 ***	78.6	31,546
Systolic BP (mmHg)	142.2 (19.3) ***	146.2 (19.4)	35,724
Diastolic BP (mmHg)	79.0 (9.6)	79.1 (9.6)	35,724
Antihypertensives (%)	52.2	52.1	40,554
Lipid-lowering drugs (%)	31.2 ***	23.7	40,437
Microalbuminuria (%)	19.5 ***	13.0	37.495

*Means (standard deviation), proportions (%) and numbers (n). Significance levels between smokers and non-smokers: *** p<0.001, ** p<0.01, * p<0.05. BMI = body mass index, BP = blood pressure; HbA_{1c} = glycated haemoglobin*
Source: Nilsson et al., 2004.[9]

Finally, in the third still ongoing study (RECORD), the cardiovascular protection (or eventual harm) of rosiglitazone treatment will be tested as add-on treatment to type 2 diabetes patients already treated with sulphonylurea or metformin.[14] This study has a primary goal of investigating effects on CVD end-points, which is very important against the background of recent claims that this glitazone is associated with an increased CVD risk, especially for congestive heart failure (CHF) and myocardial infarction, based on a meta-analysis by Nissen.[17] As a timely response to this criticism, an interim analysis was immediately made in the RECORD trial, showing non-significant increases of the cardiac end-points.[18] The study has, however, not been stopped, and according to a recent decision by the US Food and Drug Administration (FDA), rosiglitazone will stay on the market but with a label of caution against deterioration of cardiac function in patients prone to developing ischaemic heart disease or CHF. We should be grateful that the RECORD trial will continue so that eventually clear answers may be provided on the benefits or dangers associated with rosiglitazone therapy. As in many other similar studies, a wide use of background preventative drug medication and a slow event rate may cause problems in the study; only time will tell.

Quality of Preventative Care in Diabetes Must Be Followed

In summary, CVD prevention in diabetes is one of the most important clinical challenges of preventative medicine in our time.[3,4] The evidence base for tight risk-factor control is now solid for blood pressure and lipid control, but less solid for glycaemic control. Smoking cessation is still not achieved in many at-risk patients, and new methods should be developed. New trial data are expected to change guidelines in the future, especially those from ONTARGET, ACCORD and RECORD. However, it is not only treatment of risk that matters, even if great success can been shown in a structured programme such as found in the Danish Steno-2 trial,[19] but also long-term compliance and quality control. In many countries plans are being developed for regional or national follow-up programmes based on regular surveys in patients with diabetes,[20] one example being the Swedish NDR.[2] ■

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