Primary Prevention of Cardiovascular Disease in People With Dysglycemia

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Cardiovascular disease accounts for a great majority of deaths in patients with type 2 diabetes. According to the World Health Organization, the prevalence of cardiovascular disease in diabetic patients ranges from 26 to 36%. Fatality rate after myocardial infarction is greater in diabetic patients, and overall prognosis after coronary heart disease is worse. Based on these observations, it has been proposed that diabetes should be considered as a coronary heart disease risk equivalent. If that is the case, prevention of diabetes and early intervention should be pursued. This view is supported by the notion that cardiovascular risk is already increased in people with impaired glucose tolerance. Moreover, higher-than-optimum blood glucose is a major cause of cardiovascular mortality in most world regions of the world. Whether dysglycemia is a marker for a more complex metabolic condition or may directly contribute to excess cardiovascular risk is still a matter of debate. However, experimental work has shown how increased glucose level can trigger multiple mechanisms of susceptibility to atherosclerosis, and diabetes prevention trials have indicated that along with reduction of the rate of conversion toward diabetes, significant improvement in cardiovascular risk factors occurs. Moreover, in the STOP-NIDDM trial, targeting postprandial glucose was associated with reduction in new cases of hypertension, myocardial infarction, and any cardiovascular events. In conclusion, dysglycemia should be included in the list of established cardiovascular risk factors and early treatment introduced in the attempt to improve cardiovascular morbidity and mortality.

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Diabetes is associated with great risk of morbidity and mortality, with cardiovascular disease (CVD) accounting for up to two-thirds of all deaths in the diabetic population (1). A number of longitudinal epidemiological studies have shown that the risk of CVD mortality in diabetic patients is more than double compared with age-matched people (2,3). Among type 2 diabetic patients, even after correction for other known cardiovascular risk factors, the incidence of myocardial infarction or stroke is increased two- to threefold and the risk of death is increased twofold (4), suggesting that some feature of diabetes must confer such an excessive propensity toward CVD.

Hyperglycemia is the diagnostic feature for diabetes, the target for antidiabetic therapy, and, together with A1C, the marker of glycemic control. Maintaining good glycemic control has been associated with marked reduction in the risk of developing retinopathy, nephropathy, and neuropathy in both type 1 (5) and type 2 (6,7) diabetic patients. On the other hand, intensive diabetes therapy has long-term beneficial effects on the risk of CVD in both type 1 and type 2 diabetes (8).

From an epidemiological point of view, there is evidence that the risk of cardiovascular mortality increases with the increase of plasma glucose concentrations and A1C levels (9,10). However, while the effect of plasma glucose levels appears to be preponderant in determining microvascular risk, this does not seem to be the case for macrovascular complications.

Analysis of the U.K. Prospective Diabetes Study (UKPDS) data clearly indicates that for the same degree of A1C, particularly in its low range, the incidence of myocardial infarction is much greater than that of retinopathy (11). This apparent paradox can only be resolved by acknowledging the multifactorial nature of cardiovascular risk in type 2 diabetic patients. Many of these factors have emerged in the UKPDS as well. Thus, in a ranking analysis, A1C turned out to be the third most important factor in determining cardiovascular risk in type 2 diabetic patients (6).

This approach, however, underscores the intimate relationship existing among cardiovascular risk factors in diabetes. In support for a catalytic effect of diabetic hyperglycemia are the classic results of the Multiple Risk Factor Intervention Trial (MRFIT) (12). In that study, cardiovascular mortality was shown to increase with the number of coexisting cardiovascular risk factors (hypercholesterolemia, hypertension, smoking). Notably, the same occurred in the diabetic population, though the risk was magnified by concomitant hyperglycemia. More recently, re-analysis of the UKPDS results have clearly documented a powerful interaction between glycemic and blood pressure control in increasing risk for all-cause mortality, myocardial infarction, and stroke (13).

An even more direct association between glycemic control and severity of the cardiovascular risk profile can be postulated. In a recent analysis performed in our institution, the prevalence of metabolic syndrome (based on the Adult Treatment Panel III criteria) increased with the increase of A1C (Fig. 1), suggesting that improvement of glycemic control may be associated with beneficial influence of many other CVD risk factors (14). This association seems to exceed the diabetic range. In the past few years, we have

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Abbreviations: CVD, cardiovascular disease; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; UKPDS, U.K. Prospective Diabetes Study.

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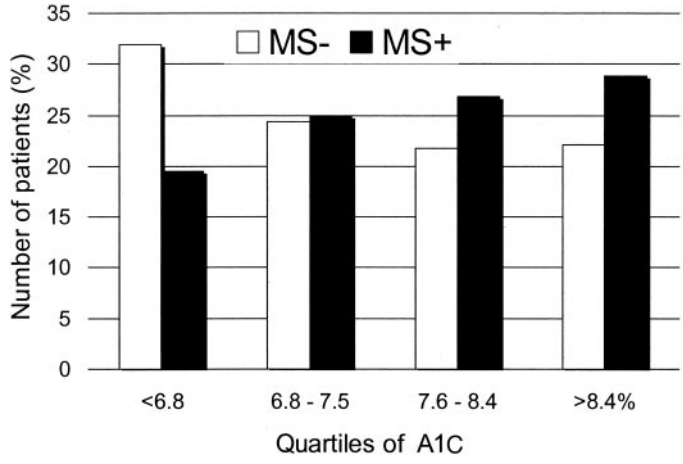

Figure 1—*Prevalence of metabolic syndrome (MS) in type 2 diabetes, according to glycemic control.*

recruited 1,300 individuals in an Italian multicenter study designed to identify subjects at risk of developing type 2 diabetes: Genetic and Pathophysiology of Type 2 Diabetes Evolution (GENFIEV). When this population was analyzed in terms of prevalence of the metabolic syndrome, a trend was found for an increase in such prevalence as a function of glucose tolerance. A similar relationship between glucose tolerance and cardiovascular events has been reported (15–17). In the Diabetes Epidemiology Collaborative Analysis of Diagnostic Criteria in Europe (DECODE), the risk for CVD, coronary artery disease, and stroke increased, moving from a condition of impaired fasting glucose (IFG) to impaired glucose tolerance (IGT) to overt diabetes (18). These observations support the view that glucose is a continuous risk factor for cardiovascular mortality (19).

HYPERGLYCEMIA AS A CARDIOVASCULAR RISK FACTOR IN THE NONDIABETIC SUBJECT

— The first indication that hyperglycemia may represent a cardiovascular risk factor dates back to 1965 when the Bedford Study (20) and the Tecumseh Study (21) were published. These cross-sectional studies indicated that increased blood glucose levels were associated with greater cardiovascular mortality. However, it was only 15 years later that the first systematic analysis of this relationship appeared. The International Collaborative Group reviewed findings from 11 different studies with an observation period of 4–15 years (22). However, this analysis did not yield univocal results, and it was not possible to support a clear-cut association between asymptomatic hyperglycemia and CVD (22). A close association between fasting plasma glucose or A1C levels and CVD was found during a 10-year follow-up in the Uusitupa study, which included 133 newly diagnosed diabetic subjects (22).

Coutinho et al. (17) carried out a meta-analysis of 20 studies for a total of 95,783 nondiabetic subjects who had, during a mean follow-up of 12.4 years, 3,707 cardiovascular events. In this meta-analysis, an exponential relationship between the risk of cardiovascular events and both fasting and postload plasma glucose levels was found. Such a relationship extended below diagnostic blood glucose levels for IFG or IGT. The Cardiovascular Health Study (23) assessed cardiovascular risk factors in people aged ≥65 years and showed that CVD was related to both fasting and postchallenge glucose. Even if much research has been performed in Western populations, recent evidence demonstrated similarly increased risks in Asian populations. Analysis of cohorts from the Asia Pacific region indicates a positive continuous association between usual blood glucose and cardiovascular risk. This association holds for glucose levels as low as 4.9 mmol/l, i.e., below diagnostic fasting plasma glucose for diabetes and IGT (24). Evidence has been recently published to support that higher-than-optimum blood glucose is a major cause of cardiovascular mortality in most world regions (25). While diabetes was associated with a total of 959,000 deaths, 1,490,000 deaths for ischemic heart disease and 709,000 from stroke were attributable to higher-than-optimum blood glucose, accounting for 21 and 13% of all deaths from those conditions.

An even greater cardiovascular risk is likely to be associated with excessive postload glucose levels (18,26–29). The DECODE study (26) evaluated data from 13 epidemiologic studies and found that the mortality risk of IFG subjects was 1.2, while it was 1.5 in IGT individuals. Subsequent analysis of the DECODE database explored the association between categories of glucose tolerance and ischemic heart disease, CVD, and mortality for all causes (18). Upon adjustment for BMI, blood pressure, total cholesterol, and smoking habit, relative mortality risk did not increase as a function of fasting plasma glucose levels, while it remained highly significant for postload glucose values. Moreover, when excess mortality was considered, no association was found with isolated fasting hyperglycemia, whereas IGT and IFG+IGT accounted for 44 and 14% of the excess mortality, respectively. Similarly, in the Funagata Diabetes Study (27), cardiovascular mortality in IGT was very close to that of subjects with diabetes and much greater that that in IFG individuals. Among 3,092 adults aged 30–74 years (28), an increased relative risk of all-cause mortality of 1.6 (95% CI 1.0–2.6) was found in subjects with newly diagnosed diabetes based on isolated postchallenge hyperglycemia (glucose ≥11.1 mmol/l), whereas the relative risk of death in those with known diabetes was 2.1 (95% CI 1.4–3.2). Mortality was also increased in IGT subjects who had a relative risk of 1.3 (95% CI 1.0–1.6). In the Hoorn Study (29), the relative risk of cardiovascular mortality started to be significant from a fasting glucose level of 6.1 mmol/l onward. Both postloading glucose and A1C showed a linear correlation to cardiovascular risk, even in the nondiabetic range. However, the authors of this study recently showed that the association between IFG and the risk of CVD mortality depends on the conversion to diabetes during the follow-up (30). In fact, subjects who converted from IFG to diabetes had a more than twofold risk of CVD mortality (IFG 6.1: 2.47 [1.17–5.19]; IFG 5.6: 2.14 [1.12–4.10]) than subjects with normal fasting glucose, whereas IFG subjects who did not develop diabetes did not have significantly higher CVD mortality risks (IFG 6.1: 1.50 [0.72–3.15]; IFG 5.6: 1.15 [0.69–1.93]).

A1C level provides an integrated measure of glycemic control, including

both fasting and postprandial glucose levels. A meta-analysis of observational studies has documented increased risk of CVD associated with higher levels of A1C in diabetic patients (31).

Unfortunately, few longitudinal studies are available in nondiabetic subjects. In a study carried out in the U.K. including ~5,000 individuals with A1C >5.0%, a direct correlation was found with total and coronary heart disease mortality (15), with a 41% increase in the relative risk per percent point increase in A1C. Similar results have been produced in a Dutch study including 2,363 nondiabetic individuals, in whom the mortality risk increased by 51% per 1.4% point of A1C (29). In the Rancho Bernardo Study (32), an association between A1C and cardiovascular mortality was found among women but not among men. The association between A1C levels and peripheral arterial disease has been recently analyzed in the National Health and Nutrition Examination Survey (NHANES) 1999–2002 (33). The study confirmed that A1C was a significant predictor of peripheral arterial disease, an association that persisted even within the normal range and after multivariable adjustment.

Whether hyperglycemia is the culprit of such an elevated cardiovascular risk remains to be elucidated, since it may be a simple but very useful marker for a condition characterized by concomitance of multiple cardiovascular risk factors. Participants in the San Antonio Heart Study who did not have diabetes at baseline but developed type 2 diabetes during an 8-year follow-up had higher total and LDL cholesterol, triglycerides, BMI, and blood pressure measurements and lower HDL cholesterol than subjects who did not develop type 2 diabetes (34). Based on these observations, the "ticking clock" hypothesis was formulated, which postulates that "the clock for coronary heart disease starts ticking before the onset of clinical diabetes" (34). The findings of the Nurses' Health Study (35) provide support to this hypothesis, showing that the risk for CVD occur long before the onset of overt hyperglycemia. In this large prospective cohort study, an elevated risk of myocardial infarction and stroke was found before clinical diagnosis of type 2 diabetes, compared with women who remained nondiabetic throughout the study. Increased risk persisted in obese and nonobese women as well as in those with or without a family history of diabetes (35). Cardiovascular risk was already increased 15 years before diagnosis of diabetes and increased further upon clinical diagnosis of the disease. In that study, women converting to type 2 diabetes had a more atherogenic risk profile (e.g., higher BMI values and greater prevalence of hypertension and hypercholesterolemia) than individuals retaining normal glucose tolerance during the study (35).

In the Botnia Study, ~50% of the subjects classified as IFG and/or IGT also met the diagnosis of metabolic syndrome, and these individuals had greater risk for both coronary heart disease and stroke (36). This finding is in agreement with the results of a pooled analysis of several prospective studies published from 1988 to 2004 indicating that the relative risk for CVD in individuals with metabolic syndrome, as defined by National Cholesterol Education Program Adult Treatment Panel III, was 1.65 (95% CI 1.38–1.99) and that the relative risks for all-cause mortality and diabetes were 1.27 (0.90–1.78) and 2.99 (1.96–4.57), respectively (37).

MECHANISMS OF VASCULAR DAMAGE OF HYPERGLYCEMIA

— Pre-diabetic dysglycemia acts in concert with other cardiovascular risk factors within the picture of the metabolic syndrome. Subjects with dysglycemia often have insulin resistance and hyperinsulinemia, elevated blood pressure, high total and VLDL triglycerides, low HDL cholesterol, small and dense LDL, central adiposity, elevated levels of plasminogen activator inhibitor 1, and low-grade inflammation (38). In spite of all this, experimental evidence supports a direct effect of mild alteration of glucose homeostasis on the atherogenic process. Early alterations of glucose homeostasis is often heralded by postprandial hyperglycemia. Higher and persistent elevation of postprandial plasma glucose levels contribute significantly to overall glycemic exposure of body tissues (39). Moreover, excessive and repeated glucose excursions lead to increased glycemic variability. Overall, glycemic exposure and glycemic variability can both contribute to favor development of atherosclerosis. The arterial wall is indeed a critical target for such glycemic insult. Protein glycosylation causes cross-linking of collagen and other extracellular matrix proteins in the arterial wall, increasing susceptibility to atherosclerosis. Glycosylation of LDL results in more atherogenic particles, macrophage activation, and foam cell formation. A more direct action is exerted on endothelial cells leading to endothelial dysfunction, an early manifestation of atherosclerosis, and a strong predictor for CVD (40).

In type 2 diabetes, glucose fluctuations during postprandial periods and, more generally, during swings exhibited a more specific triggering effect on oxidative stress than chronic hyperglycemia (41). Several in vitro studies have demonstrated increased expression of markers of oxidative stress in cells exposed to fluctuating glucose concentrations (42). Hyperglycemia in non–insulin-dependent tissues such as endothelium results in overproduction of superoxide and free radicals by the mitochondrial electron transport chain. Free radicals may mediate some of the effects associate with hyperglycemia: vasoconstriction, activation of coagulation, and increased adhesion molecule expression. As described by Brownlee (43), NADPH inhibition by superoxide slows down the glycolytic flux and leads to accumulation of glycolytic precursors, which in turn allow activation of pathways that normally account for a small proportion of intracellular glucose metabolism: the polyoil pathway, the hexosamine pathway, protein kinase C activation, and the advanced glycation end product formation. Chronic and acute hyperglycemia alter the activity of protein kinase C (44), a key enzyme in signal transduction. Its activation increases secretion of endothelin, type IV collagen, and fibronectin; enhances expression of adhesion molecules in endothelial cells; and activates macrophage migration processes.

Postprandial hyperglycemia and glycemic instability are also associated with a proinflammatory state, as indicated by generation of advanced glycation end products, increased C-reactive protein, and tumor necrosis factor-α. Acute hyperglycemia also activates carbonyl stress, leading to formation of highly reactive species such as 3-deoxyglucosone and methylglyoxal (45).

In summary, epidemiological data linking dysglycemia with cardiovascular risk are supported by experimental findings illustrating the mechanisms through which even mild alterations in glucose homeostasis may favor development and progression of the atherosclerotic lesion.

CARDIOVASCULAR RISK REDUCTION IN DYSGLYCEMIC SUBJECTS — Final evidence for glucose as a cardiovascular risk factor can be based only on intervention studies. The heated discussion about the 15% reduction of myocardial infarction in the UKPDS has not yet settled (11). Still, epidemiologic analysis of those data has indicated a 14% risk reduction for myocardial infarction for each 1% reduction in A1C (11). These results have received further support from recent work in type 1 diabetic patients. In the follow-up report of the Diabetes Control and Complications Trial, reduced carotid intima-media thickness was found in intensively treated patients compared with those on conventional insulin therapy (46). Reduced progression of atherosclerosis was then confirmed by a more recent publication reporting a 42% reduction of the risk of any predefined CVD outcome ($P = 0.02$) and 57% reduction of the risk of the first occurrence of nonfatal myocardial infarction, stroke, or death from CVD ($P = 0.02$) (47).

If strict glycemic control is recommended to reduce risk for micro- and macrovascular complications, a large number of individuals still present signs of cardiovascular involvement at the time of diabetes diagnosis. Therefore, effort should be made to reduce cardiovascular risk at the time when dysglycemia develops rather than when hyperglycemia develops. A few years ago, the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) (48) identified diabetes as a coronary heart disease risk equivalent. If that is the case, prevention of diabetes should be pursued with the same effort paid to reduce other known cardiovascular risk factors. Direct evidence for such an opportunity is still scanty, but all diabetes prevention trials indicate a positive effect on cardiovascular risk profile.

In the Finnish Diabetes Prevention Study (49), lifestyle modification in IGT patients reduced conversion to diabetes by 58%. Along with lower risk of diabetes, almost all cardiovascular risk factors were significantly reduced. At the end of the 3.2-year follow up, diastolic and systolic blood pressure, serum triglycerides, and plasma insulin levels were all much lower in the intervention group than in control individuals (49). The results of the Diabetes Prevention Program (50) provide further evidence of the potential benefit of lifestyle changes beyond diabetes prevention. Hypertension was present in 30% of participants at study entry and then increased in the placebo and metformin groups, although it significantly decreased with intensive lifestyle intervention. Triglyceride levels fell in all treatment groups, but fell significantly more with intensive lifestyle intervention. Total cholesterol and LDL cholesterol levels were similar among treatment groups. Intensive lifestyle intervention significantly increased the HDL cholesterol level and reduced the cumulative incidence of the proatherogenic LDL phenotype B. After a 3-year follow-up, the use of pharmacologic therapy to achieve established goals in the intensive lifestyle group was 27–28% less for hypertension and 25% less for hyperlipidemia compared with placebo and metformin groups. Lifestyle intervention also reduced levels of nontraditional cardiovascular risk factors, such as C-reactive protein, relative to both placebo and to a lesser degree to metformin (51). Finally, incidence of the metabolic syndrome was reduced by 41% in the lifestyle group ($P < 0.001$) and by 17% in the metformin group ($P < 0.03$) compared with placebo (52).

Though lifestyle modification appears to be highly effective, use of medications for prevention of or early treatment of dysglycemia also results in the improvement of cardiovascular risk factors, as indicated by the use of metformin in the Diabetes Prevention Program. Anti-obesity drugs such as orlistat, an inhibitor of pancreatic and gastrointestinal lipases, have been shown to reduce conversion toward diabetes in obese individuals irrespective of their glucose tolerance. In the XENDOS (Xenical in the Prevention of Diabetes in Obese Subjects) trial ($n = 3,305$ obese nondiabetic individuals), orlistat, combined with lifestyle changes, reduced the incidence of type 2 diabetes compared with placebo (plus lifestyle changes) by 37.3% ($P = 0.0032$) (54). In those individuals, a 7-kg body weight reduction was associated with lower levels of LDL cholesterol and greater reduction blood pressure values as compared with control subjects (54). Rimonabant, a cannabinoid receptor (CB1) antagonist, has generated even greater expectation. The RIO (Rimonabant in Obesity) studies have shown that rimonabant, at the dose of 20 mg/day, causes >5% weight loss in 30–40% of patients and >10% in 10–20% of them compared with diet alone over a 2-year period, as well as an extra 8–10% increase in HDL cholesterol and a 10–30% reduction in triglycerides. In patients with type 2 diabetes, the treatment results in improvement in insulin resistance, glycemic control, adipokines, and inflammatory proteins (54–56).

A 62% reduction in diabetes and greater conversion to normal glucose tolerance has been documented in the DREAM (Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication) study in IGT subjects treated with 8 mg rosiglitazone compared with the control group. Active treatment was also associated with modest though highly significant reduction in diastolic and systolic blood pressure (57). No effect was found in terms of cardiovascular events with the exception of increased risk for heart failure in people on rosiglitazone. However, none of the prevention trials so far discussed was powered nor designed to detect an effect on cardiovascular events. Still, supportive observation is available. The Malmö Prevention Study was carried out 30 years ago (58). In that study, 147 pre-diabetic individuals were randomly treated with diet and placebo, diet and tolbutamide, or no therapy at all. As expected, diet was effective in reducing conversion to diabetes when compared with no treatment. However, even more effective was the concomitant use of tolbutamide, with not a single case of diabetes observed over a 10-year follow-up. Fifteen years after the publication of those results, data of a longer follow-up were reported showing significant reduction in all-cause mortality and ischemic heart disease in individuals initially treated with tolbutamide (60). The study is questionable because of small sample size. The NAVIGATOR study will test a similar hypothesis in >9,000 dysglycemic individuals by targeting postprandial glucose with nateglinide (61).

The results of the Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) (62) seem to confirm the role for specific treatment of postprandial glucose levels, at least in individuals who still have a moderate increase in fasting plasma glucose concentration. In IGT patients, treatment with acarbose, an intestinal α-glucosidase inhibitor, not only reduced conversion to type 2 diabetes by 30%, but was also associated with reduction of the risk of any cardiovascular event by 49%, of an acute myocardial infarction by 91%, and of developing hy-

pertension by 34%. Still lacking is the evidence that strict maintenance of normal fasting plasma glucose levels also may reduce cardiovascular risk. The results of the ORIGIN study may provide an initial answer to the question (63).

CONCLUSIONS — In summary, epidemiologic data support the hypothesis of a direct and independent relationship between blood glucose levels and CVD. The lack of a clear-cut threshold value in diabetic patients and the persistence of the relationship in the nondiabetic population suggest that blood glucose is a continuous variable, similarly to other CVD risk factors. Prevention or delay in onset of diabetes is of utmost importance because chronic hyperglycemia is associated with CVD, and the risk starts to increase long before the onset of clinical diabetes.

Moreover, dysglycemia is often associated with other risk cardiovascular factors to result in the metabolic syndrome, a condition loaded with high propensity to atherosclerosis. Reducing the burden of CVD will then require identification of initial alteration of glucose homeostasis, as well as careful search of any associated CV risk factor. Lifestyle modification has been shown to be quite effective in preventing conversion of IGT patients toward overt diabetes, also resulting in effective improvement of many cardiovascular risk factors. Pharmacological intervention may provide benefit as well, although further studies are needed to characterize the benefits of these therapeutic strategies to reduce cardiovascular risk. In the meantime, clinicians should evaluate and treat all cardiovascular risk factors (64), including dysglycemia.

References

1. Haffner SM, Lehto S, Ronnemaa T, Pyorala L, Laakso M: Mortality from coronary heart disease in subjects with type 2 diabetes and non-diabetic subjects with and without prior myocardial infarction. *N Engl J Med* 339:229–234, 1998
2. Kannel WB, McGee DL: Diabetes and cardiovascular disease: the Framingham Study. *JAMA* 241:2035–2038, 1979
3. Pan WH, Cedres LB, Liu K, Dyer A, Schoenberger JA, Shekelle RB, Stamler R, Smith D, Collette P, Stamler J: Relationship of clinical diabetes and asymptomatic hyperglycemia to risk of coronary heart disease mortality in men and women. *Am J Epidemiol* 123:504–516, 1986
4. Almadal T, Scharling H, Jensen JS, Vestrgaard H: The independent effect of type 2 diabetes mellitus on ischemic heart disease, stroke, and death. *Arch Intern Med* 12:1422–1426, 2004
5. Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:977–986, 1993
6. UK Prospective Diabetes Study (UKPDS) Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352:837–853, 1998
7. Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, Kojima Y, Furuyoshi N, Shichiri M: Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. *Diabetes Res Clin Pract* 28:103–117, 1995
8. Stettler C, Allemann S, Juni P, Cull CA, Holman RR, Egger M, Krahenbuhl S, Diem P: Glycemic control and macrovascular disease in types 1 and 2 diabetes mellitus: meta-analysis of randomized trials. *Am Heart J* 152:27–38, 2006
9. Laakso M: Glycemic control and the risk for coronary heart disease in patients with non-insulin-dependent diabetes mellitus: the Finnish Studies. *Ann Intern Med* 124: 127–130, 1996
10. Wei M, Gaskill SP, Haffner SM, Stern MP: Effects of diabetes and level of glycemia on all-cause and cardiovascular mortality. *Diabetes Care* 21:1167–1173, 1998
11. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley Se, Cull CA, Hadden D, Turner RC, Holman RR: Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 321:405–412, 2000
12. Stamler J, Vaccaro O, Neaton JD, Wentworth D, for the Multiple Risk Factor Intervention Trial Research Group: Diabetes, other risk factors, and 12-year cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 16:434–444, 1993
13. Stratton IM, Cull CA, Adler AI, Matthews DR, Neil HA, Holman RR: Additive effects of glycaemia and blood pressure exposure on risk of complications in type 2 diabetes: a prospective observational study (UKPDS 75). *Diabetologia* 49:1761–1769, 2006
14. Bianchi C, Penno G, Malloggi L, Barontini R, Corfini M, Giovannitti MG, Di Cianni G, Del Prato S, Miccoli R: Non-traditional markers of atherosclerosis potentiate the risk of coronary heart disease in patients with type 2 diabetes and metabolic syndrome. *Nutr Metab Cardiovasc Dis*. In press
15. Khaw KT, Wareham N, Luben R, Bingham S, Oakes S, Welch A, Day N: Glycated haemoglobin, diabetes, and mortality in men in Norfolk cohort of European Prospective Investigation of Cancer and Nutrition (EPIC-Norfolk). *BMJ* 322:15–18, 2001
16. DECODE Study Group, European Diabetes Epidemiology Group: Is the current definition for diabetes relevant to mortality risk from all causes and cardiovascular and noncardiovascular diseases? *Diabetes Care* 26:688–696, 2003
17. Coutinho M, Gerstein HC, Wang Y, Yusuf S: The relationship between glucose and incident cardiovascular events. a metaregression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. *Diabetes Care* 22:233–240, 1999
18. DECODE Study Group: Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-hour diagnostic criteria. *Arch Intern Med* 161:397–405, 2001
19. Gerstein HC: Is glucose a continuous risk factor for cardiovascular mortality? *Diabetes Care* 22:659–660, 1999
20. Jarrett RJ, McCartney P, Keen H: The Bedford survey: ten year mortality rates in newly diagnosed diabetics, borderline diabetics and normoglycaemic controls and risk indices for coronary heart disease in borderline diabetics. *Diabetologia* 22:79–84, 1982
21. Butler WJ, Ostrander LD Jr, Carman WJ, Lamphiear DE: Mortality from coronary heart disease in the Tecumseh study: long term effect of diabetes mellitus, glucose tolerance and other risk factors. *Am J Epidemiol* 121:541–547, 1985
22. Uusitupa MIJ, Niskanen LK, Voutilainen E, Pyorala M, Forhan A, Eschewege E: Ten year cardiovascular mortality in relation to risk factors and abnormalities in lipoproteins composition in type 2 (non-insulin-dependent) diabetic and non-diabetic subjects. *Diabetologia* 36:1175, 1993
23. Barzilay JI, Spiekerman CF, Wahl PW, Kuller LH, Cushman M, Furberg CD, Dobs A, Polak JF, Savage PJ: Cardiovascular disease in older adults with glucose disorders: comparison of American Diabetes Association criteria for diabetes mellitus and WHO criteria. *Lancet* 354:622–625, 1999
24. Asia Pacific Cohort Studies Collaboration: Blood glucose and risk of cardiovascular disease in the Asia Pacific region. *Diabetes Care* 27:2836–2842, 2004
25. Danaei G, Lawes CM, Vander Hoorn S, Murray CJ, Ezzati M: Global and regional mortality from ischaemic heart disease and stroke attributable to higher-than-optimum blood glucose concentration: comparative risk assessment. *Lancet* 368:

1651–1659, 2006
26. DECODE Study Group, on behalf of the European Diabetes Epidemiology Group: Glucose tolerance and mortality: comparison of WHO and American Diabetes Association diagnostic criteria. *Lancet* 354: 617–621, 1999
27. Tominaga M, Eguchi H, Manaka H, Igarashi K, Kato T, Sekikawa A: Impaired glucose tolerance is a risk factor for cardiovascular disease, but not impaired fasting glucose: the Funagata Diabetes Study. *Diabetes Care* 22:920–924, 1999
28. Saydah SH, Miret M, Sung J, Varas C, Gause D, Brancati FL: Post-challenge hyperglycaemia and mortality in a national sample of U.S. adults. *Diabetes Care* 24: 1397–1402, 2001
29. de Vegt F, Dekker JM, Ruhe HG, Stehouwer CD, Nijpels G, Bouter LM, Heine RJ: Hyperglycaemia is associated with all-cause and cardiovascular mortality in the Hoorn population: the Hoorn Study. *Diabetologia* 42:926–931, 1999
30. Rijkelijkhuizen JM, Nijpels G, Heine RJ, Bouter LM, Stehouwer CD, Dekker JM: High risk of cardiovascular mortality in individuals with impaired fasting glucose is explained by conversion to diabetes: the Hoorn study. *Diabetes Care* 30:332–336, 2007
31. Selvin E, Marinopoulos S, Berkenblit G, Rami T, Brancati FL, Powe NR, Golden SH: Meta-analysis: glycosylated haemoglobin and cardiovascular disease in diabetes mellitus. *Ann Intern Med* 141:421–431, 2004
32. Park S, Barrett-Connor E, Wingard DL, Shan J, Edelstein S: GHb is a better predictor of cardiovascular disease than fasting or postchallenge plasma glucose in women without diabetes: the Rancho Bernardo Study. *Diabetes Care* 19:450–456, 1996
33. Muntiner P, DeSalvo KB, Wildman RP, Chen J, Reynolds K, Fonseca V: Relationship between HbA1c level and peripheral arterial disease. *Diabetes Care* 28:1981–1987, 2005
34. Haffner SM, Stern MR, Hazuda HE, Mitchell BD, Patterson JK: Cardiovascular risk factors in confirmed prediabetic individuals: does the clock for coronary heart disease start ticking before the onset of clinical diabetes? *JAMA* 263:2893–2898, 1990
35. Hu FB, Stampfer MJ, Haffner SM, Solomon CG, Willett WC, Manson JE: Elevated risk of cardiovascular disease prior to clinical diagnosis of type 2 diabetes. *Diabetes Care* 25:1129–1134, 2002
36. Isomaa B, Almgren P, Tuomi T, Forsen B, Lahti K, Nissen M, Taskinen MR, Groop L: Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care* 24:683–689, 2001
37. Ford ES: Risks for all-cause mortality, cardiovascular disease, and diabetes associated with the metabolic syndrome: a summary of the evidence. *Diabetes Care* 28:1769–1778, 2005
38. De Fronzo R, Ferrannini E: Insulin resistance: a multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. *Diabetes Care* 14:173–194, 1991
39. Del Prato S: In search of normoglycaemia in diabetes: controlling postprandial glucose. *Int J Obes Relat Metab Disord* 26 (Suppl. 3):S9–S17, 2002
40. Behrendt D, Granz P: Endothelial function: from vascular biology to clinical application. *Am J Cardiol* 90 (Suppl.):40L–48L, 2002
41. Monnier L, Mas E, Ginet C, Michel F, Villon L, Cristol JP, Colette C: Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. *JAMA* 295:1681–1687, 2006
42. Ceriello A: Impaired glucose tolerance and cardiovascular disease: the possible role of post-prandial hyperglycemia. *Am Heart J* 147:803–807, 2004
43. Brownlee M: Biochemistry and molecular cell biology of diabetic complications. *Nature* 414:813–820, 2001
44. Ceolotto G, Gallo A, Miola M, Sartori M, Trevisan R, Del Prato S, Semplicini A, Avogaro A: Protein kinase C activity is acutely regulated by plasma glucose concentration in human monocytes in vivo. *Diabetes* 48:1316–1322, 1999
45. Beisswenger PJ, Howell SK, O'Dell RM, Wood ME, Touchette AD, Szwergold BS: alpha-Dicarbonyls increase in the postprandial period and reflect the degree of hyperglycemia. *Diabetes Care* 24:726–732, 2001
46. Nathan DM, Lachin J, Cleary P, Orchard T, Brillon DJ, Backlund JY, O'Leary DH, Genuth S, Diabetes Control and Complications Trial, Epidemiology of Diabetes Interventions and Complications Research Group: Intensive diabetes therapy and carotid intima-media thickness in type 1 diabetes mellitus. *N Engl J Med* 348: 2294–2303, 2003
47. Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ, Raskin P, Zinman B, Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group: Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* 353:2643–2653, 2005
48. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III): Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 106:3143–3421, 2002
49. Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, Keinanen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, Uusitupa M, for the Finnish Diabetes Prevention Study Group: Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 344:1343–1350, 2001
50. Diabetes Prevention Program Research Group: Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 346:393–403, 2002
51. Diabetes Prevention Program Research Group: Intensive lifestyle intervention or metformin on inflammation and coagulation in participants with impaired glucose tolerance. *Diabetes* 54:1566–1572, 2005
52. Orchard TJ, Temprosa M, Goldberg R, Haffner S, Ratner R, Marcovina S, Fowler S, Diabetes Prevention Program Research Group: The effect of metformin and intensive lifestyle intervention on the metabolic syndrome: the Diabetes Prevention Program randomized trial. *Ann Intern Med* 142:611–619, 2005
53. Torgerson JS, Hauptman J, Boldrin MN, Sjostrom L: XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. *Diabetes Care* 27:155–161, 2004
54. Pi-Sunyer FX, Aronne LJ, Heshmati HM, Devin J, Rosenstock J, RIO-North America Study Group: Effect of rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factors in overweight or obese patients: RIO-North America: a randomized controlled trial. *JAMA* 295:761–775, 2006
55. Van Gaal LF, Rissanen AM, Scheen AJ, Ziegler O, Rossner S: Effects of the cannabinoid-1 receptor blocker rimonabant on weight reduction and cardiovascular risk factors in overweight patients: 1-year experience from the RIO-Europe study. *Lancet* 365:1389–1397, 2005
56. Despres JP, Golay A, Sjostrom L, for the RIO-Lipids study group: Effect of rimonabant on body weight and the metabolic syndrome in overweight patients. *N Engl J Med* 353:2121–2134, 2005
57. Scheen AJ, Finer N, Hollander P, Jensen MD, Van Gaal LF, RIO-Diabetes Study Group: Efficacy and tolerability of rimonabant in overweight or obese patients with type 2 diabetes: a randomised controlled study. *Lancet* 368:1660–1672, 2006
58. DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators, Gerstein HC, Yusuf S, Bosch J, Pogue J, Sheridan P,

Dinccag N, Hanefeld M, Hoogwerf B, Laakso M, Mohan V, Shaw J, Zinman B, Holman RR: Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. *Lancet* 368:1096–1105, 2006

59. Sartor G, Scherstén B, Carlström S, Melander A, Nordén A, Persson G: Ten-year follow-up of subjects with impaired glucose tolerance: prevention of diabetes by tolbutamide and diet regulation. *Diabetes* 29: 41–44, 1980
60. Knowler WC, Sartor G, Melander A, Schersten B: Glucose tolerance and mortality, including a substudy of tolbutamide treatment. *Diabetologia* 40:680–686, 1997
61. Navigator press release: the NAVIGATOR study [article online], 2001. Available from http://www.bioportfolio.com/news/novartis_2.htm. Accessed 24 September 2004
62. Chiasson JL, Gomis R, Hanefeld H, Josse RG, Karasik A, Laakso M: The STOP NIDDM Trial Research Group: the STOP NIDDM randomised trial. *Lancet* 359: 2072–2077, 2002
63. http://www.bermancenter.org/studies trials/diabetes/origin.html
64. Kahn R, Buse J, Ferrannini E, Stern M, American Diabetes Association, European Association for the Study of Diabetes: The metabolic syndrome: time for a critical appraisal: joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 28:2289–2304, 2005