Will prevention of type 2 diabetes reduce the future burden of cardiovascular disease? The evidence base today

JOHN HB SCARPELLO

Abstract

The prevalence of type 2 diabetes is set to double over the next 25 years, leading to substantial morbidity and mortality, particularly from macrovascular diabetic complications. Pre-diabetic dysglycaemia, characterised by impaired glucose tolerance (IGT) and/or impaired fasting glucose (IFG), is associated with an increased risk of developing both type 2 diabetes and cardiovascular disease. IGT and IFG appear well before type 2 diabetes is diagnosed, thereby presenting an opportunity for intervention to reduce the future burden of diabetes and cardiovascular disease. Intensive lifestyle interventions are effective in preventing or delaying diabetes but are difficult to sustain long term. Intervention trials with pharmacological agents, e.g. the Diabetes Prevention Program (DPP) with metformin, and the STOP-NIDDM study with acarbose, have demonstrated significant decreases in the risk of progression to type 2 diabetes in populations with IGT. Moreover, preliminary evidence with these agents supports a possible beneficial effect on cardiovascular outcomes.

Key words: type 2 diabetes, impaired glucose tolerance, impaired fasting glucose, cardiovascular disease, metformin, acarbose.

Br J Cardiol 2004;**11**:138–43

John HB Scarpello

The need for diabetes prevention

Type 2 diabetes mellitus is a major health concern. Estimates suggest that the number of people with diabetes will increase from the current figure of 194 million worldwide to 333 million by the year 2025.[1,2] Type 2 diabetes usually develops in adults of age 40 years and older and is most common in adults over the age of 55 years.[3] In recent years the disease has been diagnosed more frequently in children and adolescents.[4,5]

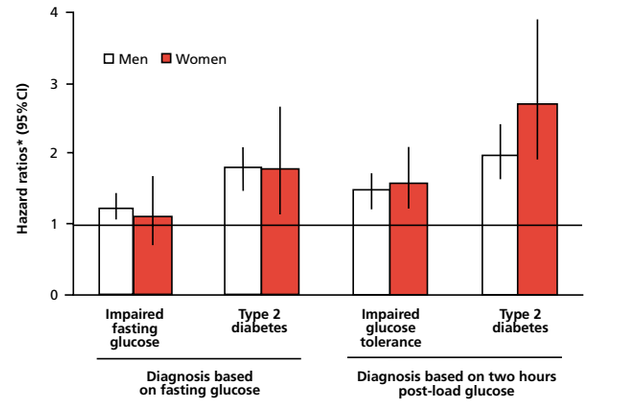
Department of Diabetes and Endocrinology, University Hospital of North Staffordshire NHS Trust, Stoke-on-Trent, ST4 6QG.
John HB Scarpello, Consultant Physician
Correspondence to: Dr JHB Scarpello
(email: john.scarpello@nstaffsh.wmids.nhs.uk)

Such a trend can only have resulted from environmental influences and especially those affecting childhood obesity.

Diabetes is a life-long disease that is associated with microvascular and macrovascular complications (including cardiovascular disease, retinopathy, peripheral neuropathy and end-stage renal failure). The most striking effect is the increased mortality from cardiovascular disease, which is two to three times that of the non-diabetic population. Together, these place a substantial burden on healthcare costs.[2,6,7] In 2002, the American Diabetes Association (ADA) estimated that US $92 billion were attributable to the direct costs of diabetes care, with US $23 billion for diabetes management, US $25 billion for managing diabetic complications, and US $44 billion for the management of other medical conditions that are common in diabetic patients.[8] A further US $39[8] billion represented indirect costs (lost workdays, restricted activity, mortality, and permanent disability due to diabetes).[8]

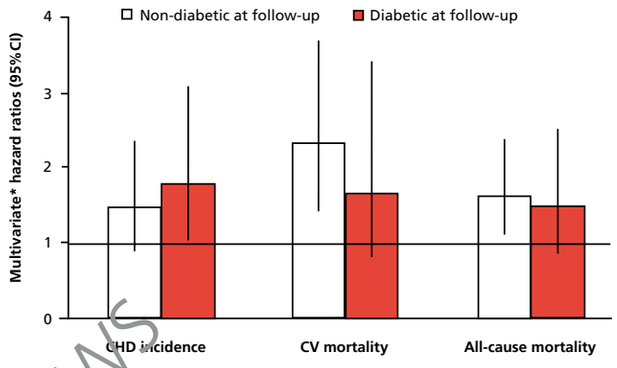
While both genetic and non-genetic factors are associated with the development of type 2 diabetes, the non-genetic factors including obesity, sedentary lifestyles, high-fat and saturated fatty acid-rich diets have been shown to be particularly important.[9] Epidemiological studies have also indicated that the risk of developing type 2 diabetes is increased in people whose diet is low in dietary fibre, low-glycaemic carbohydrates and whole grain cereals.[9]

Figure 1. Mortality according to category of dysglycaemia from the Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe (DECODE) study[11]



Key: *Compared with normal fasting or two hours post-load blood glucose levels, as appropriate; CI = confidence interval

Figure 2. Subjects with elevated two hours post-load glucose (6.7–9.9 mmol/L) are at increased risk of cardiovascular and all-cause mortality irrespective of whether they went on to develop type 2 diabetes[16]



Key: *Adjusted for age, sex, waist-hip ratio, systolic blood pressure, cholesterol, high-density lipoprotein cholesterol, and smoking; CHD = coronary heart disease; CV = cardiovascular; CI = confidence interval

In most people type 2 diabetes results from a combination of insulin resistance and relative insulin deficiency (decreased insulin secretion) and the former is usually present for several years before the onset of clinical diabetes is diagnosed.[10] Prior to the diagnosis of type 2 diabetes, worsening insulin resistance often leads to the development of impaired glucose tolerance (IGT) and/or impaired fasting glucose (IFG),[2] both of which signify an increased risk of developing type 2 diabetes and increase the risk of premature mortality.[11,12] In practice, insulin resistance in pre-diabetic subjects often clusters with other cardiovascular risk factors, such as obesity, IGT, hypertension, dyslipidaemia and impaired fibrinolysis, collectively known as the dysmetabolic syndrome (also known as insulin resistance syndrome or syndrome X).[13-15]

Data from the Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe (DECODE) study emphasise the importance of pre-diabetic dysglycaemia in determining subsequent prognosis (figure 1).[11] Baseline fasting glucose levels, and glucose levels two hours after a 75 g oral glucose tolerance test, were analysed from 10 prospective European cohort studies involving a total of 22,514 individuals, who were then followed up for an average of 8.8 years. Subjects who were found to have had IFG and, especially, IGT were at greater risk of mortality. Subjects with established diabetes, whether diagnosed using fasting or post-load values, were at the highest risk.

A further observational cohort study subjected 2,710 individuals to an oral glucose tolerance test in 1987 and followed them for 10 years.[16] Subjects who had elevated post-load glucose were at increased risk of developing coronary heart disease and had a higher risk of death from cardiovascular disease, or from any cause (figure 2). Interestingly, these associations were equally strong in subjects who did not go on to develop diabetes as in those who did, which confirms the prognostic importance of pre-diabetic dysglycaemia.

The markedly increased risk of progression from impaired glucose tolerance to type 2 diabetes and the strong association of both pre-diabetic dysglycaemia and type 2 diabetes with increased cardiovascular risk emphasise the need for diabetes prevention. There is increasing evidence that intensive lifestyle changes or pharmacological intervention can reduce progression from IGT to type 2 diabetes; preliminary evidence suggests that such interventions may reduce the burden of cardiovascular disease. This evidence is reviewed in this article.

Intervention trials in pre-diabetes

Four well-controlled clinical trials, which evaluated the effect of lifestyle changes and/or pharmacological agents on the development of type 2 diabetes in individuals with IGT, have recently been published (table 1). Other intervention trials, including the Indian Diabetes Prevention Program (IDDP), Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) and Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR), are currently ongoing. The results from these trials will not be available for some years.

Diabetes Prevention Program

The Diabetes Prevention Program (DPP) is the largest of the trials[17,18] and addressed three questions:

1. Does either lifestyle intervention or treatment with metformin (a biguanide antihyperglycaemic agent) prevent or delay the onset of diabetes?

2. Do the two interventions differ in effectiveness?

Table 1. Key features of intervention studies

Study	Number of participants	Treatment	Change in weight (kg) or BMI (kg/m²)*	Relative reduction in risk of type 2 diabetes (%)
DPP	3,234	Placebo + standard lifestyle recommendations	+0.1	–
		Metformin + standard lifestyle recommendations	-2.1	31
		Intensive lifestyle intervention (culturally sensitive and individualised counselling on diet and exercise)	-5.6	58
FDPS	522	Diet + exercise (general oral and written information)	-0.8	–
		Intensive diet + exercise (detailed and individualised counselling)	-3.5	58
STOP-NIDDM	1,429	Diet + exercise + placebo (counselling on diet and exercise)	+0.3	–
		Diet + exercise + acarbose (counselling on diet and exercise)	-0.5	25
Da Qing	530	Control (general instructions for diet and/or activities)	-0.34*	–
		Diet (individualised counselling)	-0.30*	31
		Exercise (individualised counselling)	-0.46*	46
		Diet + exercise (individualised counselling)	-0.87*	42

All data are means except where indicated.

Key: BMI = body mass index; * = mean changes in BMI (kg/m²); DPP = Diabetes Prevention Program; FDPS = Finnish Diabetes Prevention Study; STOP-NIDDM = Study To Prevent Non-Insulin-Dependent Diabetes Mellitus

3. Does their effectiveness differ according to age, gender or ethnic group?

A further arm of the study had been designed to evaluate the potential of troglitazone (a thiazolidinedione), to prevent progression to type 2 diabetes. This part of the study was discontinued when troglitazone was withdrawn due to hepatotoxicity.

The DPP was a prospective trial involving 3,234 subjects from diverse ethnic/racial groups and was conducted in 27 clinical centres in the US. All subjects had IGT (plasma glucose concentrations of 7.8–11.0 mmol/L two hours after a 75 g oral tolerance test) and elevated fasting plasma glucose (FPG) concentrations of 5.3–6.9 mmol/L. The patients were randomly allocated to intervention with i) placebo tablets twice-daily plus standard lifestyle advice, ii) metformin 850 mg twice-daily plus standard lifestyle advice, or iii) intensive lifestyle changes alone (intensive nutrition and exercise counselling, which was individualised and culturally sensitive). The participants were followed up for an average of 2.8 years (range 1.8 to 4.6).

At the close of the study, 99.6% of the participants were alive, of whom 92.5% had attended a scheduled visit within the previous five months. In the intensive lifestyle intervention group, 50% of the subjects achieved the goal of weight loss ≥ 7% of body weight during the first six months of the study. The incidence of diabetes was 58% lower in the intensive lifestyle intervention group and 31% lower in the metformin-treated group, compared with the placebo-treated group.

Although there were no significant differences in the incidence of diabetes and risk reductions between the interventions on the basis of sex, race or ethnic group, intensive lifestyle intervention markedly reduced the incidence of diabetes in all age groups, but especially in older subjects (≥ 60 years old; 71% reduction), leaner subjects (initial BMI between 22 and 30 kg/m²; 65% reduction) and subjects with higher FPG (6.1–6.9 mmol/L; 63% reduction), compared with placebo. Metformin was as effective as intensive lifestyle intervention in reducing the incidence of diabetes in younger (22–44 years old; 44% reduction) and severely obese (BMI ≥ 35 kg/m²; 53% reduction) individuals, compared with placebo. Importantly, the beneficial effects of metformin in reducing the incidence of type 2 diabetes were sustained even after it was withdrawn for one to two weeks (25% reduction, relative to placebo).[19] This suggests that long-term exposure to metformin may induce chronic rather than acute changes in glucose tolerance in high-risk subjects.

The principal side effects of metformin are gastro-intestinal in nature, though this agent was selected for evaluation in the DPP partly on the basis of its relatively good tolerability profile.[17] Accordingly, rates of adherence to treatment (defined as patients taking 80% of their prescribed medication) were high throughout the study in both metformin and placebo groups (71% and 76%, respectively).[18,20] Only 7% of patients reported side effects as a barrier to continuing with study medication.[20]

Thus, evidence from the DPP favours metformin as a strategy for preventing or delaying the onset of type 2 diabetes in addition to its proven benefits in established type 2 diabetes. Health economic analyses from the same study have shown that the cost of metformin intervention relative to placebo was US $2,412 per participant and the cost of the intensive lifestyle intervention was US $3,540 per participant over three years[21] and that metformin intervention was cost-effective.[22]

Finnish Diabetes Prevention Study

The Finnish Diabetes Prevention Study (FDPS) compared the effects of a general diet and exercise (control group) intervention programme with an individualised and intensive diet and exercise intervention programme, in 523 Finnish subjects with IGT.[23] The subjects, recruited from five centres, were 40–65 years of age (mean age 55 years), overweight (mean BMI = 31 kg/m^2) and had IGT. They were followed up for a mean duration of 3.2 years.

Intensive diet and exercise intervention caused a significantly greater weight loss from baseline after two years, compared with the control group ($p<0.001$) and a significant 58% reduction ($p<0.001$) in the risk of developing type 2 diabetes in the intensive intervention group, relative to the control group. Nevertheless the study also demonstrated a cumulative incidence of diabetes in the intensive group of 11%, compared with 23% in the controls. In other words, there remained a high incidence of diabetes progression even with intensive diet and exercise therapy.

Study To Prevent Non-Insulin-Dependent Diabetes Mellitus

The Study To Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) trial was a multi-centre study, which investigated the effect of randomised treatment with the alpha-glucosidase inhibitor, acarbose 100 mg or placebo three times daily in 1,429 mainly white/europid subjects with IGT.[24] As in the FDPS, the subjects in this study were 40–70 years of age (mean age 54 years), overweight (mean BMI = 31 kg/m^2), had IGT, and FPG values of 5.6–7.7 mmol/L. Subjects were followed up for a mean of 3.3 years.

At the end of the study, the incidence of diabetes was 42% in the placebo group and 32% in the acarbose group. This corresponded to a significant 25% reduction in the risk of progression to diabetes with acarbose, relative to placebo ($p=0.0016$). In addition, acarbose treatment was associated with improved glucose tolerance. The beneficial effect of acarbose was independent of age, sex and BMI.

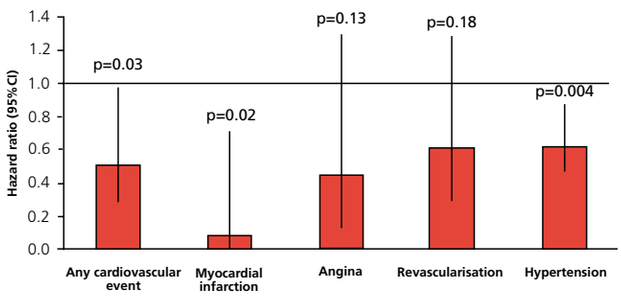
Gastro-intestinal side effects associated with acarbose treatment, however, may limit its use in pre-diabetic populations. In the STOP-NIDDM trial, 30% (211/714) of the subjects randomised to treatment with acarbose discontinued the study early, of whom 13% (93 patients) did so for gastro-intestinal side effects.[24] In contrast, only 18% (130/715) of the subjects treated with placebo discontinued early, including 3% for gastro-intestinal side effects.[24]

Da Qing IGT and Diabetes Study

The Da Qing study was also a multi-centre randomised study that assessed the effect of intervention with diet, exercise, or diet plus exercise, relative to control, in 530 Chinese subjects with IGT.[25] Subjects were middle-aged individuals, with a mean age of 45 years, a BMI of 26 kg/m^2, IGT, and a mean FPG of 5.59 mmol/L. Follow-up was conducted over a period of six years.

The cumulative incidence of diabetes in the diet (43.8%), exercise (41.1%) or diet plus exercise (46.0%) group was significantly lower when compared with the control group (67.7%; $p<0.05$). After adjusting for differences in baseline BMI and fasting glucose, this corresponded to significant reductions in risk of developing diabetes of 31% ($p=0.03$), 46% ($p<0.0005$) and 42% ($p<0.005$) in the diet, exercise, and diet plus exercise interventions, respectively.

Figure 3. Selected cardiovascular outcomes from the Study To Prevent Non-Insulin-Dependent Diabetes[15]



Footnote: Numbers of cardiovascular events that occurred in the study were: any event 47; myocardial infarction 13; angina 17; revascularisation 31. Outcomes not shown: congestive heart failure (2 events in the study); cerebrovascular accident/stroke (6 events); peripheral vascular disease (2 events)

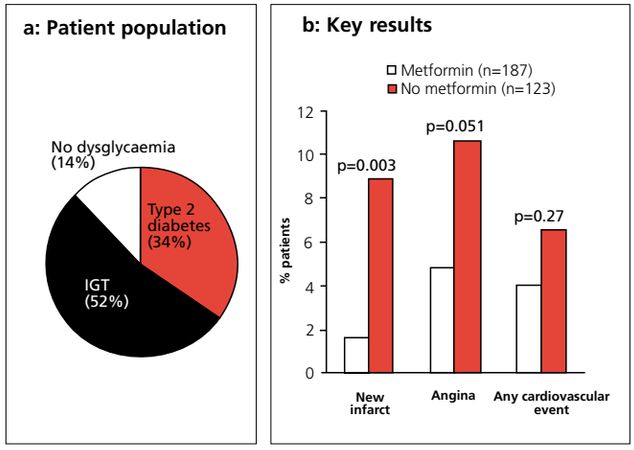
Prospects for preventing cardiovascular disease

Given the poor cardiovascular prognosis of type 2 diabetic patients, it would seem reasonable to expect that preventing diabetes would prevent the development of cardiovascular disease in those subjects. However, we have only limited data on the prevention of cardiovascular disease with oral antidiabetic agents, either before or after the development of diabetes.

Acarbose treatment was associated with a significant reduction in the risk of a combined cardiovascular end point, and of myocardial infarction, in the STOP-NIDDM trial (figure 3).[26] These data should be interpreted with caution, however, as they were based on a broadly-defined end point (coronary heart disease, cardiovascular death, congestive heart failure, cerebrovascular event, or peripheral vascular disease), and the study generated only a small number of cardiovascular events (47 events in total contributed to the combined end point).

Metformin-treated patients from the DPP are currently being followed for cardiovascular events and these data are eagerly awaited. Preliminary indications of the effectiveness of metformin in a largely dysglycaemic population are available from a study published more than two decades ago, in 310 patients with ischaemic cardiomyopathy and a history of myocardial infarction, who were followed for three years.[27,28] Most patients (86%) were dysglycaemic, either through the presence of type 2 diabetes or IGT (figure 4a). The principal outcomes from this study are shown in figure 4b. Re-infarction rates were reduced from 8.9% in the control group to 1.6% in patients receiving metformin ($p=0.003$), while the observed reduction in the inci-

Figure 4. Effect of metformin on cardiovascular prognosis in a mainly dysglycaemic population with a history of myocardial infarction[27,28]



Key: IGT = impaired glucose tolerance

Statistics were carried out post-hoc on data presented in the original publication[28]

dence of symptoms of angina almost achieved statistical significance (p=0.051). These reductions in cardiovascular events are in line with findings from the UK Prospective Diabetes Study (UKPDS), which showed that metformin reduced cardiovascular morbidity and mortality in overweight patients with type 2 diabetes.[6] In particular, significant risk reductions were reported for diabetes-related complications (32%), diabetes-related death (42%) and all-cause mortality (36%) compared with conventional diet intervention. No prospective data in type 2 diabetic patients are available for acarbose, although a recent meta-analysis of seven randomised, placebo-controlled studies involving a total of 2,180 patients revealed a significant reduction in the incidence of a combined cardiovascular end point, and of myocardial infarction.[29]

Putting the evidence into practice

These four large intervention studies from different countries suggest that appropriate intensive lifestyle changes or medical interventions are likely to decrease the risk of progression from IGT to type 2 diabetes in high-risk individuals from different regions and cultures. Lifestyle interventions and weight loss are important components of strategies for preventing or delaying the progression to type 2 diabetes in pre-diabetic individuals[12] but they are not effective in all subjects. Co-morbid conditions (e.g. arthritis) and cultural issues may present barriers to successful intervention.

Pharmacological interventions may be implemented more easily. The evidence base for the different drug options for prevention and treatment of type 2 diabetes is currently limited but suggests that pharmacological interventions are effective in preventing the onset of type 2 diabetes and may be effective in reducing the future burden of cardiovascular disease.

Key messages

- Type 2 diabetes has reached epidemic proportions and the increase in prevalence worldwide is set to continue
- People with pre-diabetic dysglycaemia have a substantially increased risk of developing type 2 diabetes and cardiovascular disease
- Intensive lifestyle changes can prevent or delay the onset of type 2 diabetes, but such changes are difficult to sustain over the long term
- Pharmacological interventions, including metformin and acarbose, have been shown to reduce progression from impaired glucose tolerance to type 2 diabetes and may improve cardiovascular outcomes

Conclusions

Both pre-diabetic dysglycaemia and clinical type 2 diabetes carry an unacceptable burden of cardiovascular disease. Governments must develop strategies designed to improve health by encouraging better understanding of the importance of diet and exercise in the prevention of obesity. Unfortunately lifestyle changes necessary to achieve effective prevention of type 2 diabetes are difficult to maintain long-term and pharmacological intervention may be more practicable for many. Large, well-designed studies with metformin or acarbose have demonstrated significant reductions in the incidence of type 2 diabetes in populations with impaired glucose tolerance, although the high withdrawal rate with acarbose may present a barrier to its successful use in this population. Preliminary evidence for prevention of cardiovascular disease is encouraging. The prevention or delay of type 2 diabetes is an urgent clinical priority.

Conflict of interest

Dr Scarpello has received study grants and occasional lecture fees from Merck Lipha.

References

1. International Diabetes Federation. New diabetes figures. (Press release Paris, 25th August 2003). Available from: http://www.idf.org/home/index.cfm
2. Zimmet P. The burden of type 2 diabetes: are we doing enough? *Diabetes Metab* 2003;**29**:6S9-6S18.
3. National Institute of Diabetes and Digestive and Kidney Diseases - National Institutes of Health. *Diabetes overview*. NIH Publication No. 03-3873, May 2003.
4. Fagot-Campagna A, Narayan VKM, Imperatore G. Type 2 diabetes in children. *BMJ* 2001;**322**:377-8.
5. American Diabetes Association. *Children and diabetes*. Available from: http://www.diabetes.org/info/risk/defauly4.jsp
6. UK Prospective Diabetes Study Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with

type 2 diabetes (UKPDS 34). *Lancet* 1998;**352**:854-65.
7. Gray A, Raikou M, McGuire A *et al*. Cost effectiveness of an intensive blood glucose control policy in patients with type 2 diabetes: economic analysis alongside randomised control trial (UKPDS 41). *BMJ* 2000;**320**:1373-8.
8. American Diabetes Association. Economic costs of diabetes in the U.S. *in 2002*. *Diabetes Care* 2003;**26**:917-32.
9. Uusitupa M. Lifestyles matter in the prevention of type 2 diabetes. *Diabetes Care* 2002;**25**:1650-1.
10. Ferrannini E. Pre-diabetes: to treat or not to treat? *Br J Diabetes Vasc Dis* 2003;**3**(suppl 1):S2-S5.
11. DECODE Study Group. Glucose tolerance and mortality: comparison of WHO and American Diabetic Association diagnostic criteria. *Lancet* 1999;**354**:617-21.
12. American Diabetes Association and National Institute of Diabetes and Digestive and Kidney Diseases. Position paper – the prevention or delay of type 2 diabetes. *Diabetes Care* 2002;**25**:742-9.
13. Eschwège E. The dysmetabolic syndrome, insulin resistance and increased cardiovascular (CV) morbidity and mortality in type 2 diabetes: aetiological factors in the development of CV complications. *Diabetes Metab* 2003;**29**:6S19-6S27.
14. Turner RC. The UK prospective diabetes study – a review. *Diabetes Care* 1998;**2**(suppl 3):C35-C38.
15. Chiasson J-L, Josse RG, Gomis R *et al*. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance - the STOP-NIDDM trial. *JAMA* 2003;**290**:486-94.
16. Qiao Q, Jousilahti P, Eriksson J, Tuomilehto J. Predictive properties of impaired glucose tolerance for cardiovascular risk are not explained by the development of overt diabetes during follow-up. *Diabetes Care* 2003;**26**:2910-14.
17. Diabetes Prevention Program Research Group. The Diabetes Prevention Programme. Design and methods for a clinical trial in the prevention of type 2 diabetes. *Diabetes Care* 1999;**22**:623-34.
18. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002;**346**:393-403.
19. Diabetes Prevention Program Research Group. Effects of withdrawal from metformin on the development of diabetes in the Diabetes Prevention Programme. *Diabetes Care* 2003;**26**:977-80.
20. Walker EA. Medication adherence in the Diabetes Prevention Program (DPP). *Diabetologia* 2003;**46**(suppl 2):A87.
21. Diabetes Prevention Program Research Group. Costs associated with the primary prevention of type 2 diabetes mellitus in the diabetes prevention program. *Diabetes Care* 2003;**26**:36-47.
22. Diabetes Prevention Program Research Group. Within-trial cost-effectiveness of lifestyle intervention or metformin for the primary prevention of type 2 diabetes. *Diabetes Care* 2003;**26**:2518-23.
23. Tuomilehto J, Lindstrom J, Eriksson JG *et al*. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 2001;**344**:1343-50.
24. Chiasson J-L, Josse RG, Gomis R *et al*. Acarbose for the prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. *Lancet* 2002;**359**:2072-7.
25. Pan XR, Li GW, Hu YH *et al.* Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes study. *Diabetes Care* 1997;**20**:537-44.
26. Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. *JAMA* 2003;**290**:486-94.
27. Sgambato S, Varricchio M, Tesauro P, Passariello N, Carbone L. L'utilisation de la metformin dans la cardiopathie ischémique. *Clin Ter* 1980;**94**:77-85.
28. Scarpello JHB. Improving survival with metformin: the evidence base today. *Diabetes Metab* 2003;**29**:6S36-6S43.
29. Hanefeld M, Cagatay M, Petrowitsch T, Neuser D, Petzinna D, Rupp M. Acarbose reduces the risk for myocardial infarction in type 2 diabetic patients: meta-analysis of seven long-term studies. *Eur Heart J* 2004; **25**:10-16.