Diabetocardiology: Heart Disease in Diabetes

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“Chance favors only the prepared mind”

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CARDIOVASCULAR DISEASE (CVD) WAS THOUGHT TO BE ASSOCIATED with diabetes as early as 1883 when the testing of urine for glucose in patients with angina was first recommended. However, even well into the 20th century, the occurrence of CVD was considered infrequent and its pathophysiology was not understood.

By the late 1950s, CVD had reached epidemic proportions in the industrialized world and soon risk factors such as hypertension, cigarette smoking, and dyslipidemia were identified, and diabetes became established as an important contributor to CVD risk and mortality. The reverse association is very strong as well, and today we know that atherosclerosis accounts for 70% to 80% of deaths in diabetic individuals compared with roughly 30% in the general population. This has led many authors to consider diabetes not only as a disorder of glucose metabolism, but also as a cardiovascular disease in its own right.

In a recent investigation performed in Toronto, Canada, Booth et al studied the risk of cardiovascular disease in some 379,000 people with diabetes and over 9 million without the condition. They found that diabetes led to earlier CVD and that diabetic men and women were about 15 years younger than those without diabetes in the same risk category. For those who had a myocardial infarction, stroke, or died of any cause, the transition from moderate to high risk of CVD took place at about age of 48 years for men with diabetes and 54 years for women with diabetes. When cardiovascular procedures (eg, bypass surgery) were included in the definition of CVD, this transition took place at age 41 years for men with diabetes and 48 years for women with diabetes. The study concluded that the risk to health conferred by diabetes was equivalent to aging 15 years.

The increased risk of CVD in diabetic individuals can be explained in part by the clustering of traditional risk factors such as dyslipidemia, hypertension, hyperglycemia, and an increased tendency to thrombosis. While these factors are important, cardiovascular mortality and morbidity in diabetes exceed by more than 50% the risk that would have otherwise been predicted by these factors. Recent evidence shows that increased oxidative stress and excess production of advanced glycation end-products contribute to the development of diabetic complications, which are mediated at least in part by endothelial dysfunction. This and probably other as yet unknown factors explain the worse clinical outcome of CVD in diabetic individuals, which even after adjustment for age and gender-associated CVD mortality remains at least twice as severe in these patients.

Since the worldwide prevalence of diabetes is expected to increase in ever-alarming proportions, CVD stands to become the most frequent cause of death. Diabetes can thus lay claim to being one of humanity’s deadliest enemies, one that must be fought on all fronts. This certainly won’t be possible with a wave of a magic wand, but will require a judicious combination of changes in lifestyle, pharmacological interventions, or attempts at gene or device therapy.
A welcome move has been the Resolution adopted on December 20, 2006 by the United Nations General Assembly recognizing that “diabetes is a chronic, debilitating, and costly disease associated with severe complications, which poses severe risks for families, Member States, and the entire world and serious challenges to the achievement of internationally agreed development goals including the Millennium Development Goals.” The Resolution further invited all Member States to “raise public awareness on diabetes and related complications…”

The complexity and pandemic proportions of heart disease and diabetes call for a comprehensive understanding of the pathophysiological mechanisms involved and their integration into a broader picture, the judicious use of currently available treatments, which, at present merely address the tip of the iceberg, and of course the ambitious implementation of proven preventive measures against atherosclerosis and diabetes.

This issue of Medicographia is entirely devoted to the momentous problem posed by heart disease in diabetes. The “Theme Articles” review the epidemiological findings and demographic forces at play, the pathophysiological links between diabetes and heart disease, the inflammatory component, as well as more clinical aspects such as the presentation and treatment of myocardial infarction and heart failure in diabetic individuals. The “Interview” presents the rationale, baseline data, and current status of ADVANCE (Action in Diabetes and Vascular disease: Preterax and DiamicroN MR Controlled Evaluation), the largest-ever ongoing randomized controlled outcomes trial on cardiovascular disease. The “Controversial Question” has contributions from an international panel of authors on risk assessment optimization. The “Focus” article stresses the fact that cardiovascular disease risk reduction is a “mission possible.” Finally, the “Update” looks at cardiac outcomes in the long-term treatment of type 2 diabetes with current and potential antidiabetic treatments. A review on glimepiride in modified-release formulation completes this issue.

The ever-growing number of patients with diabetes and heart disease represents a major health care challenge for clinicians. Whether efforts aiming to improve the care of these patients succeed will strongly depend on the collaboration of the various medical specialties involved, above all on that between cardiologists and diabetologists.

We would like to conclude by citing Eugene Braunwald: “Surely the time has come for cardiologists to learn more about diabetes and for diabetologists to learn more about cardiology. Perhaps it is now appropriate to establish a new specialty, ‘diabetocardiology,’ whose practitioners will become the front line troops in this war.”

FURTHER READING
La combinaison de facteurs de risque traditionnels tels que dyslipidémie, hypertension artérielle, hyperglycémie ainsi qu'une forte tendance à la thrombose expliquent en partie l'augmentation du risque de MCV chez les sujets diabétiques. Toutefois, dans le diabète, malgré l'importance de ces facteurs, le risque de morbidité et de mortalité cardio-vasculaires est en fait majoré de plus de 50 % par rapport au risque qui leur est directement imputable. Des études récentes indiquent que l'augmentation du stress oxydatif et la production excessive de produits de glycation avancée des protéines, conduisant au moins en partie à la dysfonction endothéliale, contribuent au développement des complications diabétiques. Ces mécanismes connus et d'autres encore inconnus expliquent l'évolution clinique plus grave de la MCV chez les patients diabétiques, cette dernière étant au moins deux fois plus sévère que chez les patients non diabétiques, même après ajustement pour l'âge et la mortalité par MCV liée au sexe.

La MCV est en passe de devenir la cause la plus fréquente de décès puisqu'une augmentation mondiale de la prévalence du diabète est attendue dans des proportions de plus en plus alarmantes. Le diabète peut donc être déclaré comme un des ennemis publics parmi les plus néfastes, qu'il faut combattre sur tous les fronts. Ceci ne sera sûrement pas possible d'un coup de baguette magique, mais nécessitera tout un ensemble de mesures faites de modifications du style de vie, de mesures pharmacologiques ou d'interventions sur les gènes ou de mesures instrumentales.
La résolution adoptée le 20 décembre 2006 par l’Assemblée générale des Nations Unies a été la bienvenue. Elle reconnaît que le diabète est une maladie chronique, invalidante et coûteuse, qui s’accompagne de graves complications, fait courir des risques graves aux familles, aux États Membres et au monde entier et entравe sérieusement la réalisation des objectifs de développement convenus sur le plan international, notamment les objectifs du Millénaire pour le développement. La résolution a ensuite invité tous les États Membres à sensibiliser le public au diabète et à ses complications…

La complexité et les taux pandémiques du diabète et des MCV nécessitent une compréhension globale des mécanismes physiopathologiques impliqués et leur intégration dans une perspective plus large. Il faut aussi utiliser judicieusement les traitements actuellement disponibles, qui ne s’adressent qu’à la partie émergée de l’iceberg, et bien sûr mettre en œuvre les mesures préventives reconnues contre l’athérosclérose et le diabète.

Cet article de Medicographia est entièrement consacré au problème monumental posé par la maladie cardiaque au cours du diabète. Les articles thématiques passent en revue les données épidémiologiques et démographiques en jeu, les relations physiopathologiques entre le diabète et les MCV, la composante inflammatoire, ainsi que certains aspects plus immédiatement pratiques comme le tableau clinique ou le traitement de l’infarctus du myocarde et de l’insuffisance cardiaque chez les patients diabétiques. La rubrique « Interview » présente l’argumentaire, les données initiales et l’état actuel de l’étude ADVANCE (Action in Diabetes and Vascular disease: Preterax and DiamicroN MR Controlled Evaluation), la plus grande étude d’évolution contrôlée randomisée en cours jamais menée sur la MCV. La rubrique « Question à Controverse » donne la parole à une brochure internationale d’auteurs sur l’optimisation de l’évaluation du risque. L’article « Focus [Mise au Point] » souligne le fait que la réduction du risque de MCV est une mission possible. Enfin, la rubrique « Update [Actualités] » examine les résultats cardiaques dans le traitement à long terme du diabète de type 2 avec les traitements actuels et en cours d’investigation. Une synthèse sur le gliclazide à libération modifiée complète cet article.

Le nombre toujours croissant de patients atteints de diabète et de maladie cardiaque représente, pour les médecins, un défi majeur de santé publique. Quels que soient les efforts ayant pour but d’améliorer les soins aux patients, le succès dépendra largement de la collaboration entre les différentes spécialités médicales impliquées, et par dessus tout de la collaboration entre cardiologues et diabétologues.

Nous conclurons en citant Eugène Braunwald : « Il est grand temps pour les cardiologues d’approfondir leurs connaissances sur le diabète et pour les diabétologues d’approfondir leurs connaissances en cardiologie. Il semble désormais opportun de créer une nouvelle spécialité, la diabétocardiole, dont les praticiens constitueront l’escadron de première ligne dans cette guerre ».  

The prevalence of diabetes among adults is increasing worldwide and is expected to rise from a figure of 135 million in 1995 to 300 million in the year 2025. Cardiovascular disease (CVD), coronary artery disease (CAD), cerebrovascular disease, and peripheral vascular disease (PVD) are the major macrovascular complications of diabetes, which account for more than 50% of mortality among diabetic patients. It is estimated that the relative risk (RR) of death from coronary heart disease (CHD) is 1.5 to 2.5 times higher in diabetic men and more than 4 times higher in diabetic women compared with age-matched nondiabetic subjects. Natural protection in women against CVD is lost with the development of diabetes.

Macrovascular complications are not specific to diabetes. It is well known that multiple CHD risk factors exist even before the clinical diagnosis of type 2 diabetes, and the “ticking clock” phenomenon has been proposed. The high risk of finding CHD in newly-diagnosed diabetic patients—especially women—is attributed to this phenomenon. Nevertheless, a diabetic person has a 2- to 4-fold greater risk of developing CVD. In the US, diabetes is the fourth most common cause of death and CHD in particular accounts for nearly 75% of all mortality among diabetics. In the United Kingdom Prospective Diabetes Survey (UKPDS), fatal CVD was 70 times more common than microvascular complications after 9 years of follow-up. Life expectancy decreased by 5 to 10 years in diabetic subjects with CVD.

Type 2 diabetes carries not only a greater risk of developing CHD, but development occurs at a
Epidemiology of heart disease in type 2 diabetes – Ramachandran and Snehalatha

Younger age compared with the general population and produces a high rate of multivessel disease with decreased coronary flow reserve. The occurrence of cardiovascular events predicts a poorer outcome in subsequent myocardial infarction and also carries a high risk of congenital heart failure and death. The Tecumseh study showed that the elimination of CVD risk factors (ie, hypertension, hypercholesterolemia, and cigarette smoking) in diabetics would reduce the 8-year incidence of CHD in about 60% of the affected population. The Adult Treatment Panel III (ATP III) considered diabetes as a CHD equivalent on the basis of studies revealing high cardiovascular risk in the presence of diabetes.

**Coronary risk factors**

The coexistence of multiple CHD risk factors is seen even in nondiabetic patients with blood glucose disorders such as impaired glucose tolerance (IGT). The role of certain risk factors is well established and they confer similar relative risk of CHD in diabetic and nondiabetic individuals. They may be additive and perhaps multiplicative. This was well illustrated by the Multiple Risk Factors Intervention Trial (MRFITT). In this trial, the risk of CHD death with diabetes alone was associated with an absolute excess of about 25/1000 person-years; diabetes plus any other risk factor increased this figure to 47/1000 person-years, and when these two risk factors coexisted, the figure rose to 78/1000 person-years. The various definitions and threshold levels used to define hypertension make comparisons between different studies rather difficult. In addition to the variation seen with the classic risk factors in diabetic subjects, several stronger risk variations exist such as with elevated small, dense low-density lipoprotein (LDL) cholesterol or oxidized LDL, which confer a higher risk in diabetics than in nondiabetic individuals with elevated LDL. Hypertension and obesity are more common in the diabetic population. In the Framingham study and the National Health And Nutrition Examination Survey (NHANES) of 1972 to 1977, the CHD risk was nearly 4 times higher in the presence of type 2 diabetes.

Although the validity of the definitions and existence of hard evidence for the metabolic syndrome have been debated, ample evidence exists to show that multiple risk factors do cluster and that the phenomenon is enhanced by the presence of diabetes.

**Blood glucose and CHD**

Hyperglycemia may accelerate atherogenesis through various mechanisms, such as glycation of collagen and other vessel wall proteins, excess production of atherogenic lipoproteins and reactive oxygen species, increased oxidative stress, glycation of several lipids and lipoproteins, and also through endothelial damage and hemorrhological abnormalities. Both the Diabetes Control and Complications Trial (DCCT) in type 1 diabetes and UKPDS in type 2 diabetes produced data suggestive of a cardiovascular benefit with the lowering of blood glucose levels, although both studies failed to show a statistically significant reduction.

Although the data in diabetic subjects do not fully support a relationship between the degree of hyperglycemia and the occurrence of CHD, evidence exists in the nondiabetic population for a correlation between elevated blood glucose and CHD. This correlation is stronger in women than men and persists after adjustment for multiple risk factors. There seems to be a continuum of risk with rising glucose level—even within the normal range. The Diabetes mellitus Insulin Glucose infusion in Acute Myocardial Infarction (DIGAMI) study showed that intensive insulin treatment immediately after a myocardial infarction, followed by multiple dose injections thereafter, reduced the mortality rate in subjects with diabetes.

**Microalbuminuria as a risk factor for CVD**

Microalbuminuria is considered to be an equivalent of endothelial dysfunction. Several studies have shown microalbuminuria to be an early marker of both impending nephropathy and CVD. The Botnia study, consisting of 3606 subjects with a median follow-up of 6.9 years, found that among components of the metabolic syndrome, the highest relative risk for cardiovascular death (RR, 2.8; P<0.002) was conferred by microalbuminuria. A separate study found that the albumin/creatinine ratio (indicator of microalbuminuria) and smoking correlated with the extent of coronary artery calcification. Coronary artery calcification did not, however, correlate with blood glucose control or body mass index.

**Congestive heart failure**

In the US, the most common cause of left ventricular systolic dysfunction with congestive heart failure (CHF) is ischemic heart disease. However, after adjusting for the prevalence of CAD, diabetes remains an independent predictor of CHF and an independent predictor of mortality among patients with CHF. Glucose intolerance—even in the prediabetic setting—has been associated with CHF, suggesting that the glycometabolic state might play a pathophysiologic role. Patients with diabetes develop heart failure after myocardial infarction at higher rates than do patients without diabetes, independent of the infarct size. The increased risk for CHF associated with diabetes has been demonstrated across the entire spectrum of acute coronary syndromes (ACSs).

**Acute coronary syndrome**

Impaired glucose metabolism is also frequently observed subsequent to an acute event in nondiabetic subjects. A study in India showed that the prevalence of abnormal glucose tolerance among urban Asian-Indians with ACS was higher than among populations in European countries. Norhammer et al reported that after excluding those
with known diabetes, <35% of European subjects had normal glucose tolerance at either admission to the hospital or 3 months after follow-up. In India, by contrast, <16% had normal glucose tolerance at the time of these events. Other striking variations between the Asian-Indian and European cohorts were the younger mean age, and the higher prevalence of hypertension and treated hyperlipidemia in Asian-Indians. In addition, insulin resistance and increased levels of plasma insulin and proinsulin were associated with ACS, regardless of blood glucose status.

Cerebrovascular disease

The constellation of metabolic and physiologic abnormalities that coexist with diabetes confers a high risk of stroke on this population. However, even after adjustment for these factors, diabetes remains an independent predictor of ischemic neurologic events, indicating the involvement of additional diabetes-related factors. In both the Framingham Study and the Honolulu Heart Study, diabetes was associated with twice the risk of stroke after adjustment for other cardiovascular risk factors.

In the UK, ethnic differences have been noted in the susceptibility to stroke and related mortality. UK African-Caribbeans with diabetes were over five times more likely to die of stroke than Europeans with diabetes and hypertension.

Peripheral vascular disease

Patients with diabetes who have PVD have a 70% to 80% higher mortality rate than diabetics without PVD. Because of the compromised peripheral circulation, diabetes is responsible for approximately 45% of extremity amputations in the US, and amputation is 15 times more common in diabetics than in patients without diabetes. Male gender, duration of diabetes, poor glucose control, and the presence of cardiovascular, retinal, or renal complications, are major risk factors for foot ulcers.

In diabetes, the distal lower extremity arterial circulation appears to be affected, whereas in patients without diabetes, the proximal vessels are mostly affected. The prognosis for patients with diabetes following the development of peripheral arterial disease is poor, especially if amputation is required.

Hypertension

Hypertension affects up to 70% of diabetic patients, especially older patients and men, and accounts for 35% to 45% of cardiovascular and renal complications among the diabetic population. In NHANES III, approximately 60% of subjects with diabetes, 50.7% of those with IGT, and 38.3% of those with normal glucose, had hypertension. Mean systolic pressure was highest among whites in the Rancho Bernardo Diabetes Study, and lowest among Dakota Indians in the Strong Heart Study (SHS), whereas diastolic pressure was highest among blacks and lowest among Mexican-Americans and whites in the San Antonio Texas Diabetes Study.

In UKPDS, tight control of blood pressure (144/82 vs 154/87 mm Hg) was associated with an 11% reduction in risk for myocardial infarction. The absolute benefits of blood pressure reduction are higher in the diabetic population than in the nondiabetic population. The choice of antihypertensive drugs is less important than lowering the blood pressure, and the tight targets advised in diabetes (130/80 mm Hg) often require a combination of at least three drugs.

Dyslipidemia

Dyslipidemia in diabetes is of a complex nature, and involves a cluster of factors including both lipid and lipoprotein abnormalities. It is typically associated with increased triglycerides, low high-density lipoprotein (HDL) concentration, a high concentration of LDL with a preponderance of small, dense LDL particles, and increased apolipoprotein B-100. Postprandial lipemia and lipoprotein remnants are increased, leading to endothelial dysfunction and platelet aggregation. Several studies have shown that, among diabetic subjects, mean total cholesterol and HDL levels are higher in women compared with men.

The absolute or relative insulin deficiency in type 2 diabetes causes lipid abnormalities. Free fatty acid release from adipose tissue, delivery of free fatty acids to the liver, and hepatic synthesis of very-low-density lipoproteins (VLDL) are increased. The beneficial effects of various statins have been shown to lower the mortality from CHD in diabetes. The Collaborative Atorvastatin Diabetes Study (CARDS) and the Heart Protection Study (HPS) have shown that treatment with statins reduces the risk of major cardiovascular events in 37% of diabetic patients. The RR reduction is similar in the diabetic and nondiabetic populations, so the absolute benefit is greater in the former group.

Recommendations on the use of fibrates to treat hypertriglyceridemia are less clear. In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, fenofibrate did not reduce the risk of coronary events in type 2 diabetes. However, it is recommended that a fibrate is added to statin therapy if triglycerides are >2.3 mmol/L. Fibrates predominantly reduce triglycerides and raise HDL cholesterol. The PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) suggested that pioglitazone had an antiatherogenic effect in preventing macrovascular events. It showed that pioglitazone reduced mortality, nonfatal myocardial infarction, and stroke in patients with type 2 diabetes. In the Steno-2 study, multifactorial care that targeted tight control of blood glucose, blood pressure, and lipids was shown to be effective in patients with type 2 diabetes and microalbuminuria. If lifestyle modification alone failed after 3 months, the patients received either metformin or glitazide. If their HbA1c exceeded 7.0% despite receiving the maximum dose of oral drugs, NPH insulin was recommended. The risk of progression of microvascular and macrovascular disease was reduced by 40% to 60% in the intensively treated groups.
Inflammation biomarkers and adipokines

In addition to C-reactive protein (CRP), several adipokines have been proposed to be linked with insulin resistance in atherosclerosis. These proinflammatory adipokines include tumor necrosis factor-α, interleukin 6, leptin, plasminogen activator inhibitor–1, angiotensinogen, resistin, and CRP. The important role of adiponectin as an anti-inflammatory and antiatherosclerotic source has attracted great attention.

Silent myocardial ischemia

Silent myocardial ischemia (SMI) is more common in diabetic patients than in the general population. CAD is very often present at the time of diagnosis in diabetic patients, and it is more advanced, with an unfavorable prognosis. Late diagnosis of this may be explained by the presence of SMI. SMI is probably more prevalent in diabetic patients because of diabetic neuropathy. Neuropathy is seen in the diabetic population and in only 1 out of 4 of the normal population with SMI.

Because of the long symptom-free period in diabetes and its early stages such as IGT, the atherosclerotic process takes place in the vasculature undetected, leading to more severe and diffuse CAD in diabetic subjects.

Ethnic predisposition

In most populations, macrovascular disease is the most common complication of diabetes, but Pima Indians, who have the highest prevalence of type 2 diabetes, are more prone to developing microvascular complications—a phenomenon known as the “Pima paradox.”

A similar disparity in the risk of diabetic complications has been reported in other ethnic groups such as African-, Hispanic-, and Asian-Americans. Among these populations, the rate of end-stage renal disease is higher relative to whites, and the rates of macrovascular complications are relatively lower.

South-Asian migrants in the Western world have one of the highest rates of CHD worldwide, with rates 50% to 200% higher than those in Europe. Studies suggest that hitherto unmeasured variables should be investigated—whether associated with insulin resistance or not—to explain the excess CHD seen in this group of individuals. Farouhi et al. observed that in the UK, South-Asian men had double the CHD mortality of European men; this was the case with or without the presence of diabetes, and after adjusting for conventional risk factors such as blood glucose disorders, features of insulin resistance, or the metabolic syndrome. It is also suggested that abnormalities of the adiponectin—inulin sensitivity axis may exist in South Asians, linking visceral adiposity to atherogenesis.

Economic burden

In many countries, treatment of diabetes consumes up to 10% of the total national health care budget. Nearly half these expenses are caused by diabetic complications, of which cardiovascular complications account for the bulk.

In developing countries, the burden of treating diabetes and its complications is enormous, as there are no comprehensive state-level health care policies. The cost is borne by the individuals and their families. It is estimated that the poorer section of society spend nearly 25% of their annual income on the treatment of diabetes, and the cost escalates severalfold with the treatment of complications.

Prevention of diabetic cardiovascular complications

Diabetes doubles the risk for ACSs, and there is an additional doubling of clinical risk once these events occur. The influence of blood glucose control on cardiovascular risk has yet to be definitively established. UKPDS demonstrated a beneficial effect of intensive blood glucose control, but this effect was much more modest than expected, and the trial was not adequately powered to evaluate the effects of such a strategy specifically on cardiovascular risk. Furthermore, it appears that the strategy used for blood glucose control may be more important than the degree of control achieved.

In the light of evidence accrued from various studies, guidelines have been formulated for preventing the complications in diabetes. Blood glucose control should be aimed at achieving an HbA1c of <7%, and blood pressure control should be aimed at <130/80 mm Hg, or <125/75 mm Hg in the presence of nephropathy or CVD. The use of statins and fibrates is recommended for dyslipidemia.

REFERENCES


ÉPIDÉMILOGIE DE LA MALADIE CARDIAQUE DANS LE DIABÈTE DE TYPE 2

L’ diabète est associé à un risque 3 à 4 fois plus élevé de maladie cardio-vasculaire et les événements cardio-vasculaires aigus sont responsables de la moitié des décès des patients diabétiques. Les facteurs de risque classiques de coronaropathie sont plus fréquents même chez les patients non diabétiques présentant des troubles de la glycémie, par exemple une diminution de la tolérance au glucose, et semblent varier selon l’origine ethnique. Dans les pays développés, la charge économique et les coûts sociaux des complications cardio-vasculaires chez les patients diabétiques sont élevés. La mortalité et la morbidité cardio-vasculaires sont diminuées lorsque l’hyperglycémie, l’hypertension artérielle et la dyslipidémie des patients diabétiques sont traitées de façon intensive.
Diabetes mellitus (DM) is a heterogeneous group of metabolic diseases, characterized by hyperglycemia that is caused by defects in insulin secretion, insulin action, or both.1 There are approximately 200 million diabetic individuals worldwide, with only around half of these being diagnosed, and the number is expected to double by 2030.1,2 The vast majority of cases of DM fall into one of two broad categories known as type 1 and type 2. Type 1 DM (T1DM) is characterized by an absolute insulin insufficiency that is caused by the immunological destruction of pancreatic β cells that produce and secrete insulin, and it accounts for 5% to 10% of all cases of DM.3 Type 2 DM (T2DM), which represents approximately 90% of all cases, is more complex in etiology, and is characterized by reduced

Pathophysiological links between diabetes and heart disease
by P. Marchetti, A. Coppelli, and R. Giannarelli, Italy

Diabetes mellitus is responsible for a spectrum of cardiovascular diseases. Atherosclerotic coronary artery disease is caused by the contribution of several metabolic, hormonal, and hemodynamic factors, which often cluster with obesity and lead to endothelial dysfunction and damage. Independent of the severity of coronary artery lesions, diabetic patients are at an increased risk of developing heart failure; this is caused by the result of what is considered to be a distinct disease process, known as diabetic cardiomyopathy, and which is characterized by structural abnormalities of the myocardium, and systolic as well as diastolic dysfunction. This review focuses on the role of hyperglycemia, dyslipidemia, hypertension, insulin resistance, oxidative stress, enhanced glycosylation, and neural alterations in the creation of the vicious circle that initiates and sustains vascular, myocyte, and interstitial alterations to the diabetic heart.

Medicographia. 2007;29:213-219. (see French abstract on page 219)

Keywords: diabetes; coronary artery disease; diabetic cardiomyopathy; hyperglycemia; insulin resistance; dyslipidemia; hypertension; endothelium

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Coronary artery disease

CAD, which causes occlusion of the arteries that supply the heart, is responsible for most of the burden of CVD in patients with DM. The atheromatous plaques found in people with DM are not qualitatively different from those affecting the general population. However, atheroma in DM occurs at an earlier age, is more extensive, more diffuse, involves more distal branches, and is more prone to ulceration and instability.

◆ The role of hyperglycemia

Several epidemiological studies have shown that, in diabetic patients, there is no clear glycemic threshold for cardiovascular risk, which increases progressively from values below the diabetic range.6,7 The association between glucose status and cardiovascular risk by up to fourfold when compared with the general population, and cardiovascular disease (CVD) accounts for 70% to 75% of deaths in diabetic patients.8,9 The association between glucose status and CVD also extends beyond the diabetic threshold, and a relationship between the two can be detected in the presence of impaired glucose tolerance (IGT), impaired fasting glucose, and the upper-normal levels of both the fasting and 2-hour post–oral glucose tolerance tests.1 The importance of DM in this regard is also demonstrated by the fact that pancreatic transplantation to cure DM is associated with improved cardiovascular risk profile, better cardiac performance, and reduced progression of vascular lesions.8,9

There is an increased risk of coronary artery disease (CAD) in diabetic patients, which is the result of the contribution of several cardiovascular risk factors; hyperglycemia, insulin resistance, dyslipidemia, hypertension, and endothelial dysfunction. These often cluster with obesity, and they may have a different impact in T1DM and T2DM.10,11 Furthermore, independent of CAD, diabetic patients are at an increased risk of developing heart failure through diabetic cardiomyopathy (DCM), which is considered to be a distinct disease process.10,11 The concept of this distinct process is based on the assumption that DM leads to changes at the myocardial cellular level, causing structural abnormalities that eventually result in left ventricular hypertrophy, and systolic as well as diastolic dysfunction. Some of the pathophysiological mechanisms linking DM with CAD and DCM will be reviewed in this article. The topic of inflammation is dealt with in a separate article in this issue.

◆ The role of insulin resistance

Insulin resistance is associated with both T1DM and T2DM.12 In addition, it may cluster with several classic CVD risk factors, such as visceral obesity, lipid abnormalities, and hypertension, to form a

comes. However, an observational follow-up study to DCCT known as the Epidemiology of Diabetes Interventions and Complications (EDIC) study, clearly showed that previous intensive DM treatment was associated with less coronary atherosclerosis — mainly as a result of reduced HbA1c levels.14 In addition, using the UKPDS data, a prospective observational study lasting over 10 years found that each 1% reduction in HbA1c value was associated with a significant reduction in the DM-related risk of death (21%) and myocardial infarction (14%).15 As proposed by, among others, the Multiple Risk Factor Intervention Trial (MRFIT),16 it appears, therefore, that hyperglycemia is a cardiovascular risk factor in its own right that additionally amplifies the effects of other individual risk factors.
condition known as the metabolic syndrome.\textsuperscript{22,24} Controversy remains regarding whether insulin resistance per se is involved in the pathogenesis of atherosclerosis.\textsuperscript{25} At the cellular level, there are two major insulin-regulated pathways, known as the metabolic and mitogenic pathways (Figure 2).\textsuperscript{22-25} Normally, insulin binds to its receptor (IR) and activates insulin receptor substrate (IRS)-1 by phosphorylation of tyrosine residues. This, in turn, activates phosphatidylinositol 3-kinase (PI-3K), resulting in glucose transport into the cell. In people with obesity, IGT, T2DM, and other insulin-resistant states, there is a severe defect in the activation of IRS-1, and as a result, glucose transport into the cell is impaired. This leads to a rise in blood glucose levels, and the resultant hyperglycemia stimulates insulin release and the development of hyperinsulinemia.

Although the metabolic (IRS-1/PI-3K) pathway is severely impaired in any condition of insulin resistance, the mitogenic pathway (proceeding through mitogen-activated protein [MAP] kinase) seems to retain its sensitivity to insulin, and any prevailing hyperinsulinemia would, therefore, lead to an excessive stimulation of this pathway.\textsuperscript{22-26} This may result in the release of a number of growth and inflammatory factors, and promote proliferation and migration of vascular smooth muscle cells.\textsuperscript{22-26}

\textbf{The role of plasma lipids}

Lipid abnormalities are often found in diabetic patients.\textsuperscript{27} In T1DM, alterations in lipid metabolism are largely related to the level of glycemic control achieved. Sustained hyperglycemia is associated with increased concentrations of total cholesterol, LDL cholesterol, and triglycerides, and low concentrations of high-density lipoprotein (HDL) cholesterol. All of these abnormalities are reversed with the normalization of blood glucose. The pattern of dyslipidemia in T2DM is determined by the presence of insulin resistance, and is characterized by raised triglyceride concentrations and low HDL cholesterol concentrations. LDL cholesterol levels in T2DM are almost normal, but they are likely to be dominated by the highly atherogenic small, dense LDL particles.\textsuperscript{28}

The mechanisms leading to plasma lipid–induced vascular damage are, in part, understood, and the link between elevated LDL cholesterol and atherosclerosis has long been recognized. In addition to binding with scavenger receptors on monocytes or macrophages to fuel formation of foam cells, LDL particles can undergo oxidation through several mechanisms, thereby contributing importantly to atherogenesis at an early stage.\textsuperscript{20,24} Several study findings are in agreement with this concept: oxidized LDL has been shown to support foam cell formation in vitro; lipids found in human lesions are substantially oxidized; there is evidence for the presence of oxidized LDL in vivo; oxidized LDL has a number of potentially proatherogenic activities; several structurally unrelated antioxidants inhibit atherosclerosis in animals.\textsuperscript{20,31} Small, dense LDL particles have been shown to be more readily oxidized than their larger counterparts in this regard.


Figure 1. Increased glucose levels cause enhanced production of reactive oxygen species through nonmitochondrial and mitochondrial (oxidative phosphorylation) mechanisms.

Abbreviations: AGE, advanced glycation end-product; ROS, reactive oxygen species.

Furthermore, because of their reduced size, they are likely to penetrate the arterial wall more easily. Finally, it has been demonstrated that these particles have an enhanced affinity for arterial wall proteoglycans, thus prolonging their residence time in the subendothelial space.\textsuperscript{30,33} Hypertriglyceridemia is considered to be an independent risk factor for CVD in patients with DM.\textsuperscript{22} It is possible, however, that rather than being actual atherogenic agents themselves, elevated triglycerides serve as a marker of triglyceride-rich remnant lipoprotein increases, and that it is these latter particles that are involved in the development of atherosclerosis. In fact, triglyceride-rich lipoproteins comprise a great variety of nascent and metabolically modified lipoprotein particles that differ in size, density, and lipid and apolipoprotein composition.\textsuperscript{31} Studies have shown an inverse relationship between the size of lipoproteins, and their


Figure 2. Binding of insulin to its receptor triggers the metabolic and/or mitogenic effects of insulin through IRS-1 and IRS-2 phosphorylation. The metabolic effects are mediated by PI-3 kinase and are blunted in the case of insulin resistance, whereas the mitogenic effects, which are mediated by MAP kinase and Shc, remain sensitive to the action of insulin.

Abbreviations: IRS-1, insulin receptor substrate–1; IRS-2, insulin receptor substrate–2; MAPK, mitogen-activated protein kinase; PI-3K, phosphatidylinositol 3-kinase.
◆ Increase reverse cholesterol transport
◆ Protect endothelial cells
  – Activate eNOS and NO release
  – Attenuate the expression of VCAM-1, ICAM-1, E-selectin, IL-8
  – Reduce apoptosis by inhibiting caspases and activating protein kinase Akt
◆ Reduce oxidative stress
  – Inhibit LDL oxidation by transition metal ions
  – Prevent lipid hydroperoxide formation

Table I. Antiatherogenic roles of HDL particles.
Abbreviations: eNOS, endogenous nitric oxide synthase; HDL, high-density lipoprotein; ICAM-1, induced endothelial cell adhesion molecule–1; IL-8, interleukin 8; LDL, low-density lipoprotein; NO, nitric oxide; VCAM-1, vascular cell adhesion molecule–1.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Actions</th>
</tr>
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<tbody>
<tr>
<td>Nitric oxide</td>
<td>↑ Vasodilation, ↓ platelet aggregation</td>
</tr>
<tr>
<td>Prostacyclin (PGI2, prostaglandin I2)</td>
<td>↑ Vasodilation, ↓ platelet aggregation</td>
</tr>
<tr>
<td>Endothelium-derived hyperpolarizing factor</td>
<td>↑ Vasodilation</td>
</tr>
<tr>
<td>C-type natriuretic peptide</td>
<td>↑ Vasodilation</td>
</tr>
<tr>
<td>Endothelin I</td>
<td>↑ Vasocostriction</td>
</tr>
<tr>
<td>Angiotensin II</td>
<td>↑ Vasocostriction</td>
</tr>
<tr>
<td>Thromboxane A2</td>
<td>↑ Vasocostriction</td>
</tr>
<tr>
<td>Reactive oxygen species</td>
<td>↑ Vasocostriction</td>
</tr>
<tr>
<td>Thrombomodulin</td>
<td>↑ Thrombosis</td>
</tr>
<tr>
<td>Tissue plasminogen activator</td>
<td>↓ Fibrinolysis</td>
</tr>
<tr>
<td>Plasminogen activator inhibitor–1</td>
<td>↑ Fibrinolysis</td>
</tr>
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Table II. Some of the compounds produced/released by endothelial cells, and their respective main actions.

◆ The role of hypertension
Hypertension affects up to 70% of patients with DM.14 In T1DM, hypertension is usually a manifestation of diabetic nephropathy, while in T2DM it clusters with the other components of the metabolic syndrome—obesity, insulin resistance, and dyslipidemia. Hypertension in DM has some unique characteristics, such as increased salt sensitivity, volume expansion, loss of nocturnal dipping and pulse, and isolated systolic hypertension.23,24 Several studies have shown that sustained hypertension is associated with structural and functional alterations of both large arteries and arterioles.28 A key characteristic of the hypertensive artery is increased vascular stiffness, which is probably caused by the accumulation of collagen, as suggested by the observation of increases in collagen type I, III, and IV in hypertensive patients and in animal models of hypertension.29 Remodeling of the arterial walls requires the activity of matrix-degrading enzymes and extracellular matrix protein synthesis. These phenomena are driven, at least in part, by increased NF-κB and MAP kinase activity.30-32 NF-κB regulates the transcription of numerous matrix metalloproteinases (MMPs), including MMP-1, MMP-2, MMP-3, and MMP-9. On the other hand, smooth muscle cell proliferation in hypertension requires extracellular signal-regulated kinase–1/2 (ERK1/2), in a step modulated by MAP kinase.

◆ The role of endothelial dysfunction
Endothelial dysfunction is a precursor to, and an effect of, atherosclerosis. In addition to its obvious role as a mechanical lining, the endothelium also has crucial biological functions, which are mediated by various molecules produced and released by the endothelial cells, and include regulation of leukocyte adhesion and trafficking, prevention of platelet adhesion, and regulation of blood flow via modulation of vessel patency (Table II).33

In DM, hyperglycemia promotes the formation of ROS and AGEs, which, in addition to the proatherosclerotic actions mentioned above, stimulate the endothelial expression of proinflammatory cytokines such as interleukin-6 and monocyte chemoattractant protein–1, as well as leukocyte adhesion molecules.41 In addition, increased oxidative stress leads to quenching of NO and degradation of endogenous nitric oxide synthase (eNOS) cofactor tetrahydrobiopterin (BH4).42-44 The presence of insulin resistance also causes alterations to the PI-3K/Akt pathway (see above), which, in turn, lead to a marked decrease in eNOS activation. Taken together, these alterations confer a strong proatherogenic profile, which plays a major role in the development of CAD.

Interestingly, a role has been proposed for C-peptide in the modulation of endothelial function.45 C-peptide is cosecreted with insulin (both are derived from the common precursor proinsulin), and patients with T1DM lack C-peptide as well as insulin. C-peptide was previously considered to be biologically inert; however, it has recently been reported that the molecule can have a biological function,46-48 and enhances skeletal muscle, skin, and renal blood flow.49-50 It was recently demonstrated that, in T1DM patients, impaired myocardial perfusion can be improved by replenishing C-peptide levels. C-peptide induces vasodilation mainly via the endothelium-dependent mechanism. It increases NO concentrations in a dose-dependent manner, and eNOS inhibition has been reported to abolish C-peptide–induced vasodilation and NO release.49-50

Diabetic cardiomyopathy
DCM is a disease of the myocardium, associated with DM, which leads to cardiac dysfunction.50,51 As previously discussed, CAD is the most common form
of cardiac manifestation in DM. However, nonischemic heart failure is also an important cause of morbidity and mortality in diabetic patients. In the Framingham Heart Study (FHS), the relative risk of congestive heart failure was up to fivefold higher in people with diabetes than in the general population. Early pathological features of DCM include nonspecific interstitial changes within preserved monocytes, which progress to more marked interstitial and perivascular fibrosis, with deposition of periodic acid Schiff (PAS)-positive material, myocyte hypertrophy, microvascular alterations (thickening of the basement membrane and microaneurysms), ventricular dilatation, and diastolic dysfunction with either decreased or maintained systolic function. Metabolic and hormonal factors, autonomic neuropathy, and microangiopathic alterations are the main etiopathologic factors. Some of these factors (in particular AGEs, oxidative stress, and endothelial alterations) have been discussed above; below we will focus on a few additional points.

**The role of metabolic and hormonal factors**
The overall myocardial response to the diabetic milieu is a reduction in glucose uptake and oxidation, and an increase in fatty acid uptake and oxidation. It has been proposed that in people with DM, myocytes cannot metabolize pyruvate in the normal manner, and in the presence of an energy deficit (such as that caused by ischemia), they sustain reperfusion injuries. Furthermore, accumulation of pyruvate inhibits glycolysis, therefore more glucose is directed to form glycogen. As adenosine triphosphate (ATP) derived from glycolysis is preferentially used by the myocyte for calcium reuptake into the sarcoplasmic reticulum, reduced glycolysis results in impaired myocyte relaxation. In the earlier stages of DM, glucose metabolism is regulated by compensatory hyperglycemia, and at the same time, the myocyte responds to the increased fatty acid levels resulting from insulin resistance and increased systemic lipolysis by upregulating mitochondrial β-oxidation. Exacerbation of chronic hyperglycemia induces lipid esterification and intracellular triglyceride accumulation, which lead to ceramide (a toxic lipid compound) production, oxidative stress, apoptosis, and decreased myocardial function. In addition, as discussed above, hyperglycemia increases the oxidative stress and glycosylation processes. Among the consequences of this are that glycosylation of the p53 protein leads to activation of angiotensin II synthesis, which in turn, contributes to enhanced apoptosis and necrosis. Furthermore, angiotensin II has dose-dependent effects on collagen production and secretion, thus favoring interstitial fibrosis. Hyperglycemia can also activate the protein kinase C-ph pathway, again promoting myocardial necrosis and fibrosis.

**The role of cardiac autonomic neuropathy**
Cardiac autonomic neuropathy (CAN) has been associated with myocardial dysfunction, and the development of CAN results in a 44% to 85% survival reduction in patients with DM. Other studies found that, in coronary resistance vessels, CAN was associated with an impaired vasodilator response to increased sympathetic stimulation, and that about 20% of patients with DM who did not have ischemic heart disease had abnormal diastolic filling that was related to the severity of CAN. Similarly, ventricular filling abnormalities are most prominent in patients with CAN, and a correlation has been found between myocardial sympathetic innervation as recorded on scintigraphy, and the E/A ratio (ratio of early to late peak mitral filling wave velocities in Doppler echocardiography), providing evidence that an abnormal sympathetic innervation of the heart might contribute to a disturbance in left ventricular filling.

Catecholamines regulate the contractility of cardiac myocytes by acting on sarcoplasmic reticulum calcium uptake, and under conditions of β-adrenergic receptor stimulation, cardiac performance is enhanced. These effects are mediated by cAMP-dependent phosphorylation of proteins located in the sarcolemma, the membrane of the sarcoplasmic reticulum, and in the myofibrils of the cardiomyocytes. In DM, the cardiac β-adrenergic system may be enhanced, which can induce myocyte hypertrophy, interstitial fibrosis, and reduced contractile function, accompanied by myocyte apoptosis. On the other hand, α-adrenergic stimulation, which has antiapoptotic effects, seems to be decreased in DM.

**Cardiac allograft vasculopathy**
Cardiac allograft vasculopathy (CAV) is a type of cardiovascular disease that occurs in heart transplant recipients. It is a rapidly progressive form of atherosclerosis characterized in its early stages by intimal proliferation, and in its later stages by luminal stenosis of epicardial branches, occlusion of smaller arteries, and myocardial infarction. There are some important differences between CAV and classic coronary atherosclerosis. In CAV, intimal proliferation is concentric rather than eccentric, and the lesions are diffuse, involving both distal and proximal portions of the coronary tree. Calcification is uncommon, and the elastic lamina remains intact. Both immunologic and nonimmunologic mechanisms are involved in the pathogenesis of CAV. The initiating event is subclinical endothelial cell injury in the coronary graft, probably caused by ischemia–reperfusion damage or the host-versus-graft immune response. This leads to a cascade of immunologic processes involving cytokines, inflammatory mediators, complement activation, and leukocyte adhesion molecules. These changes produce inflammation, and ultimately, thrombosis, smooth muscle cell proliferation, and vessel constriction. Among the nonimmunologic factors, DM—both preexisting and new-onset after transplantation (mainly caused by immunosuppression)—and the metabolic abnormalities associated with insulin resistance, play a major role in accelerating vascular damage, probably through the same mechanisms described above for CAD in the nontransplant setting.
### A role for oral insulin secretagogue agents?

Insulin secretagogues (sulfonylureas and glinides) are widely used in T2DM therapy. They bind to sulfonylurea receptors on the β-cell membrane, causing closure of the ATP-sensitive potassium channel (K_{ATP} channel) and depolarization of the cell membrane. This, in turn, opens voltage-gated calcium channels, leading to an influx of calcium ions and subsequent secretion of preformed insulin granules. The K_{ATP} channels are formed of two sub-units: a sulfonylurea receptor (SUR), which binds sulfonylurea agents, and the actual potassium pore. K_{ATP} channels are found in several cell types that share a common Kir6.2 unit, but have different sulfonylurea receptors. In particular, the isoform SUR1 is located in the pancreatic β cell, and SUR2A is in cardiac cells.

Structurally, sulfonylurea agents can have both the sulfonylurea component and a benzenamido group, whereas glinides are derived from the benzanamido nonsulfonylurea portion. It has been proposed that SUR1 has both sulfonylurea and benzanamido binding sites, whereas SUR2A has only a benzanamido binding site. As a consequence, agents that have both portions (such as glibenclamide) interact with both the pancreatic β cell and the cardiac cell, and those having only the sulfonylurea portion (such as glinazide) bind with the β cell only. The clinical significance of these characteristics is still a matter for debate. However, it has been observed that inhibition of K_{ATP} in the heart is associated with impaired ischemic preconditioning and reduced coronary vasodilation in response to myocardial ischemia.

### Conclusions

Diabetic heart disease is caused by complex interactions that result from overlapping mechanisms. The driving forces are related to the phenotypic alterations associated with diabetes—in particular hyperglycemia, dyslipidemia, hypertension, and possibly insulin resistance. A vicious circle develops, leading to increased oxidative stress and enhanced glycosylation of several humoral and vessel wall proteins, which cause endothelial damage and structural changes in coronary arteries. In turn, damaged endothelial cells can become a source of ROS and reactive nitrogen species in addition to other factors, sustaining the proatherosclerotic process. Some of these pathways are also involved in the development of DCM, a condition in which, among other factors, myocyte substrate utilization and neural influences play a major role. At least a few of these mechanisms are involved in coronary artery damage observed in specific situations such as diabetic allograft coronary artery. Further studies are needed to elucidate the possible beneficial role of oral antidiabetic agents in relation to diabetic heart disease.

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Pathophysiological links between diabetes and heart disease – Marchetti and others


**RELATIONS PHYSIOPATHOLOGIQUES ENTRE DIABÈTE ET MALADIE CARDIAQUE**

Le diabète est à l’origine de nombreuses maladies cardiovasculaires. Plusieurs facteurs métaboliques, hormonaux et hémodynamiques, souvent combinés à l’obésité, et conduisant à des lésions et à une dysfonction endothéliale, contribuent à la coronaropathie athéroscléreuse. Les diabétiques ont plus de risques de développer une insuffisance cardiaque, indépendamment de la sévérité des lésions coronaires. Celle-ci résulte d’un processus pathologique reconnu comme étant distinct, dénommé cardiomyopathie diabétique, qui se caractérise par des anomalies structurelles du myocarde ainsi que par une dysfonction systolique ou diastolique. Cet article évoque le rôle de l’hyperglycémie, de la dyslipidémie, de l’hypertension, de la résistance à l’insuline, du stress oxydatif, de l’exacerbation de la glycosylation et des altérations nerveuses dans la création du cercle vicieux qui instaure et maintient les altérations vasculaires, myocytaires et interstitielles au niveau du cœur diabétique.
Type 2 diabetes is strongly associated with atherosclerosis and represents a major risk factor for cardiovascular disease. Inflammation is a primary process in atherosclerosis that plays a key role in the initiation, progression, and rupture of atherosclerotic plaques. Recent evidence indicates that type 2 diabetes and atherosclerosis share a common inflammatory basis and that both conditions represent a state of heightened oxidative stress. Oxidative events are closely related to inflammation and are believed to play a causative role in the development and progression of atherosclerosis. Accordingly, antioxidant therapy may directly or indirectly reduce the risk of cardiovascular disease and may improve the prognosis of cardiovascular events in patients with type 2 diabetes. However, large clinical trials undertaken to prove the postulated beneficial effect of antioxidants on cardiovascular disease have, so far, been disappointing. These observations have called into question the effectiveness of classic antioxidants, which, by scavenging already formed toxic oxidation products, only exert symptomatic action. In this regard, use of causal antioxidants that exert preventive activity against oxidative stress could be more promising. Several drugs in common clinical use have been shown to exert vasculoprotective effects and to possess strong intracellular antioxidant activities. These include angiotensin-converting enzyme inhibitors, angiotensin receptor-1 blockers, calcium channel blockers, statins, thiazolidinediones, metformin, and gliclazide. Combined use of these compounds with adequate intake of antioxidants may be effective in preventing cardiovascular complications in diabetic patients.

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Type 2 diabetes as an inflammatory cardiovascular disorder and the role of oxidative stress

by G. Renier, Canada

Atherosclerosis is an inflammatory disease

Although atherosclerosis was believed to be exclusively a cholesterol storage disease for over a century, we rather understand atherogenesis today as a chronic inflammatory response driven by, and probably initiated by, hypercholesterolemia. The most persuasive and clear-cut evidence that atherosclerosis is an inflammatory disease comes from the identification of immune system.
activity involving T cells, macrophages, antibodies, and complement in the developing plaque, even in the very earliest fatty streak lesions. Monocytes and T cells, through immune responses and complex interactions with vascular elements, modulate the development of the lesion and its stability.\(^3\) Inflammation probably occurs as a response to hypercholesterolemia and accumulation of oxidized lipids in the arterial intima, leading to endothelial dysfunction and monocyte penetration into the subendothelial space. These initial events are followed by a broad array of complex inflammatory and immune reactions that lead to atherosclerotic plaque development (Figure 1). It is now widely accepted that inflammation links dyslipidemia to atheroma formation and plays a key role in all phases of the atherosclerotic disease process, from lesion initiation to progression and, ultimately to plaque rupture and the ensuing thrombotic complications of cardiovascular disease (CVD). The revision of our classic views of atherosclerosis identifies both low-density lipoprotein (LDL) and inflammation as critical therapeutic targets for reducing coronary artery disease in coming years.

**Type 2 diabetes, an inflammatory cardiovascular disorder**

In the last 50 years, health care systems throughout the world have faced a new epidemic dual disease: CVD-diabetes mellitus, which results in a large economic burden and a devastating toll of human suffering. CVD is the leading cause of death in diabetic patients and is responsible for much of morbidity-related diabetes. As the number of adults with diabetes is increasing dramatically worldwide, development of new strategies for preventing diabetic cardiovascular complications undoubtedly represents a major challenge.

The striking association between CVD and diabetes since the publication of the first large-scale epidemiologic investigation in the 1970s, has forced physicians to investigate the pathophysiological connection among these clinical conditions. Recent and compelling evidence has shown the significant and independent role of inflammation and insulin resistance in the development of both CVD and type 2 diabetes.\(^4\) These observations and the recognition that both atherosclerosis and type 2 diabetes share a common inflammatory basis have fueled the speculation that these two conditions might result from a shared antecedent, the so-called “common soil” hypothesis, and that chronic inflammation may represent a candidate mechanism linking type 2 diabetes and CVD.

**Inflammation: the widening interface between atherosclerosis and diabetes**

As discussed above, atherosclerosis is an immune-mediated inflammatory disease in which the secretion of multiple factors by infiltrating mononuclear cells plays a key role. Major mediators of this inflammatory response include the T helper type 1 proinflammatory cytokines and the IκB/nuclear factor-κB (NF-κB) system. Perhaps one of the most compelling aspects of basic science research into the inflammatory mechanisms involved in atherogenesis has been its headfirst collision with evidence from epidemiological trials showing the predictive value of circulating inflammatory markers on the development of CVD.\(^5,10\)

While the idea that insulin resistance and impaired insulin secretion are central to the pathogenesis of type 2 diabetes is not new, the notion that inflammation might be an accomplice in the pathogenesis of type 2 diabetes has been developed only recently.\(^7\) Since this hypothesis was first proposed in 1997 and 1998,\(^12,13\) at least 12 studies have shown that circulating markers of inflammation predict the development of type 2 diabetes and that an ongoing cytokine-induced acute phase response is present in patients with diabetes and in those at risk for developing diabetes. The evidence implicating inflammation as a contributor to both atherosclerosis and type 2 diabetes carries embedded within it the prospect that inflammation may represent the common antecedent of both type 2 diabetes and...
Insulin resistance also carries with it detectable inflammation and oxidation. Advanced glycation end-products (AGEs) as well as oxidized LDL (oxLDL) are products (AGEs) as well as oxidized LDL (oxLDL) are detectable in prediabetic subjects with high insulin resistance.22 Insulin resistance also carries with it detectable inflammation and oxidation. Advanced glycation end-products (AGEs) as well as oxidized LDL (oxLDL) are able to interact with a variety of cells to induce the release of proinflammatory mediators.21 These proteins are also immunogenic and immune complexes that contain modified lipoproteins have proinflammatory properties, inducing the release of cytokines and metalloproteinases. Inflammatory responses can also be elicited by oxidized lipids, generated by the action of the lipoxygenase and cyclooxygenase enzymes, which are produced under diabetic conditions.23 Proposed connections between environmental/genetic factors, insulin resistance, type 2 diabetes, inflammation, and atherosclerosis are illustrated in Figure 2.

**Mechanisms of inflammation in type 2 diabetes**

Elements unique to diabetes mellitus, such as hyperglycemia, insulin resistance, and modified proteins may contribute to inflammation in diabetic atherosclerosis. The importance of hyperglycemia per se in the inflammatory response associated with type 2 diabetes is still debated, with evidence for and against. Proinflammatory proteins are related to glycemia cross-sectionally,18,19 and lowering glucose levels in type 2 diabetic patients is accompanied by reduced levels of inflammatory markers.20,21 Exposure of monocytes to high concentrations of glucose leads to increased expression of multiple inflammatory cytokines, chemokines, and related factors, many of which are regulated by the proinflammatory transcription factor NF-κB, and acute hyperglycemia in nondiabetic subjects elevates plasma cytokine concentrations. On the other hand, acute-phase markers are not elevated in type 1 diabetic subjects who have the same degree of hyperglycemia as type 2 diabetic patients. Thus, it seems that chronic hyperglycemia is not sufficient to induce inflammation, although it may contribute to it. In contrast to hyperglycemia, there is strong evidence that inflammation in type 2 diabetes independently associates with insulin resistance, being detected in prediabetic subjects with high insulin resistance.22 Insulin resistance also carries with it numerous abnormalities including hypertension, dyslipidemia, and shifts in plasminogen activator inhibitor-1 (PAI-1), which all may promote inflammation. Diabetes is a major predisposing factor for the generation of modified proteins through glycation and oxidation. Advanced glycation end-products (AGEs) as well as oxidized LDL (oxLDL) are able to interact with a variety of cells to induce the release of proinflammatory mediators.21 These proteins are also immunogenic and immune complexes that contain modified lipoproteins have proinflammatory properties, inducing the release of cytokines and metalloproteinases. Inflammatory responses can also be elicited by oxidized lipids, generated by the action of the lipoxygenase and cyclooxygenase enzymes, which are produced under diabetic conditions.23 Proposed connections between environmental/genetic factors, insulin resistance, type 2 diabetes, inflammation, and atherosclerosis are illustrated in Figure 2.

**Oxidative stress and diabetic vascular complications**

Atherosclerosis represents a state of heightened oxidative stress characterized by lipid and protein oxidation in the vascular wall. The oxidative modification hypothesis of atherosclerosis predicts that LDL oxidation is an early event in atherosclerosis and that oxLDL contributes to atherogenesis (Figure 1).24 An emerging consensus also underscores the importance in vascular damage of oxidative events in addition to LDL oxidation. These include the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) by vascular cells, as well as oxidative modifications contributing to important clinical manifestations of coronary artery disease such as endothelial dysfunction and plaque growth/disruption.25 Oxidative stress is thought to promote several key steps of plaque formation, such as impaired endothelial function, increased inflammatory cell recruitment, and lipid infiltration, as well as plaque instability.26,27 Despite this, the causative relationship between oxidative stress and atherosclerosis has been challenged by the overall poor performance of antioxidant strategies in limiting atherosclerosis and its cardiovascular events. These observations have called into question the relation between oxidative events and atherosclerosis (Figure 3). Irrespective of the different conceptual views of oxidative stress as a cause or consequence of atherogenesis,28,29 the close interrelationship be

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**Figure 2. Proposed connections between lifestyle/genetic factors, insulin resistance, type 2 diabetes, inflammation, and atherosclerosis. Abbreviations: AGE, advanced glycation end-product; oxLDL, oxidized low-density lipoprotein; PAI-1, plasminogen activator inhibitor-1.**

**Figure 3. Relationship between oxidative stress and atherosclerosis. (A) The presence of cardiovascular risk factors promotes an oxidative stress response that is central to lesion development. (B) The inflammatory process is a primary event in atherosclerosis, and oxidative stress occurs as a process secondary to inflammation. (C) Inflammation and oxidative stress are interrelated responses and both contribute to atherogenesis. Modified from reference 26: Stocker R, Keaney JF. Role of oxidative modifications in atherosclerosis. Physiol Rev. 2004;84:1381-1478. Copyright © 2004, American Physiological Society.**
between oxidative stress and inflammation is strongly established. It is well recognized that inflammation is one manifestation of oxidative stress. Pathways that generate the mediators of inflammation, such as adhesion molecules and cytokines, are all induced by oxidative stress. It is also evident that activities of several enzymes that all possess the catalytic capacity to produce ROS and RNS modulate the inflammatory process. Finally, mitochondrial overgeneration of free radicals has been recently implicated in the subclinical proinflammatory state seen in many conditions, including atherosclerosis. In turn, it is widely accepted that oxidative stress is an important secondary consequence of inflammation.

Of the established cardiovascular risk factors, diabetes is highly predictive of increased oxidative stress, being associated with enhanced levels of circulating markers of free radical-induced damage and reduced antioxidant defenses. The drivers of this oxidative stress include hyperglycemia, hyperinsulinemia, elevated free fatty acids, lipids, and leptin. Hyperglycemia can induce oxidative stress via several mechanisms. These include glucose autoxidation, the formation of AGEs, and the activation of the polyol pathway. Hyperglycemia promotes the production of ROS and RNS in many cell types and when present chronically promotes the formation of AGEs, which themselves are capable of inducing ROS production. Hyperglycemia-induced ROS production undoubtedly emanates from several different sources including mitochondria and reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidases. Evidence implicates hyperglycemia-induced ROS production as a key event in the activation of all pathways involved in the pathogenesis of diabetic vascular complications and as a key biological event leading to inflammation and endothelial dysfunction in human diabetes, through NF-κB activation and the subsequent transcriptional activation of genes relevant for inflammation, immunity, and atherosclerosis.

Because insulin resistance, impaired glucose tolerance, and overt diabetes are associated with an increased risk of CVD and the presence of oxidative stress, it has been proposed that oxidative stress may represent a pathogenic mechanism linking insulin resistance with dysfunction of both β cells and endothelial cells, eventually leading to overt diabetes and CVD. This could explain why therapeutic strategies, apparently having in common only the ability to reduce oxidative stress, appear to simultaneously lead to decreased cardiovascular mortality and lower incidence of diabetes. In conclusion, many pieces of evidence suggest that oxidative stress may be viewed as a key element in the generation of insulin resistance, diabetes, and CVD.

**Dietary and pharmacological interventions addressing oxidative stress**

Over the past decades, the free radical theory has greatly stimulated interest in the role of dietary antioxidants in preventing atherosclerosis and diabetes. Vitamins are known to scavenge ROS. Among them, vitamin E is recognized as one of the most important dietary antioxidants. While results of large prospective epidemiologic studies have supported a protective role for antioxidant vitamins in CVD, results of randomized clinical trials with vitamins C and E have been disappointing in failing to demonstrate in both diabetic and nondiabetic subjects any beneficial effect on CVD or all-cause mortality. Several theoretical explanations for these findings have been put forward. First and foremost, one must consider the possibility that oxidative events are not causally related to the process of atherosclerosis and clinical CVD. For many, this represents an unattractive explanation given the wealth of associative data linking oxidative stress to atherosclerosis. Second, failure of these clinical trials may be due to other factors such as the lack of selection of the patients on the basis of their oxidative status, the use of ROS-scavenging drugs instead of drugs preventing their generation, the choice and dose of antioxidants, the chemical form of tocopherol administered, the follow-up times and length of administration of the antioxidants, as well as the pro-oxidant effects of these compounds.

Besides vitamins, other dietary micronutrients such as minerals, coenzyme Q, lipoic acid, and flavonoids exhibit potent antioxidant activities, showing free radical–scavenging activities and regulating antioxidant enzyme functions. In that sense, the emerging role of coenzyme Q-10 in lowering blood pressure and improving glyemic control and vascular function in type 2 diabetic patients is encouraging. Other dietary components, such as n-3 fatty acids, which show cardioprotective effects and decrease oxidant stress in patients with type 2 diabetes, may also provide health benefits. Although further intervention studies in humans are needed to investigate the effects of these nutrients on cardiovascular outcomes, dietary supplementation with these compounds may be a complement to classic therapies for preventing and treating diabetic complications.

As the pathogenesis of both diabetes and CVD appears to involve oxidative stress, developing new specific and causal antioxidants may become an appealing therapy to oppose the increasing epidemic of diabetes and its cardiovascular complications. In contrast to classic antioxidants like vitamin E, which only exert “symptomatic” action, causal antioxidants exert, through various mechanisms, preventive activity against oxidative stress (Table I, page 224). Of the drugs in common clinical use that effectively reduce cardiovascular mortality, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor–1 (AT1) blockers, calcium channel blockers, statins, and thiazolidinediones have strong intracellular antioxidant activities. ACE inhibitors and AT1 blockers, which have already demonstrated beneficial effects on diabetic patients in large randomized controlled trials, prevent hyperglycemia-derived oxidative stress modulating angiotensin action and production. By inhibiting NADPH oxidase expression and activity, these drugs have proven effective in reducing vascular superoxide production and reversing endothelial dysfunc-
Inflammation and oxidation are crucial to the pathogenesis of atherosclerosis and the pathogenesis of diabetic cardiovascular complications. Early initiation of therapy aimed at reducing inflammation and oxidative stress may be of benefit for reducing CVD in diabetes. Causal antioxidant therapy with compounds that act as intracellular ROS scavengers or antioxidant enzyme mimetics and modulate ROS-sensitive signaling pathways may represent a potential avenue of therapy in diabetic patients in order to prevent the onset and progression of cardiovascular complications.

Conclusion

Type 2 diabetes as an inflammatory CV disorder and oxidative stress – Renier
REFERENCES


**RÔLE DU STRESS OXYDATIF DANS LE DIABÈTE DE TYPE 2**

Le diabète de type 2 est étroitement associé à l’athérosclérose et représente un facteur de risque majeur de maladies cardio-vasculaires. L’inflammation, processus principal de l’athérosclérose, joue un rôle clé dans l’instauration, la progression et la rupture des plaques d’athérosclérose. Il a été montré récemment que le diabète de type 2 et l’athérosclérose partagent une même base inflammatoire et sont tous deux associés à un niveau de stress oxydatif accru. Les événements oxydatifs sont étroitement liés à l’inflammation et semblent faciliter le développement et la progression de l’athérosclérose. Par conséquent, un traitement antioxydant devrait réduire de façon directe ou indirecte le risque de maladie cardio-vasculaire et améliorer le pronostic d’événements cardio-vasculaires chez les diabétiques de type 2. Cependant, les grandes études cliniques entreprises pour mettre en évidence les effets bénéfiques potentiels des antioxydants sur les maladies cardio-vasculaires ont jusqu’à maintenant été très décevantes. Ces observations ont remis en question l’efficacité des antioxydants classiques qui, en épurant les produits d’oxydation déjà formés, n’exercent qu’une activité symptomatique. Une approche alternative et peut-être plus prometteuse serait d’utiliser des antioxydants exerçant une activité préventive contre le stress oxydatif. Dans la pratique clinique courante, de nombreux médicaments exercent des effets vasculoprotecteurs ainsi qu’une forte activité antioxydante intracellulaire : ce sont les inhibiteurs de l’enzyme de conversion de l’angiotensine, les antagonistes des récepteurs de l’angiotensine I, les inhibiteurs calciques, les statines, les thiazolidinediones, la metformine et le gliclazide. L’usage de ces composés pourrait représenter une avenue thérapeutique intéressante dans la prévention des complications cardio-vasculaires associées au diabète de type 2.
Risk and mortality of myocardial infarction in type 2 diabetes mellitus

by N. Danchin, E. Durand, and V. Decalf, France

Cardiovascular complications are the main cause of death in diabetic patients. In patients with acute myocardial infarction, diabetes mellitus carries a higher risk of mortality and worse long-term outcome. Although mortality in diabetic patients with myocardial infarction has decreased over the past 10 years, there remains a gap between the outcomes of diabetic versus nondiabetic subjects. The safety of oral antidiabetic medications has been questioned, in particular as regards older-generation sulfonylureas. Among the three most commonly used sulfonylureas nowadays (glibenclamide/glyburide, glipizide, glimepiride), only the first has a documented impact on myocardial response to ischemia. Following reports in small series of patients, the impact of sulfonylurea therapy on early outcome in diabetic patients presenting with acute myocardial infarction has been assessed in two larger populations. In the French Unités de Soins Intensifs Cardiologiques–2000 (USIC 2000) registry, patients with sulfonylureas had a significantly better survival than those without. In the Danish North Jutland case-control study, acute myocardial infarction mortality in diabetic patients with newer-generation sulfonylureas (glipizide, glimepiride) was comparable with that of nondiabetic patients, while mortality in patients receiving glibenclamide was higher, suggesting the true clinical relevance of the myocardial properties of this latter medication. This differential effect according to the type of sulfonylurea has been recently confirmed by data from the French Acute ST-elevation and non-ST-elevation Myocardial Infarction (FAST-MI) registry.

Keywords: diabetes mellitus; acute myocardial infarction; sulfonylureas; outcome

Cardiovascular outcome of diabetic patients

Outcome of diabetic patients at the acute stage of myocardial infarction
Mortality of acute MI has been found to be higher in diabetic patients in most observational series. Differences in the baseline characteristics of diabetic versus nondiabetic subjects (older age, more common history of cardiovascular disease, concomitant diseases) may partly explain this difference in outcome. However, diabetes mellitus (DM) remains an independent risk factor for early mortality after confounders are taken into account (Table I, page 228).

In the French Unités de Soins Intensifs Cardiologiques–2000 (USIC 2000) registry, presence of DM was an independent correlate of in-hospital mortality (odds ratio [OR], 1.47; \( P<0.05 \)). Likewise, in the Global Registry of Acute Coronary Events (GRACE), the OR for in-hospital death in diabetic patients was 1.35 (\( P<0.001 \)), compared with nondiabetic patients. In the first Euro Heart Survey on acute coronary syndromes, \( P<0.001 \), mortality was 9.8% in diabetic patients versus 5.7% in nondiabetic patients; after multivariate adjustment, the relative risk (RR) of in-hospital mortality for diabetic patients was 1.6.

Recently, the Swedish registry of acute MI analyzed the influence of DM on 1-year mortality, also taking into account the extent of coronary artery disease (CAD). The RR of death was 5.43 for diabetic versus nondiabetic patients (\( P<0.001 \)).

Selected abbreviations and acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Explanation</th>
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<tbody>
<tr>
<td>CAD</td>
<td>coronary artery disease</td>
</tr>
<tr>
<td>DM</td>
<td>diabetes mellitus</td>
</tr>
<tr>
<td>GRACE</td>
<td>Global Registry of Acute Coronary Events</td>
</tr>
<tr>
<td>DARTS</td>
<td>Diabetes Audit and Research in Tayside Scotland</td>
</tr>
<tr>
<td>FAST-MI</td>
<td>French Acute ST-elevation and non-ST-elevation Myocardial Infarction (registry)</td>
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<tr>
<td>MI</td>
<td>myocardial infarction</td>
</tr>
<tr>
<td>UGDP</td>
<td>University Group Diabetes Program</td>
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<tr>
<td>UKPDS</td>
<td>United Kingdom Prospective Diabetes Study</td>
</tr>
<tr>
<td>USIC 2000</td>
<td>Unités de Soins Intensifs Cardiologiques–2000 (registry)</td>
</tr>
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</table>
Risk and mortality of myocardial infarction in type 2 diabetes mellitus – Danchin and others

One additional reason for the bleaker prognosis of diabetic subjects is that most surveys have shown that they receive evidence-based medications less often than nondiabetic patients. Finally, although mortality in diabetic patients with acute MI has decreased substantially in recent years, the mortality gap between diabetic and nondiabetic patients seems to persist in the current era. In the Munich registry, though, inpatient mortality in diabetic patients was comparable with that in nondiabetic subjects; the population involved in that registry, however, was small and this favorable evolution in diabetic versus nondiabetic patients with MI has not been confirmed in other recent registries.

**Long-term outcome of diabetic patients after acute myocardial infarction**

In a much-publicized study, Haffner et al showed that diabetic patients without known CAD had a 7-year risk of death or acute MI similar to that of CAD patients with a history of MI. More recent studies, though, are less pessimistic. They all show that the cardiovascular outcome of diabetic patients is definitely worse than that of nondiabetics without known CAD, although it is better than that of patients with documented CAD. Nevertheless, in all of these studies, CAD patients with DM fared less well than nondiabetics with CAD. The same holds true in patients having survived the acute stage of MI.3

**Impact of chronic oral antidiabetic medications on mortality and cardiovascular events in diabetic patients**

Metformin and sulfonylureas represent the two main classes of oral medications used in diabetic patients. However, the safety of sulfonylureas has been challenged in several studies, which have shown increased mortality in diabetic patients receiving sulfonylureas, in particular compared with metformin. Thirty-five years ago, the University Group Diabetes Program (UGDP) brought attention to the increased cardiovascular risk associated with sulfonylureas. More recently, in the United Kingdom Prospective Diabetes Study–34 (UKPDS 34) trial, patients allocated metformin had fewer diabetes-related events and lower mortality than those allocated chlorpropamide, glibenclamide, or insulin. These results in prospective trials were supported by observational data. In the early 2000s, the results of the Saskatchewan health database were reported. This database included 12 272 new users of oral antidiabetic medications. Mortality at 5 years in sulfonylurea users was significantly higher than that of metformin users (25% vs 14%). However, as sulfonylurea users had a worse initial risk profile than metformin users, adjustment on baseline variables attenuated this difference (adjusted ORs for overall mortality in metformin users versus sulfonylurea users, 0.60; 95% confidence interval [CI], 0.49-0.74). Patients who were on metformin and sulfonylurea combinations, however, had no increase in mortality. More recently, similar findings were reported from the Scottish Diabetes Audit and Research in Tayside Scotland (DARTS) database. During a maximum follow-up of 8 years, 1000 patients out of the initial 5730 population of newly treated patients died. Patients in the sulfonylurea-only cohort had increased risks of overall mortality (RR, 3.12) and cardiovascular mortality (RR, 3.71). However, here again, adjustment for differences in baseline characteristics decreased the RR of death to 1.43 (95% CI, 1.15-1.77) and the RR of cardiovascular death to 1.70 (95% CI, 1.18-2.43). Contrary to the Saskatchewan database, patients receiving metformin and sulfonylurea combinations were also at greater risk of dying (RR, >2.0). These results, however, must be interpreted with caution since in the Saskatchewan series as in all the aforementioned studies, patients received essentially first-generation sulfonylureas (tolbutamide, chlorpropamide, or glyburide/glibenclamide).

When considering only the most widely used sulfonylureas currently, it appears that there are major differences between glibenclamide, which is not specific to the pancreatic β cells, and gliclazide or glimepiride. Glibenclamide acts as an inhibitor of the K<sub>ATP</sub> channels of the myocardial cells and therefore inhibits ischemic preconditioning mechanisms in the myocardium. Indeed, glibenclamide is used in animal experiments to block myocardial preconditioning. The clinical impact of this effect of glibenclamide is not fully known, but may provide an explanation for the worse clinical outcomes observed in patients treated with first-generation sulfonylureas. Experimentally, the administration of glibenclamide results in larger infarcted areas after acute coronary artery occlusion. Data, however, are much scarcer in humans. A recent study compared the effect of glibenclamide and gliclazide modified release (MR) on ischemic preconditioning in a human heart tissue model, in which tissue injury was determined by measuring creatinine leakage. This study showed that, in contrast to glibenclamide, gliclazide MR, at therapeutic dosage, preserved ischemic preconditioning. Three studies have used a model of preconditioning with repeated balloon inflations during coronary angioplasty. In all three studies, glibenclamide inhibited the phenomenon of ischemic preconditioning caused by

### Table I. Early or in-hospital mortality in diabetic versus nondiabetic patients with acute myocardial infarction

<table>
<thead>
<tr>
<th>Study</th>
<th>Mortality in nondiabetic patients</th>
<th>Mortality in diabetic patients</th>
<th>P value</th>
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<tbody>
<tr>
<td>USIC 1995&lt;sup&gt;1&lt;/sup&gt;</td>
<td>7.0&lt;sup&gt;†&lt;/sup&gt;</td>
<td>10.2&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>0.02</td>
</tr>
<tr>
<td>USIC 2000&lt;sup&gt;6&lt;/sup&gt;</td>
<td>5.0&lt;sup&gt;†&lt;/sup&gt;</td>
<td>9.0&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>0.001</td>
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<tr>
<td>GRACE&lt;sup&gt;2&lt;/sup&gt;</td>
<td>4.1&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>5.8&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>0.001</td>
</tr>
<tr>
<td>Svensson et al&lt;sup&gt;4&lt;/sup&gt;</td>
<td>5.0&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>9.8&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Euro Heart Survey&lt;sup&gt;3&lt;/sup&gt;</td>
<td>5.7&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>9.8&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>&lt;0.05</td>
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<sup>†</sup>5-day mortality.  
<sup>‡</sup>In-hospital mortality.
the first balloon inflation. In addition, Klepzig et al. found that, contrary to glibenclamide, gliptin did not affect ischemic preconditioning. In contrast, in normal and stenotic coronary arteries, Reffelmann et al. found no change in coronary blood flow at rest, as well as coronary flow reserve, after treatment with intravenous glibenclamide compared with baseline conditions, thereby challenging the importance of the concept of vascular smooth muscle cell KATP blockade in the clinical setting; intravenous administration, however, may not have the same impact as chronic oral administration. Lastly, the effect of glibenclamide compared with insulin on left ventricular function during ischemic stress in diabetic patients with documented CAD has been assessed in a randomized crossover trial involving 19 patients. All patients were treated for two 12-week periods with either glibenclamide or insulin, and dobutamine stress echocardiography was performed at the end of each period. After glibenclamide, left ventricular ejection fraction decreased markedly and the wall-motion score index worsened significantly; in contrast, after insulin therapy, none of these parameters significantly changed compared with their baseline values.

Impact of chronic antidiabetic therapy on acute myocardial infarction development

Until recently, few studies had analyzed the influence of chronic antidiabetic medications on outcomes in diabetic patients developing acute MI. In the specific setting of acute MI treated by primary coronary intervention, Garratt et al. observed a higher mortality in 67 patients who were on sulfonylureas, compared with 118 who were not. Conversely, Klamann et al. found no increase in hospital mortality in 76 patients admitted for acute MI while on sulfonylureas, compared with 89 diabetic patients not on sulfonylureas. Brady et al. also reported reassuring data from the population-based Olmsted County cohort: over a mean follow-up of 2.7 years after acute MI, mortality was not statistically different in 46 patients receiving sulfonylureas, compared with 56 receiving insulin. In patients receiving thrombolysis by accelerated recombinant tissue plasminogen activator (rtPA) or streptokinase, receiving thrombolysis by accelerated recombinant tissue plasminogen activator (rtPA) or streptokinase, 21 patients (23.3%) had known diabetes, 95 (23%) were receiving sulfonylureas, whereas another one found no association between sulfonylurea therapy and adverse outcome. Overall, these data, always corresponding to small series of patients, appear conflicting, some suggesting more adverse outcomes in patients treated with sulfonylureas, while others do not.

In this context, we analyzed in-hospital mortality of diabetic patients according to their previous chronic antidiabetic treatment in the nationwide French USIC 2000 registry. This registry included all patients admitted to intensive care units in France in November 2000 for acute MI ≤ 48 hours from symptom onset. Among the 2320 patients included in the registry, 487 (21%) had known diabetes, of whom 215 (44%) were on sulfonylureas. This series represents the largest one studied in this respect to date. Patients on sulfonylureas were older and had a more frequent history of hypercholesterolemia than those not receiving these medications. Type and location of infarction were similar in the 2 groups, and there was no difference in Killip class on admission. In-hospital mortality was lower in patients on sulfonylureas (10.2%) than in those without sulfonylureas (16.9%) (P = 0.035). Fewer patients on sulfonylureas had ventricular fibrillation, but the difference did not quite reach statistical significance (2.3% vs 5.9%; P = 0.052). In subgroup analyses, patients on sulfonylureas consistently had a lower mortality; for instance, in those treated with primary percutaneous coronary interventions, mortality was 7.3% in those on sulfonylureas, versus 25% in those not on sulfonylureas. In order to take into account possible imbalances between patients on versus off sulfonylureas, we performed multivariate analyses using 2 different models, both including a propensity score for the use of these medications. The first model included demographic and medical history variables, as well as medications used at the time of infarction. The second model also included Killip class, heart rate, blood pressure on admission, and initial level of blood glucose, which are classic prognostic indicators but which might have been influenced by the medications used at the time of onset of the acute episode (eg, sulfonylureas might have an effect on the size of infarction, and therefore on hemodynamic variables on admission). In both models, sulfonylurea therapy was associated with decreased inhospital mortality (model 1: RR: 0.44; P = 0.012; model 2: RR: 0.37; P = 0.020) (Table II). In addition, in patients receiving sulfonylureas before admission, mortality was comparable in those who received early insulin therapy (10.0%) and in those who did not (10.5%). Unfortunately, the exact type of sulfonylurea used was not available in the USIC 2000 registry. Of note, however, the sales figures for

<table>
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<tr>
<th>Model</th>
<th>Odds ratio</th>
<th>95% confidence interval</th>
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<td>Danish registry</td>
<td>Newer sulfonylureas</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Older sulfonylureas</td>
<td>1.29</td>
</tr>
<tr>
<td>French USIC 2000</td>
<td>Use of sulfonylureas</td>
<td>0.44</td>
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Table II. Early mortality in diabetic patients with acute myocardial infarction according to the previous use of sulfonylureas in the Danish and French registries.
Diabetic patients continue to have poorer cardiovascular outcomes, compared with nondiabetic subjects. In patients with acute MI, mortality has declined in diabetic as in nondiabetic patients, so that the difference in mortality between diabetic and nondiabetic subjects presenting with acute MI persists. In patients with MI, those on chronic sulfonylurea treatment currently have better in-hospital and 1-year outcomes. Among sulfonylurea users, those on older-generation medications, such as tolbutamide or glibenclamide, appear to have a higher mortality compared with those treated with newer-generation medications (gliclazide or glimepiride).

**Conclusion**

The findings of Johnson et al are in keeping with those suggesting that outcomes differ according to the type of sulfonylurea used. These authors performed a case-control study of 6636 patients admitted for MI in the North Jutland county of Denmark from 1994 to 2002. The adjusted ORs for developing MI were 1.36 (95% CI, 1.01-1.84) for patients on never sulfonylureas (gliclazide or glimepiride), 2.07 (95% CI, 1.81-2.37) for older sulfonylureas (glibenclamide, tolbutamide, glipizide), 1.38 (95% CI, 0.90-2.11) for other oral antidiabetic medications (mainly metformin), and 2.56 (95% CI, 2.16-3.03) for insulin. Compared with nondiabetic patients with MI, the OR for 30-day death in diabetic patients with MI while on newer sulfonylures was 1.00 (95% CI, 0.53-1.90) and the OR in diabetic patients on older sulfonylures was 1.29 (95% CI, 1.00-1.67). The OR for 30-day mortality for diabetic patients on other oral antidiabetic medications was similar to that of patients on newer sulfonylures, and that of patients on insulin was similar to that of patients on older sulfonylures.

**REFERENCES**

RISQUE ET MORTALITÉ DE L’INFARCTUS DU MYOCARDE DANS LE DIABÈTE DE TYPE 2

Diabetes mellitus (DM), in particular type 2 DM (T2DM), increases the risk of developing atherosclerosis, with ischemic heart disease (IHD) being the main cause of death. The development and associated mortality rate of IHD is 2 to 4 times higher in diabetic patients compared with the general population. While the prognosis for IHD in nondiabetic patients improves markedly with invasive treatment, the risk of serious coronary incidents in diabetic patients with underlying coronary disease remains high. This indicates that there is a need for targeted care and treatment in this patient population, taking into consideration the specific pathogenic features of DM.

**Keywords:** type 2 diabetes mellitus; DIGAMI study; myocardial infarction; hypoglycemic treatment

**SELECTED ABBREVIATIONS AND ACRONYMS**

- ACC: American College of Cardiology
- AHA: American Heart Association
- DECODE: Diabetes Epidemiology, Collaborative Analysis of Diagnostic Criteria in Europe
- DIGAMI: Diabetes mellitus, Insulin Glucose infusion in Acute Myocardial Infarction (study)
- DM: diabetes mellitus
- EASD: European Association for the Study of Diabetes
- ESC: European Society of Cardiology
- IHD: ischemic heart disease
- PROACTIVE: PROspective pioglitAzone Clinical Trial In macroVascular Events
- T2DM: type 2 diabetes mellitus
- UKPDS: United Kingdom Prospective Diabetes Study
The aim of primary prevention of cardiovascular complications is to diminish the progression of atherosclerosis, and this includes multifactorial intervention. In the Steno 2 study, primary prevention was associated with a 50% reduction in the risk of cardiovascular events. Multifactorial intervention in this study included the aggressive normalization of blood glucose levels (target HbA1c value of <6.5%). This was achieved using progressive therapy with oral hypoglycemic agents—gliclazide in lean patients or overweight patients with a contra-indication to metformin, and metformin in overweight patients. For cases in which blood glucose normalization could not be achieved, the therapy was intensified by adding metformin to the regimen of lean patients and gliclazide to the regimen of overweight patients. If the HbA1c value exceeded 7.0% despite this regimen, insulin was added, lean patients stopped metformin, and overweight patients stopped gliclazide (unless it was the only oral hypoglycemic agent given). It must be emphasized that only 18% of patients in the intensive treatment group achieved the target blood glucose level. Hypoglycemic therapy was complemented by aggressive antihypertensive treatment using angiotensin-converting enzyme (ACE) inhibitors, antilipemic agents (fibrates, statins), aspirin, and a vitamin-mineral supplement. The question of whether more effective normalization of blood glucose levels would be associated with an improved reduction in cardiovascular risk is open to debate.

There is some discussion regarding whether particular types of hypoglycemic therapy (oral hypoglycemic agents vs insulin) have additional effects aside from blood glucose normalization for the prevention of cardiovascular risk. The United Kingdom Prospective Diabetes Study (UKPDS)—33 showed that the incidence of myocardial infarction (MI) was not affected by whether patients were treated with sulfonylureas (ie, glibenclamide or chlorpropamide) or insulin after diagnosis of DM. A reduction in the incidence of MI was merely associated with the improvement of glucometabolic status. This confirms the theory that it is only the achievement of blood glucose normalization—indeed of the type of glucose lowering therapy—that is crucial for the prevention of cardiovascular complications in DM. One of the UKPDS substudies (UKPDS 34) demonstrated an additional beneficial role for metformin: in a subgroup of obese patients in whom stable normoglycemia was sustained without the addition of sulfonylurea during the entire observation period, there was a significant reduction in the incidence of MI compared with the conventionally treated group in which the less restricted target values were applied. However, in those obese patients in which the addition of a sulfonylurea (glibenclamide or chlorpropamide) was necessary to sustain normoglycemia, a higher risk of cardiovascular complications was reported. The possible explanation for this “toxic” effect of the combined oral hypoglycemic treatment is that these patients were experiencing metabolic disturbances of a greater severity than those of the patients who did not require sulfonylureas (hence their need for intensified treatment), and this was the reason for the higher incidence of cardiovascular complications, rather than the drugs used to treat them per se.

Despite the improvement in our knowledge of the pathogenesis of macrovascular complications—in particular MI—and the improvement of treatment strategies to combat such complications, a large number of patients with T2DM still experience acute coronary episodes. In UKPDS, MI was found to be the main complication of T2DM, affecting around 1 in 7 patients during a 15-year observation period following the diagnosis of DM. These numbers may be underestimated, because one of the exclusion criteria for the patients randomized to UKPDS was a history of MI within 6 months before randomization.

On the other hand, high numbers of patients who experience acute coronary syndrome and are without a previous diagnosis of DM have been found to manifest different stages of glucose intolerance. DIGAMI 2 included 620 diabetic patients with MI who were followed up for 3.4 years, reported that intravenous (IV) insulin infusion during the acute phase of MI can reduce mortality by 11%. A reduction in mortality was particularly evident in the subgroup not treated with insulin before acute MI, in which the reduction exceeded 40%. Recently published guidelines prepared by the joint committees of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD) recommend the initiation of insulin infusion for blood glucose control in all diabetic patients, so that normoglycemia can be achieved as soon as possible after admission to the intensive coronary unit. In the follow-up period, strict blood glucose control should be maintained by diet and lifestyle modification, oral agents, and insulin.

The results of DIGAMI 1, however, did not determine whether acute MI is an indication for long-term insulin therapy independent of the levels of blood glucose achieved. The group of researchers who carried out the DIGAMI 1 study attempted to clarify this issue in the consecutive study known as DIGAMI 2, and its results were published in 2005. DIGAMI 2 included 1253 patients with T2DM or no history of DM, but a blood glucose level exceeding 11 mmol/L, and acute MI at admission. The patients were assigned to 3 groups: (i) treatment with a 24-hour IV insulin-glucose infusion followed by multiple subcutaneous insulin...
insulin IV infusions followed by insulin subcutaneous injections during the whole study; group 2: insulin IV infusions), DIGAMI 2 did not confirm the results of DIGAMI 1, in which insulin therapy was found to have an effect on the prognosis of diabetic patients after MI. No statistical differences were noted between the groups in terms of mortality or postinfarction complications. Epidemiological analysis of DIGAMI 2 data, however, indicates that hyperglycemia is a predictor of mortality after acute MI.\textsuperscript{16}

The results obtained failed to answer the question of whether insulin use in acute MI should be mandatory, as indicated by the results of the DIGAMI 1 study. Unequivocal conclusions require a detailed analysis of the DIGAMI 2 study:

- DIGAMI 2 incompletely fulfilled its protocol: it was designed to include 3000 patients, but included only 1253 patients.
- The target fasting blood glucose level for patients in group 1 was never achieved.
- The overall study mortality rate was lower than expected (18.4\% vs 22.3\%). In DIGAMI 1, overall mortality was 33\% in the group of patients treated aggressively, and 44\% in the control group. The lower percentages of analyzed complications in both groups in DIGAMI 2 could be a cause of the lack of a significant difference between groups.
- In the time lapse between DIGAMI 1 and DIGAMI 2, there was a marked improvement in the availability and use of revascularization techniques, which resulted in a remarkable decrease in the rates of post-MI mortality and morbidity. In DIGAMI 2, 78\% of patients underwent revascularization procedures in comparison with “nearly half” of patients in DIGAMI 1.\textsuperscript{7} Reperfusion reverses or reduces the area of necrosis and significantly improves prognosis, as indicated by the percentage of complications in both DIGAMI 1 and 2. Recently, statins, ACE inhibitors, and aspirin have been used more frequently, which also improves prognosis.

- Metabolic state—baseline HbA\textsubscript{1c} exceeded 8\% in DIGAMI 1, whereas it was 7.3\% in DIGAMI 2. This indicates an improvement in diabetic care and metabolic control in the study population during the last decade.
- Insulin therapy—in DIGAMI 2, insulin infusion in the acute phase was mandatory for groups 1 and 2. Treatment with insulin during the follow-up period was obligatory in group 1, while in the remaining two groups it depended on whether or not metabolic control could be achieved by other means (diet, oral hypoglycemic agents). In the follow-up period, insulin was given to 84\% of patients in group 1, 45\% of patients in group 2, and 39\% of patients in group 3. On examination of the patients’ characteristics, it is easy to see that insulin use was also frequent in groups in which it was not a mandatory component of the protocol (Table I), and that it resulted in similar levels of metabolic control. This might suggest that the use of insulin per se does not prevent postinfarction complications. It is, however, mandatory when other hypoglycemic agents are ineffective. The use of IV insulin infusion in the acute phase of MI is a separate issue. IV insulin infusions accelerate regeneration and tissue healing. Moreover, IV insulin infusion is alone in providing such rapid and effective metabolic control in emergency situations. Details of the mechanism underlying the benefits of lower blood glucose remain unknown, but experimental studies indicate that high glucose levels may affect endothelial function, and increase both inflammatory reactions and procoagulation activity. The hormonal reaction to the stress caused by MI involves several adverse metabolic reactions—increased resistance to insulin, intensified lipolysis (fatty acids may exert proarrhythmic effects and enlarge the area of infarction), decreased glucose utilization, and endogenous insulin release (only exogenous insulin decreases levels of free fatty acids and their uptake by myocardial cells). It may be assumed, therefore, that IV insulin therapy in patients with acute MI leads to better myocardial regeneration and improved hemodynamic adaptation of the myocardium, even in cases where there is a reduced area of necrosis following reperfusion. IV insulin infusion should be used in patients with MI immediately upon their admission to hospital. Recommendations of the American College of Cardiology and the American Heart Association (ACC, AHA) from 2004 are in line with recent European guidelines stating that IV insulin infusion is recommended for patients with both complicated and uncomplicated MI to achieve normoglycemia.\textsuperscript{11,17}

The results of DIGAMI 1 and 2 confirm the important role of metabolic control in the treatment of diabetic patients after MI.\textsuperscript{18}

The thiazolidinediones are a relatively new group of oral agents licensed for blood glucose control.\textsuperscript{18}

### Table I. Insulin use in the Diabetes mellitus, Insulin Glucose infusion in Acute Myocardial Infarction (DIGAMI) 2 study.\textsuperscript{16}

<table>
<thead>
<tr>
<th>Group</th>
<th>n=474</th>
<th>n=473</th>
<th>n=306</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subcutaneous insulin in hospital; n (%)</td>
<td>Mandatory</td>
<td>154 (32.6)</td>
<td>124 (40.5)</td>
</tr>
<tr>
<td>Subcutaneous insulin after discharge (%)</td>
<td>84</td>
<td>45</td>
<td>39</td>
</tr>
<tr>
<td>Mean dose (IU)</td>
<td>36±22</td>
<td>46±30</td>
<td>57±42</td>
</tr>
</tbody>
</table>

The thiazolidinediones are a relatively new group of oral agents licensed for blood glucose control.\textsuperscript{18}
The mechanism of action of these drugs, mainly expressed via an increase in insulin sensitivity, seemed to be a promising option for specific (independent of glucose normalization) secondary prevention in patients with cardiovascular disease. This preventive hypothesis was tested in the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROACTIVE). In this trial, 5238 patients with T2DM (including 2445 after MI) were recruited and randomized to receive either placebo or pioglitazone in addition to their existing antihyperglycemic treatment. Patients were followed up for a mean of 34.5 months, and the HbA1c target values were identical for both groups. No significant reduction was seen with pioglitazone for the principal secondary end point (hazard ratio [HR], 90% confidence interval [CI], 0.8-1.02; P=0.095), whereas a significant decrease in the so-called principal primary end point (death, MI excluding silent episode, stroke) was described (Table II). There were more adverse events reported in the group treated with pioglitazone, with the main problems being fluid retention and congestive heart failure. Taking into consideration both the positive effects of pioglitazone therapy and the risk of adverse events, one can draw the conclusion that this drug is beneficial only in those patients who have not experienced heart failure. Until an effective method can be established to predict coronary heart failure, this therapy should, therefore, be considered with great care. Some discussion has also taken place regarding whether the secondary outcome results (described in the original publication as the “principal primary end point which was calculated after exclusion of silent MI”) can be considered as significant at the level of P=0.027, and whether they allow any clinically relevant conclusions to be drawn.

Several epidemiological observations indicate an important role for postprandial hyperglycemia in the development of macrovascular complications. The original observation made by the Diabetes Epidemiology, Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study was followed by multiple confirmations. To date, no clinical trial has been published that has been able to confirm that intervention focused on postprandial hyperglycemia may have additional benefits in terms of outcome after MI in diabetic patients. This issue should be clarified by the HEART2D Study, in which 1355 patients with T2DM were identified and randomized to receive either treatment with neutral protamine Hagedorn (NPH) insulin or glargine titrated according to fasting blood glucose values (preprandial strategy), or LysPro given before meals and titrated to postprandial blood glucose levels.

In both groups, the same target HbA1c level was established, but different strategies were tested (prevs postprandial glucose level) (Figure 1). The results of this study, which are expected within 2 years, will answer the question of what impact different treatment strategies have on the outcome in post-MI diabetic patients.

**Table II.** Summary of the results observed in the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROACTIVE).

<table>
<thead>
<tr>
<th></th>
<th>Pioglitazone</th>
<th>Placebo</th>
<th>Relative risk</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point</td>
<td>21%</td>
<td>23.5%</td>
<td>10%</td>
<td>0.095</td>
</tr>
<tr>
<td>Principal secondary end point</td>
<td>12.3%</td>
<td>14.4%</td>
<td>16%</td>
<td>0.027</td>
</tr>
</tbody>
</table>

It appears undeniable that the achievement of normoglycemia by means of IV insulin infusion in patients with acute phase MI is necessary. Currently, however, there has been no confirmation as to whether acute MI is an indication for long-term insulin therapy for patients in whom metabolic control could be achieved by other means. The answer to this question, and determination of the optimal method of treatment for this patient group, require further investigation.

**REFERENCES**

Les complications macrovasculaires, en particulier l’infarctus du myocarde (IDM), sont les principaux problèmes de santé auxquels font face les diabétiques de type 2 (T2DM). Quinze pour cent de diabétiques de type 2 y ont été confrontés moins de 15 ans après avoir été diagnostiqués. Leur incidence et leur développement peuvent néanmoins être limités en agissant sur plusieurs facteurs. Le traitement d’entretien des patients devrait s’attacher à la normalisation de la glycémie, de la pression artérielle, de la lipidémie et des conseils sur les changements de mode de vie. L’un des éléments clés du traitement global des patients diabétiques est le maintien d’une glycémie correcte. Des études cliniques de prévention primaire ont montré que toute diminution de l’hyperglycémie réduit le risque d’IDM ; il a également été montré que les diabétiques ont un plus mauvais pronostic après un IDM qu’une population non diabétique équivalente. Une perfusion d’insuline pendant la phase aiguë d’un événement coronary est bénéfique en termes de réduction de la mortalité comme le montre l’étude DIGAMI-1 (Diabetes mellitus, Insulin Glucose infusion in Acute Myocardial Infarction). Reste à savoir si la classe de médicament hypoglycémiant pris après un IDM influe sur la survie. Cette question a été traitée par un ensemble d’études de référence dont les résultats sont commentés par les auteurs de cet article. À la lumière des données disponibles de ces études, la normalisation de la glycémie arrive en tête comme facteur essentiel de survie alors que l’impact potentiel éventuel du choix de l’hypoglycémiant sur le pronostic doive être discuté dans ce groupe de patients.
Heart failure (HF) is not only one of the most common deadly diseases, but it is increasingly recognized as one of the most expensive. In the European Union, there are estimated to be at least 10 million patients with HF, and another 5 million patients are found in the US, where half a million new patients are also diagnosed each year. Diabetes mellitus (DM) is a common contributor to this problem, and more than 40% of patients admitted to hospital for decompensated HF will have the condition.

Moreover, there is a close relationship between HF and glycemic control. In the United Kingdom Prospective Diabetes Study (UKPDS), HF was diagnosed in 2 patients per 1000 per year in those with a glycosylated hemoglobin (HbA1C) level of <6%, compared with 12 patients per 1000 per year in patients with HbA1C >10%. Similar findings have been reported in other studies, including a linear increase in the risk of HF, in which each 1% increase in HbA1C level corresponded to a 12% to 15% increased risk of HF.

The increase in the prevalence and incidence of HF coincides with an increase in the prevalence of DM in both the developed and developing worlds. In eight States within the US, the population prevalence of DM is >9%. DM contributes to the development of HF in several ways. First, it is clearly associated with premature atherosclerotic vascular disease and the risk of myocardial infarction. Second, when infarction or other causes of HF are present, their likelihood of precipitating HF is magnified in the presence of DM. Third, DM is itself associated with heart muscle disease, with observations in the Framingham Heart Study indicating that the frequency of cardiomyopathy was increased twofold in men and fivefold in women with DM, as well as there being a disproportionate DM representation in the major HF trials (Studies Of Left Ventricular Dysfunction [SOLVD], Health Outcomes Prevention Evaluation [HOPE], Canada Health Survey [CHS]), and accounting for the majority of patients with diastolic heart failure.

The Clinical presentation, treatment, and prognosis of heart failure in diabetes by T. H. Marwick, Australia

Diabetes mellitus (DM) is commonly associated with heart failure (HF), an association that is probably the result of its potentiation of other myocardial insults in the development of HF. Patients with cardiac dysfunction can be asymptomatic, with systolic or diastolic dysfunction identified on cardiac imaging, and this is the usual presentation of primary myocardial disease in DM. Although symptomatic HF can be caused by diabetic cardiomyopathy, it is most frequently a consequence of ischemic or hypertensive heart disease. Myocardial disease in DM is commonly multifactorial, and is caused by myocardial metabolism alterations, interstitial fibrosis, structural and functional disturbances of the coronary vasculature, and autonomic neuropathy. These mechanisms give clues as to the most likely measures for prevention of early-stage disease progression, including metabolic and antifibrotic therapies. Less specific preventive therapies, and standard treatment measures, are also thought to be effective. The prognosis for HF is particularly sinister in DM, although whether this is also true for preclinical left ventricular dysfunction remains to be determined.
Presentation of heart failure in diabetes

◆ Stages in heart failure development
The current guidelines emphasize the presence of four stages in the development of HF (Table I). Stages C and D reflect the typical clinical presentations of HF, namely, structural heart disease that involves prior or current symptoms (Stage C), or refractory symptoms (Stage D). However, by the time that patients present with symptoms, their HF prognosis is defined, and recent developments in pharmacologic and device therapy have made limited overall impact on the adverse outcome of this group.3

<table>
<thead>
<tr>
<th>Table I. Classification of heart failure (HF) stages.</th>
</tr>
</thead>
<tbody>
<tr>
<td>HF history</td>
</tr>
<tr>
<td>Normal</td>
</tr>
<tr>
<td>Stage A</td>
</tr>
<tr>
<td>Stage B</td>
</tr>
<tr>
<td>Stage C1</td>
</tr>
<tr>
<td>Stage C2</td>
</tr>
<tr>
<td>Stage D</td>
</tr>
</tbody>
</table>

It seems that early intervention to prevent the development of HF is more likely to be successful in reducing the adverse outcome of this condition, than the current focus on treatment of late stage disease. Stage B HF includes patients with structural disease who are without symptoms or signs, and Stage A categorizes patients who are at risk, but do not have overt evidence of structural heart disease or asymptomatic HF. Patients with DM are at risk of congestive HF, and are therefore in Stage A. The use of imaging strategies may, however, identify a subgroup belonging to Stage B, and this differentiation could have an impact on prophylactic therapy.3

◆ Preclinical heart failure
Preclinical HF in DM is by definition asymptomatic. Patients with this condition are identified on the basis of abnormal findings during echocardiography or other testing.

◆ Diastolic dysfunction
Diastolic dysfunction is highly prevalent in diabetic subjects. The most common presentation involves a delayed relaxation pattern of left ventricular (LV) filling (Figure 1). The frequency of this condition, however, may be underestimated if the diagnostic criteria applied do not include patients with pseudonormal filling. Fortunately, most patients with this condition are quite easy to identify: data gathered on left atrial size or volume, in addition to tissue Doppler velocity, can be used to calculate the raised filling pressure with E/E’ (diastolic filling) (Figure 2). Overall, diastolic parameters such as E wave velocity and the early/late transmitral filling velocity (E/A) ratio are 22% to 25% lower in diabetic subjects compared with controls.9 Table II summarizes recent studies that have used sophisticated testing to identify pseudonormal filling patterns, and that have reported between 50% to 75% of apparently healthy type 2 DM (T2DM) subjects to show evidence of diastolic dysfunction.10-13 The relative prevalence of subclinical ischemia, hypertrophy, and LV dysfunction in DM and obesity are summarized in Figure 3.14

◆ Systolic dysfunction
Asymptomatic systolic dysfunction is less frequently recognized than diastolic dysfunction. Nonetheless, in the Strong Heart Study (SHS), selected systolic parameters were recognized as abnormal.15 Latent systolic abnormalities can also be identified in diabetic subjects by investigating their cardiac function during provocative testing.16

The development of myocardial tissue Doppler scanning has facilitated the recognition of subclinical systolic dysfunction. Table III summarizes studies that have used systolic and diastolic tissue Doppler parameters to identify subclinical LV dysfunction.17-22 Interestingly, these markers relate to abnormal longitudinal (base-to-apex) motion of the heart, which in the early phase of the disease, appears to be compensated for by increased radial function (perhaps explaining the preservation of ejection fraction)20,23 until this too is compromised (Figure 4, page 240). This pattern suggests that the myocardial injury in diabetic subjects involves the
Table II. Prevalence of abnormal diastolic characteristics in selected studies examining techniques for the identification of pseudonormal filling in apparently healthy diabetic subjects.

<table>
<thead>
<tr>
<th>No. of study</th>
<th>Subjects</th>
<th>Methodology</th>
<th>Prevalence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boyer, 2004</td>
<td>2 61</td>
<td>Transmitral flow, Valsalva, flow propagation, tissue Doppler</td>
<td>43/57 (75%)</td>
<td>Normal systolic function</td>
</tr>
<tr>
<td>Zabalgoitia, 2001</td>
<td>2 86</td>
<td>Transmitral flow, Valsalva</td>
<td>41/86 (47%)</td>
<td>Negative ex ECG, normal systolic function</td>
</tr>
<tr>
<td>Poirier, 2001</td>
<td>2 46</td>
<td>Transmitral flow, Valsalva, pulmonary venous flow</td>
<td>28/46 (60%)</td>
<td>Negative ex ECG, no complications or comorbidity</td>
</tr>
<tr>
<td>Raev, 1994</td>
<td>1 157</td>
<td>E slope, LA emptying, IVRT</td>
<td>27%</td>
<td>Asymptomatic</td>
</tr>
</tbody>
</table>

Table III. Studies that have demonstrated abnormalities in myocardial parameters (tissue velocity, strain rate and strain) in patients with diabetes mellitus.

<table>
<thead>
<tr>
<th>No. of study</th>
<th>Subjects</th>
<th>Criteria</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hansen, 2002</td>
<td>8 T1DM 8 controls</td>
<td>Diastolic tissue velocity less in DM than controls (13.8±0.6 vs 15.6±0.5 cm/s; P&lt;0.04)</td>
<td>Functional changes corresponded with reduction of myocardial blood volume (6.6±0.6 vs 8.2±0.6 arbitrary units of contrast intensity; P&lt;0.04), but not flow. Short-term replacement of C-peptide improved both resting function and hyperemic response</td>
</tr>
<tr>
<td>Fang, 2003</td>
<td>93 DM 93 controls</td>
<td>Calibrated integrated backscatter (ie, myocardial reflectivity) was greater in DM and HT subjects than in controls (P&lt;0.05). Diabetic patients with LVH had lower peak systolic strain and strain rate than in patients with DM alone (P&lt;0.03) or LVH alone (P&lt;0.01)</td>
<td>CAD excluded with negative ExE. Subgroups with and without LVH</td>
</tr>
<tr>
<td>Andersen, 2003</td>
<td>32 T2DM 32 controls</td>
<td>DM had lower tracking score index (5.8±1.6 vs 7.7±1.1 mm; P&lt;0.001), peak systolic velocity (4.3±1.5 vs 5.4±1.0 cm/s; P&lt;0.001) and peak systolic strain rate (-1.2±0.3 vs -1.6±0.4 s⁻¹; P&lt;0.001)</td>
<td>Normotensive, normal EF, no angina, valvular heart disease or small vessel disease</td>
</tr>
<tr>
<td>Vinereanu, 2003</td>
<td>35 T2DM 35 controls</td>
<td>Longitudinal (basal segment) peak systolic velocity lower in DM (5.6±1.4 vs 6.5±1.1 cm/s; P&lt;0.01)</td>
<td>Lower longitudinal velocity compensated by radial velocity (5.4±1.3 vs 4.7±1.4 cm/s; P&lt;0.05)</td>
</tr>
<tr>
<td>Saraiva, 2005</td>
<td>79 Em&lt;8.5 cm/s or Em/Am &lt;1 in 27%</td>
<td>More specific than classic Doppler criteria (abnormal in 41%) but TVI associated with exercise tolerance</td>
<td></td>
</tr>
<tr>
<td>Von Bibra, 2005</td>
<td>744 DM 33 controls</td>
<td>DM compromised Ve at rest (8.5±1.7 vs 9.6±1.9 cm/s; P&lt;0.02)</td>
<td>DM associated with lower Vs (10.7±2.7 vs 13.6±3.4 cm/s; P&lt;0.05) and Ve (10.0±2.1 vs 13.1±3.8 cm/s; P&lt;0.05), with impaired increase of Vs (P&lt;0.05), Vd (P&lt;0.0003) and Va (P&lt;0.03)</td>
</tr>
</tbody>
</table>

Figure 3. Prevalence of silent ischemia, left ventricular (LV) hypertrophy, and subclinical LV dysfunction in apparently healthy subjects with diabetes mellitus, obesity (body mass index >30 g/m²) and both. Abbreviations: DM, diabetes mellitus; LVH, left ventricular hypertrophy; LV, left ventricle.
of the venous pressure, cardiomegaly, and evidence of pulmonary congestion. As in all cases of HF, evidence should be sought for an underlying etiology—in particular, coronary artery disease (CAD), as cardiac dysfunction can be amenable to myocardial revascularization. By the time patients with DM present with symptomatic HF, their risk is significantly increased.

**Therapy for heart failure in diabetes**

**◆ Treatment of underlying etiologic factors (Stage A)**

**Blood glucose control**

Avoidance of hyperglycemia appears to be an important component in the prevention of diabetic heart disease and inhibition of its progression. In UKPDS, achievement of a target glucose level of <6 mmol/L was associated with a reduction in the frequency of HF. However, the optimal means of glycemic control for the prevention of HF is still unresolved. Oral hypoglycemic drugs have been linked to an increased risk of HF, although this effect has been attributed to patient-specific rather than drug-specific factors. Intensive glycemic therapy of the sort associated with an increased incidence of hypoglycemia has been associated with weight gain. On the other hand, improved glucose control (especially with insulin), and treatment with C-peptide both improve perfusion and diastolic function.

**Type B natriuretic peptide**

Type B natriuretic peptide (BNP) is a marker of symptomatic HF, which is thought to reflect increased transmural wall stress in the presence of the condition. The role of BNP in the detection of subclinical HF is, however, debated. Several studies have demonstrated that BNP levels can remain in the normal range in individuals with subclinical systolic and diastolic dysfunction identified by sensitive imaging parameters.

**Noncardiac features**

Several mechanisms are thought to underlie the myocardial dysfunction associated with DM, including structural and functional abnormalities of the coronary vasculature, sympathetic neuropathy, fibrosis, and direct metabolic disturbances involving the myocyte. The physical examination of symptomatic subjects may identify some of these abnormalities and give an indication as to the presence of subclinical heart disease. Such changes might include clinical evidence of autonomic neuropathy, or abnormal arterial pressure waveforms obtained at tonometry. Hypertension and LV hypertrophy are associated conditions that are additive to diabetic changes in the myocardium.

**Symptomatic presentation with heart failure**

The symptoms of HF in DM are the same as the characteristics of the condition when caused by other diseases. Symptomatic patients present with dyspnea, including orthopnea and paroxysmal nocturnal dyspnea, and eventually with leg swelling. The usual clinical signs of HF are apparent, including volume overload as evidenced by edema, elevation of the venous pressure, cardiomegaly, and evidence of pulmonary congestion. As in all cases of HF, evidence should be sought for an underlying etiology—in particular, coronary artery disease (CAD), as cardiac dysfunction can be amenable to myocardial revascularization. By the time patients with DM present with symptomatic HF, their risk is significantly increased.
The effect of these agents on the myocardium is not well defined. Exercise training and lifestyle modification may also improve insulin resistance. Our recent experience is that both systolic and diastolic markers improve after training, but that these show their greatest response in patients with the worst metabolic profile and worst exercise capacity.

**Blood pressure control**

Treatment with aggressive blood pressure targets is an important factor in the management of DM. While the benefits of blood pressure control for the prevention of subclinical diabetic myocardial disease appear to be limited—and less impressive than metabolic interventions—an angiotensin-converting enzyme (ACE) inhibitors appear to protect against the development of subclinical myocardial disease in DM. This is possibly because their downstream effects on aldosterone production exert an antifibrotic effect (see below), and possibly because early antagonism of inappropriate homeostatic mechanisms may prevent the progression of HF.

**Therapy for subclinical heart disease (Stage B)**

The optimal treatment strategy to prevent the progression of myocardial dysfunction to HF is currently undefined. A number of factors have been linked to the development of subclinical heart disease, including metabolic disturbance, fibrosis, disturbances of vascular function, and autonomic neuropathy, and these seem to be appropriate therapeutic targets.

**Disruption of cross-linked proteins**

Poor glycemic control is associated with a variety of vascular complications in DM, as well as subclinical myocardial dysfunction. The formation of advanced glycation end-products (AGEs) may be an important consequence in relation to vascular function, and activation of the AGE receptor may engender a series of profibrotic and proapoptotic changes. Disruption of the cross-links between glycosylated proteins with the use of cross-link breakers, such as alagebrium chloride, reduces the deposition of proteins via second messengers, particularly those that are already in clinical use in Japan for the treatment of fibrotic reactions. In experimental work published last year, TGFβ1, its nuclear second messenger Smad, and interstitial fibrosis were all found to have increased levels in the hearts of diabetic animals, but all of these findings were attenuated after treatment with tranilast. Various strategies of TGFβ inhibition have also been translated into improvements in fibrosis and cardiac function in a variety of non-diabetic models. Nonetheless, this approach is in its infancy, and the possible adverse effects of steps to reduce the extracellular matrix are unknown.

**β-Adrenoceptor blockade**

β-Blockers prevent the progression of HF, but their efficacy in the setting of DM is not well defined, with only about 110 patients identified with DM in the four largest trials—most of which involved patients with moderate or severe HF. Their specific role in relation to subclinical heart disease is also undefined.

**Therapy for overt heart disease**

The management of symptomatic HF in patients with DM is congruous with management of overt HF in other situations, and includes optimal control of intravascular volume, and treatment of inappropriate homeostatic responses using ACE inhibitors, and angiotensin, β-adrenergic, and aldosterone blockade. Revascularization of viable myocardium in patients with DM may be limited by the presence of small target vessels.
Prognosis of heart failure in diabetes

The mortality rate for HF remains high; half of all diagnosed patients die within 4 years, and half of all patients with severe HF die within 1 year. Full-blown HF with DM is a very malignant combination, both with and without associated CAD. In a community-based cohort of 665 patients from Olmsted county who had HF, the 5-year survival rate was lower among subjects with DM (37% vs 46%; P=0.02), but, interestingly, subjects with DM who were without CAD had a higher risk of death (relative risk [RR], 1.79; 95% confidence interval [CI], 1.33-2.41) than those with CAD (RR, 1.11; 95% CI, 0.81-1.51), independent of age, gender, obesity, renal function, duration of HF, comorbidity, and ejection fraction. The outcome of subclinical heart disease associated with DM is undefined. Moreover, the adverse effect of DM on HF is not only limited to survival time. Patients with HF and DM have a lower quality of life and worse exercise capacity than those who are without DM. Health care costs are greater in patients with DM, and macrovascular disease and HF, and HF is a contributor to the greater incidence of hospitalizations in patients with DM than the remainder of the community.

Conclusions

Asymptomatic LV dysfunction (especially diastolic dysfunction) is highly prevalent among subjects with DM, and several mechanisms for this subclinical dysfunction have been proposed. In addition to improved glycemic control, ACE inhibition, antiinflammatory agents, and cross-link breakers can be effective for the treatment and prevention of this disease. If we are to avoid the burgeoning epidemic of DM from further augmenting the anticipated age-related increase in HF, further understanding of diabetic myocardial disease will urgently be required.

REFERENCES

DIABETOCARDIOLOGY: HEART DISEASE IN DIABETES

D iabete et insuffisance cardiaque (IC) sont fréquemment associés, cette association étant probablement liée au fait que le diabète potentielise les agressions myocardiques à l’origine du développement de l’IC. Les patients présentant une dysfonction cardiaque peuvent être asymptomatiques, les troubles systoliques et diastoliques étant mis en évidence par imagerie cardiaque, ce qui est le mode de présentation habituel de la maladie myocardique primitive au cours du diabète. Bien que la cardiomyopathie diabétique puisse entraîner une IC symptomatique, cette dernière est plus fréquemment la conséquence d’une cardiopathie ischémique ou hypertensive. La maladie myocardique au cours du diabète est habituellement multifactorielle, provoquée par des altérations du métabolisme myocardique, une fibrose interstitielle, des troubles structuraux et functionnels du réseau coronaire et une neuropathie végétative. Ces mécanismes fournissent des pistes permettant d’instituer les mesures les mieux adaptées pour prévenir la progression de la maladie au stade précocé, associant des traitements métaboliques et antifibrotiques. Il semble également que des traitements préventifs moins spécifiques ainsi que des mesures thérapeutiques standard soient également efficaces. Le pronostic de l’IC est particulièrement sombre dans le diabète, reste à savoir s’il en va de même pour la dysfonction ventriculaire gauche préclinique.

**TABLEAU CLINIQUE, TRAITEMENT ET PRONOSTIC DE L’INSUFFISANCE CARDIAQUE AU COURS DU DIABÈTE**

**Diabète et insuffisance cardiaque (IC) sont fréquemment associés, cette association étant probablement liée au fait que le diabète potentielise les agressions myocardiques à l’origine du développement de l’IC. Les patients présentant une dysfonction cardiaque peuvent être asymptomatiques, les troubles systoliques et diastoliques étant mis en évidence par imagerie cardiaque, ce qui est le mode de présentation habituel de la maladie myocardique primitive au cours du diabète. Bien que la cardiomyopathie diabétique puisse entraîner une IC symptomatique, cette dernière est plus fréquemment la conséquence d’une cardiopathie ischémique ou hypertensive. La maladie myocardique au cours du diabète est habituellement multifactorielle, provoquée par des altérations du métabolisme myocardique, une fibrose interstitielle, des troubles structuraux et fonctionnels du réseau coronaire et une neuropathie végétative. Ces mécanismes fournissent des pistes permettant d’instituer les mesures les mieux adaptées pour prévenir la progression de la maladie au stade précocé, associant des traitements métaboliques et antifibrotiques. Il semble également que des traitements préventifs moins spécifiques ainsi que des mesures thérapeutiques standard soient également efficaces. Le pronostic de l’IC est particulièrement sombre dans le diabète, reste à savoir s’il en va de même pour la dysfonction ventriculaire gauche préclinique.**
Is it possible to optimize cardiovascular risk assessment in diabetic patients?

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Coronary artery disease (CAD) is the leading cause of morbidity and mortality in patients with diabetes mellitus, which has been designated as a CAD equivalent. In general, CAD in diabetic patients is detected at an advanced stage and, whereas the disease is premature, asymptomatic stages unfortunately remain undetected. A screening program aimed at identifying patients with diabetes who have CAD and who will benefit from medical intervention or invasive intervention or both to prevent cardiovascular events is an appealing concept, but still represents a challenge. Indeed, there are still many arguments against implementing a broad-based screening program for CAD in diabetic patients. So we still lack published data demonstrating that a prospectively applied screening program improves outcome in asymptomatic diabetic patients, and the true prevalence of CAD, and in particular prognostically important CAD, in this population is uncertain. It is true that consensus documents recommend more aggressive treatment of hypertension, hyperlipidemia, and other risk factors solely on the basis of diabetes status, without differentiation based on the presence or absence of identifiable CAD, and this ensures a broad-based prevention strategy. However, the decision to evaluate patients with diabetes who are asymptomatic for CAD still presents a great challenge. Few guidelines are available to aid in the choice of testing modalities for a given patient. The American Diabetes Association recommends exercise tolerance testing alone in symptomatic patients with ≥2 CAD risk factors or an abnormal resting electrocardiogram (ECG). However, that recommendation is based not on hard data but merely the consensus of an expert panel; moreover, it has been challenged by recent experimental data where a substantial proportion of type 2 diabetic patients with ≤1 risk factor were found to have significant CAD. Furthermore, in both a cross-sectional and a longitudinal study, multiple risk factors did not predict which diabetic patients had abnormal single-photon emission tomography (SPECT) images. Besides “who to screen?”, another important issue related to detection of CAD in diabetic patients is “how to screen?”. Current diagnostic tools include exercise ECG, stress echocardiography, stress myocardial perfusion imaging (usually performed by SPECT), and cardiac catheterization. Exercise ECG is a well-established, relatively inexpensive test; however, it might have lower sensitivity than other techniques, particularly in diabetic patients who might not experience exercise-induced angina. Stress echocardiography is a useful noninvasive procedure, which improves sensitivity and specificity compared with exercise ECG. Although there is still limited experience with this technology in the diabetic population, an increasing body of evidence supports its diagnostic accuracy and prognostic ability to risk stratify diabetic patients for future cardiac events. SPECT has the most extensive literature supporting its use in diabetic patients for both diagnostic and prognostic purposes, and might offer the best sensitivity and specificity. In symptomatic patients with diabetes, the presence and extent of abnormal stress myocardial perfusion imaging (MPI) findings have been found to be highly accurate independent predictors of subsequent cardiac events. Furthermore, among asymptomatic diabetic patients, SPECT detected perfusion defects consistent with CAD in 18% to 26% of cases. However, outcome data following SPECT screening for CAD in diabetic subjects are not yet available and the cost of SPECT is significantly higher than that of exercise ECG and stress echocardiography. A cost-effectiveness analysis using a Markov model has indicated that by using stress echocardiography as a screening tool in diabetic patients with two or more additional atherogenic risk factors, the incremental cost-effectiveness would be $40,800 per quality-adjusted life year. This was slightly better than the cost-effectiveness of exercise ECG and definitely better than SPECT. It is interesting to note that a comparable analysis would result in a cost-effectiveness of $30,000 per quality-adjusted life year for annual screening for cervical cancer in women 21 years and older, which is deemed widely acceptable from a societal perspective. In conclusion, in view of the increasing prevalence of diabetes, detection of silent CAD in diabetic patients is an increasingly important health issue. At present it is still difficult to support a broad recommendation to screen all diabetic patients with any particular screening tool. An increasing body of evidence supports the no-
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This controversial issue should be considered in the light of two important questions. First, do we really need to risk-stratify patients with diabetes when we already know they are at much higher cardiovascular (CV) risk than the general population? The American Heart Association considers diabetes as “risk equivalent” to the presence of coronary heart disease (CHD). Patients with diabetes and no history of myocardial infarction were found to have the same risk as nondiabetic patients with a history of myocardial infarction. Thus diabetic patients should be managed aggressively as regards traditional risk factors, eg, hypertension, dyslipidemia, etc. The result of any additional screening test for nontraditional risk factors will not add anything and will not lead to a change in management. Other investigators, however, showed heightened but variable degrees of CV risk among diabetic patients. In one study, although most patients with type 2 diabetes had a 10-year cumulative incidence of CV events >20%, only those with multiple risk factors were “risk equivalent” to patients with CHD. Therefore, the investigators recommended basing CV risk on the entire risk factor profile rather than just the presence of diabetes. Only diabetic patients at the highest risk can be managed aggressively, eg, using statins to reach LDL targets <70 mg/dL. The latter recommendation is appropriate to underdeveloped communities where resources are obviously limited. The second question is, how can we wisely and cost-effectively identify diabetic patients at the highest risk? Simple office-based risk factor assessment is the best-studied method for CV disease (CVD) risk prediction. This can be supplemented with an ECG and one of the risk score calculators. The United Kingdom Prospective Diabetes Study (UKPDS) risk engine is a type 2 diabetes-specific risk calculator based on 53,000 patient-years of data from UKPDS. CVD risk can be calculated for any given duration of type 2 diabetes based on age, sex, ethnicity, smoking, presence or absence of atrial fibrillation and levels of HbA1C, systolic blood pressure, and total and HDL cholesterol. An alternative strategy is to proceed to more advanced tests for risk stratification like echocardiography, carotid intima media thickness, endothelial dysfunction, plasma homocysteine, or electron-beam computed tomography coronary calcification. I think that as yet there is no clear evidence to justify using these modalities routinely in diabetics, especially in underdeveloped countries. Microalbuminuria is the only emerging nontraditional risk factor that can be used as a routine test for all diabetic patients. Why? First, because several studies have demonstrated that microalbuminuria is a sensitive and very early marker for susceptibility to CVD. In the Health Outcomes Prevention Evaluation (HOPE) Study, those with microalbuminuria and diabetes had respective 1.97-fold and 2.15-fold increased risks for a composite outcome of myocardial infarction, stroke, or CVD death, as well as all-cause mortality, compared with subjects with diabetes without microalbuminuria. Second, progression of microalbuminuria is associated with a worsening prognosis, while lowering albuminuria is associated with CV and renal protection. Thus microalbuminuria is changing from being a mere risk marker into a therapeutic target, and there is now a compelling indication for using treatments that can reduce it. Thus, screening for microalbuminuria should be a routine tool to optimize CV risk assessment of diabetic patients because it is a simple, accurate, and relatively inexpensive laboratory test, and so its use would be feasible and cost-effective, especially among resource-limited communities.
Diabetes is one of the most challenging health problems in China, whose 40 million diabetics constitute the world’s second highest affected population. The prevalence of hypertension, coronary heart disease, and cerebrovascular disease in Chinese patients with diabetes is 41.8%, 25.1%, and 17.3%, respectively. Although the prevalence of cardiovascular disease (CVD) is a little lower in China than in developed countries, 80% of affected patients die of CVD. To some extent, the aim of diabetes treatment is to prevent premature mortality and morbidity caused by cardiovascular (CV) complications. Many CV deaths are potentially preventable if high-risk patients are identified early. For primary care, the CV risk assessment should be easy and the resources available. We believe it is possible to optimize the CV risk assessment. Traditional CV risk factors include fixed risk factors, such as age, gender, and genetic background, and modifiable ones, such as high blood pressure, lipid abnormalities, obesity, and smoking. The 2003 China Guideline for Diabetes Prevention and Treatment considers modifiable risk factors: (i) hyperglycemia: the relation between hyperglycemia and CVD is well established. It is recommended that HbA1c be determined at least twice a year. Postprandial hyperglycemia is very common in nonobese Chinese patients with diabetes and is closely related to CVD. So postprandial glucose monitoring is highly recommended; (ii) hypertension: as mentioned before, 41.8% of Chinese patients with diabetes suffer from hypertension. In addition, stroke is the most common form of CVD, and the relationship between blood pressure and stroke is stronger among Asians than Europeans. Blood pressure should be measured at every routine diabetes visit and treated to target aggressively; (iii) dyslipidemia: patients with diabetes should have yearly tests of their lipid profile, including total cholesterol, triglycerides, HDL cholesterol, and LDL cholesterol. Regular visits are helpful in increasing the compliance of patients taking lipid-lowering agents; (iv) obesity: the criteria for being overweight and obese are body mass index (BMI) >24–<27.9 and BMI ≥28, respectively; and (v) smoking: there are 350 million Chinese smokers. Cessation of cigarette smoking should be addressed at medical visits. A number of other new cardiovascular risk factors have also been identified, for example, microalbuminuria, homocysteine, lipoprotein(a), and C-reactive protein. At the present time, these factors are not recommended as routine risk assessment in China for they are not available in primary care. In order to minimize the risk of CVD, it is essential to pay strict attention to all treatable risk factors. The Steno-2 study showed that a target-driven, long-term, intensified intervention aimed at multiple risk factors (hyperglycemia, hypertension, dyslipidemia, microalbuminuria) in patients with type 2 diabetes and microalbuminuria reduces the risk of CV events by about 50%. It is a mistake to focus on treating hyperglycemia alone. Framingham risk equations and the United Kingdom Prospective Diabetes Study (UKPDS) risk engine are the most popular risk assessment tools for estimating the 10-year risk of developing CVD. Both are applicable in primary care, but need further validation in the Chinese population. In short, CV risk assessment can be optimized by assessing the major treatable risk factors, including hyperglycemia, high blood pressure, lipid abnormalities, obesity, and smoking, in addition to the fixed ones. Moreover, Chinese guidelines recommend yearly screening for complications in patients with type 2 diabetes as yet without complications.

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Is it possible to optimize cardiovascular risk assessment in diabetic patients?
Cardiovascular disease (CVD) is the major cause of morbidity and mortality in patients with diabetes mellitus (DM). The pathophysiology of CVD in diabetes involves traditional and novel cardiac risk factors, including hypertension, dyslipidemia, smoking, genetic factors, hyperglycemia, insulin resistance/hyperinsulinemia, metabolic abnormalities, oxidative/glucotoxicative stress, inflammation, endothelial dysfunction, a procoagulant state, and myocardial fibrosis. Risk factor modification for CVD is an established, effective strategy in patient care. Risk stratification is used to set treatment goals. Patients with DM start with one risk factor, often have additional risk factors, and have higher rates of existing CVD. Vigilance is required in identifying risk factors, and persistence in management is often necessary to modify the important risk factors successfully. The need for early assessment of cardiovascular (CV) risk in diabetic patients is crucial. The use of intima-media thickness measurements (eg, carotid and femoral) for the early detection and prevention of the macrovascular complications of diabetes (cerebral, cardiac, and peripheral) is an area for further research. It is an efficient, reasonable, and cost-effective method of assessing CV risk. Current guidelines for CV risk assessment in diabetic patients are numerous and confusing. The National Cholesterol Education Program (NCEP) Adult Treatment Panel (NCEP ATP) III guidelines for prevention of CVD are based on the intensity of therapy, which should be determined by the absolute risk of development of coronary heart disease (CHD). Risk is initially assessed by counting the number of major risk factors. If an individual has two or more major risk factors, the absolute risk for CHD should be calculated using the Framingham risk algorithm. This approach has evolved from the initial concept of “primary” versus “secondary” prevention, recognizing that this dichotomous classification, although simple, may not be the best approach when there is a risk continuum. An estimation of global vascular risk is mandatory in people with diabetes, especially in populations with a high CV risk. There are many validated tables of vascular risk assessment that are very useful in general populations. Global vascular risk is usually restricted to coronary risk, and sometimes to CV risk. The majority of the methods used to calculate vascular risk are designed to estimate risk in primary prevention. This is the main goal, as previously stated. As was shown in the Cardiovascular Health Study, around 50% of patients had clinical CVD. Thus, vascular risk is of very limited use in these patients, and ignores the fact that diabetes in people with myocardial infarction increases the risk of subsequent CHD, although this is not necessarily true for other CVDs like stroke. Another point of controversy is that all risk assessment tables score diabetes as a dichotomous variable. Having diabetes adds risk, regardless of the degree of metabolic control. However, randomized clinical trials (mainly United Kingdom Prospective Diabetes Study [UKPDS]) have shown that treating the disease (including hyperglycemia) has a beneficial effect on vascular outcomes, with a smooth relationship between HbA1c and CV outcome. Some methods overestimate this issue by producing specific risk tables/risk equations for patients with diabetes, and more precisely with type 2 diabetes, but they do not solve the remaining problems of the other methods. CV risk has been calculated using the Framingham Study (FHS) database. The FHS equations do not predict the risk in other populations from the same country, like those participating in the Cardiovascular Health Study. Furthermore, although FHS-based equations might reflect the actual risk for northern European populations, they may underestimate the risk in these same populations when the annual risk is lower than 1.5%, and clearly overestimate the risk in populations from southern Europe.

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Assessment of cardiovascular (CV) risk is normally based on the Framingham Risk Equation, which includes a range of risk factors: age, sex, blood pressure, total and HDL cholesterol, left ventricular hypertrophy, cigarette smoking, and diabetes.\(^1\) The US Framingham Study was an epidemiological study and should only be used to assess risk for primary prevention. There are considerable problems, however, when using this approach in the diabetes population. Framingham and derived risk tables do not take into account diabetes duration, degree of control, presence or absence of microalbuminuria, and racial origin (eg, greatly increased CV risk in South Asians).\(^2\) The fact that risk charts underestimate risk in diabetes generally, and particularly in certain ethnic groups, leads to an important question—is calculation of risk a useful tool in the diabetic patient? This may seem a naive question given that 80% of all diabetic patients will die, many prematurely, of CV disease!\(^3\) But risk tables/charts are about primary prevention. They should not be used once a CV event has occurred, since these patients are ALL at such high risk they need active intervention. The same applies to diabetic patients. A diabetic patient who has never previously had a CV event is at just as high a risk of having an event as a nondiabetic person who has previously had a myocardial infarction.\(^4\) This means that the concept of CV risk assessment in the patient with diabetes is redundant! All type 2 diabetic patients are at enhanced CV risk and should be treated in the same way that we treat a nondiabetic person who has previously had an event. This includes close attention to the major CV risk factors, including use of a statin, commonly several antihypertensives in combination, low-dose aspirin (once blood pressure is controlled), and appropriate antidiabetic agents. The value of lowering total and LDL cholesterol by the use of statins in people with type 2 diabetes is now well established through the Heart Protection Study (HPS)\(^7\) and the Collaborative Atorvastatin Diabetes Study (CARDS).\(^8\) The former study of 20,000 patients included almost 4000 with diabetes, but without clinically evident CV disease. The age range was up to 80 years and the lower limit for total cholesterol entry into the trial was 3.5 mmol/L. All patients received a fixed dose of 40 mg simvastatin. Over 5 years there was a relative risk reduction for coronary heart disease of approximately 30% in both the diabetic and nondiabetic subjects. The same relative risk reduction was seen at all levels of serum cholesterol with benefit up to 80 years of age. There was also reduced risk for stroke, transient ischemic attack, and peripheral vascular disease. CARDS showed equally impressive results using atorvastatin 10 mg once daily in a group of type 2 diabetic patients with no known CV disease and relatively normal LDL cholesterol. These studies strongly suggest that all adult patients with type 2 diabetes, irrespective of their initial cholesterol level, should be on an evidence-based dose of a powerful statin unless there is a contraindication or tolerability problem (caution in females of reproductive age). Target total cholesterol should be <4 mmol/L and LDL <2.5 (or even 2.0) mmol/L. In addition, around 80% of all diabetic patients are hypertensive and there is now an overemphatic weighing of evidence that testifies to the benefits of blood pressure lowering.\(^9\) The British Hypertension Society (BHS) recommends a threshold for intervention at systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg, with a target <130/80 mm Hg, and even lower in the presence of nephropathy.\(^10\) To reach such tight targets, most patients will require at least two or more antihypertensives from different drug classes. This should normally include an inhibitor of the renin-angiotensin system (an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker) in combination with a thiazide, or thiazide-like, diuretic or a long-acting calcium channel blocker or both. Once blood pressure is controlled, low-dose aspirin 75 mg once daily is recommended, unless there is a contraindication or tolerability problem. Attempts should be made to achieve good diabetes control, ideally with HbA1c <7% or (better) <6.5%, although this may not be a realistic target in all patients. Type 2 diabetes is a progressive disease. Although initial primary management is commonly diet and exercise alone, except in patients with very high blood glucose or significant symptoms or both, fairly rapid progression to oral antidiabetic therapy should be normal practice. Metformin is recommended first-line, followed by other oral antidiabetic agents until the target is reached. Many patients with type 2 diabetes will eventually need insulin either as a monotherapy or in combination with oral agents (note: glitazones contraindicated in combination with insulin) to get close to achieving glycemic targets. Although there is very good evidence from the United Kingdom Prospective Diabetes Study (UKPDS) of the benefits of tight glycemic control in reducing risk of microvascular complications, the evidence is less good from the point of view of CV end points.\(^11\) Epidemiological extrapolation of UKPDS data, however, does suggest CV benefit, and there is much epidemiological evidence of a strong relationship between glycemia per se and CV risk. In conclusion, CV risk assessment in diabetes raises a number of practical problems, particularly since the basic tools available for providing accurate prediction of CV risk are flawed! \(^12\) If risk charts/tables are used at all in the South Asian population, for example, 50% should be added to the value obtained to gain some idea of true CV risk. The author’s advice is that risk tables/charts should not be used in patients with diabetes except as an educational tool or
Health professionals need to accept that diabetes is a major risk factor for CV disease and the latter is responsible for most of the morbidity and mortality of the condition. There is also now an overwhelming weight of evidence testifying to the overwhelming nature of the disease (CVD). It is estimated that diabetes and its complications consume approximately 5% to 20% in some cases. More people each year die of diabetes and its complications than of AIDS. The risk factors, which may contribute to the so-called late complications of diabetes, are well known. But in spite of the constant stream of information received by health care professionals, these risk factors are well controlled in only a relatively small number of patients within the diabetic population. The challenge we face today, in our high-tech society, is to identify, early and correctly, the diabetic patients who need further investigation to diagnose CVD. The most adequate methods, strategies, and approaches should be chosen, i.e., the best way to optimize the evaluation in terms of cost/benefit. We should concentrate strictly on high-risk individuals, improve early detection, and try to prevent serious events (heart attacks, amputations, surgery) and subsequent hospitalization. Has the strategy followed hitherto been successful? Have we been able to reduce cardiovascular (CV) morbidity and mortality and their subsequent cost? The figures suggest not. Diabetic patients still have a two-fold risk of death after a heart attack, in spite of all the diagnostic and therapeutic improvements of the last 40 years. In the 21st century, a diabetic who has suffered a CV event does not receive the most recommended treatment as often as a nondiabetic patient. This is certainly a paradox: the risk is higher but the treatment is less aggressive. What strategies should be adopted? New risk markers, besides the traditional ones, might be included in the selection of patients at risk. In addition to complications, such as renal failure (even during the phase of microalbuminuria) and peripheral vascular disease, greater importance should be accorded to autonomic neuropathy, as well as to inflammatory and rheological parameters. New imaging techniques for diagnosis of ischemic disease are being tested and stress echocardiography is increasingly used in daily practice, despite their limited availability and high cost. Other methods such as quantification of the calcium score and computed tomography angiography have been discussed as alternative approaches for a more precise evaluation of CVD in diabetic patients. Timely diagnosis of the disease (before the appearance of major events) is a priority, but the question then is what to do once it is detected. An effective approach includes revascularization of less irrigated regions and careful removal of ob-

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CONTRIBUTION

PROF GABRIEL CORREIA continued

Structures from injured vessels. But it goes much beyond that. Since CVD is generalized, there will be other vessels without significant blockage, but with atherosclerotic damage. In many cases of nonstenotic disease with significant signs of inflammation, local and systemic instability can cause CV accidents. It is important to be more active in intervention, preventive measures, and control of predisposing factors. However, the fact is we have failed in our approach to these questions and to another fundamental aspect of chronic diseases, which will constitute the majority of ailments that health professionals will have to deal with in the 21st century: communicating with the patient. Profound changes over the past few years (what we call evidence-based medicine) have led to "guidelines" for most clinical situations. But we have relegated to a secondary role communication and empathy, which are very important to chronic patients who have to follow lifelong daily procedures. In diabetes, for example, health experts often undervalue or fail to appreciate the tremendous effort it takes, in our consumer society, to change one’s lifestyle, sometimes radically. We forget that people live in tight-knit social circles affording few opportunities to escape from daily professional and social pressures. We all know the dangers of a sedentary lifestyle, of smoking, of above-normal triglycerides, cholesterol, and arterial blood pressure. But if we consider adherence to the respective treatments, the results are very poor: in the case of blood pressure, only about 27% of the patients in the European Union (EU) are controlled, versus 11% in Portugal (members of the Portuguese Health Direction). In relation to cholesterol values, good control is achieved in 20% to 25% of patients in the EU and 15% to 20% in Portugal. This is not due to lack of access to health care or to medical information, to insufficient counseling or to the unavailability of treatments. However, low compliance is one of the main causes of failure in the treatment of chronic disease. If we have created conditions for the success of our therapeutic objectives, what is missing? Communication, motivation, and creating real empathy between the health care provider and the person with diabetes are essential, as is, even more so, the emphasis the patient places on them. The daily flood of medical information, often vaunting contradictory approaches, makes this entire process very difficult. In a recent study in the EU concerning patients’ attitudes, practice, and perception of CV complications, 91% of those questioned considered that diabetes confers a high or very high probability of a CV event. But when asked which parameter is the most important to control, blood glucose, blood pressure, or cholesterol, most chose glycemic control. Yet we now know that the latter two are just as or even more important. As to the main difficulties encountered by physicians in terms of compliance when they attempt to reduce CV risk, we find a failure rate of 86% in attempted lifestyle changes and 77% in adherence to a complex therapeutic regimen. Because of lack of time, only 24% of physicians considered nonadherence. Two-thirds of patients did not consider CVD a serious concern, but instead worried about blindness or amputations. Very few patients considered medication or lifestyle changes important in the reduction of CV risk factors. We should reflect on the problem as a whole and be aware that the patient and health care provider have different conceptions of the disease, which hampers communication. In many cases, the health care provider’s only concern is to ensure that the patient follows the prescription, while the patient lives in a world of social and psychological difficulties, where he or she is suddenly obliged to follow guidelines that are not an overriding concern at that time. We hope that the path outlined by Ernesto Roma during the last century and by Jean-Phillippe Assal over the last few years, in the field of "therapeutic education" will be better understood in the future and will in time be included in university courses.

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Cardiovascular (CV) physicians have been developing risk scores for use in accurately defining the probability of major CV events in individuals without symptoms or identifiable CV disease (CVD). In asymptomatic diabetic patients, risk stratification might be extremely useful. The prevalence of silent coronary artery disease (CAD) in the diabetic population is about 20%, and when symptomatic, the disease is usually at an advanced stage. The rationale of risk assessment is to identify properly those individuals who have no clinical manifestation of CVD, but are at high risk of CV events.

**Do diabetic patients deserve a specific risk score?**

The Framingham Study Risk Score is the most accurate way to assess CV risk in a primary prevention setting, but its performance is not ideal in patients with diabetes mellitus. Additionally, population-based risk scores, when applied to diabetics, need to be recalibrated, but there is no guarantee of accuracy. The effectiveness of risk scores needs to be critically appraised in clinical practice, since their uncritical use may lead to substantial under- or overestimation of individual CV risk.

**Should asymptomatic diabetic patients be screened for cardiovascular disease?**

The concept of screening asymptomatic diabetic patients for CVD is particularly interesting due to both the higher prevalence of CAD and the high risk of CV events. However, there is still a lack of published data confirming that a screening program improves outcome in such patients. Also, the cost implications should be considered if screening were indicated for all.

**Are other markers useful for risk assessment?**

Myocardial perfusion imaging (MPI) crops up increasingly in discussions about risk assessment in asymptomatic diabetic patients, and is well established because of its risk-stratifying properties. The prevalence of silent ischemia in diabetic patients varies markedly, from 6% to 59%. Low-risk patients have an annual risk of death below 1%. In general populations with normal MPI, the mortality rate is 0.6%. However, the scientific evidence shows that MPI is not an ideal screening test to characterize low-risk diabetic patients, whose annual rate of cardiac death or nonfatal myocardial infarction is at least 1.6%. A similar observation can be made regarding stress echocardiography, suggesting that none of the tests used at the moment are accurate for this purpose. Due to the relatively low prevalence of silent ischemia, screening all asymptomatic diabetic patients by MPI may not be cost-effective. Recent data have suggested that MPI and coronary artery calcium (CAC) scoring are complementary. The higher the CAC score, the higher the CV risk. Data on CAC and MPI values for the detection of silent ischemia and definition of its prognostic consequences are currently scarce. According to some authors, the likelihood of positive MPI increases in parallel with the CAC score, suggesting that the latter may be useful in identifying patients who would benefit from risk stratification with MPI. An algorithm has been proposed for screening asymptomatic diabetic patients. When the CAC score is more than 400, MPI is indicated. If the CAC score is between 100 and 400, MPI would be justified if at least one of the following criteria applies: metabolic syndrome, age greater than 65 years, duration of diabetes more than 10 years, diabetic complications. When ischemia is identified by MPI, coronary angiography is considered. If the MPI is normal, more aggressive therapy should be tried. Microalbuminuria (30 to 300 mg/day) is a good predictor of CV events in diabetic patients. In addition, diabetic glomerulosclerosis is associated with atherosclerosis, which is a risk factor for CAD and stroke. This association is based on the efficacy of renin-angiotensin system blockade in improving CV outcomes only in hypertensive patients. Inflammatory markers have been extensively discussed as good predictors of events. They increase during acute events, and postevent increases in C-reactive protein levels have been associated with the likelihood of a new event. However, the Framingham Study suggests that C-reactive protein has little additional predictive power over and above risk factors considered conventional.

**How to improve daily clinical practice in diabetic patients?**

CV risk in diabetic patients is well known and established. Evaluation of the exact risk so as to intervene to reduce CV events is necessary and imperative, but risk assessment needs to be applied systematically. Efforts should be made to implement risk assessment tools and to validate the accuracy of the risk scores in clinical practice.
CONTROVERSIAL QUESTION

The selection of patients for clinical intervention for the prevention of cardiovascular disease (CVD) is done through the identification of high-risk conditions and CVD risk factors. High-risk conditions, as mentioned by the International Atherosclerosis Society, are established by the presence of coronary heart disease (CHD), noncoronary forms of atherosclerotic disease, diabetes, or multiple risk factors such as cigarette smoking, hypertension, dyslipidemia, a family history of premature CHD, and old age. Patients characterized by high-risk conditions deserve intensive clinical intervention to reduce the risk of major cardiovascular (CV) events. This is the rationale for risk assessment. A number of algorithms have been developed to calculate patient risk. In the US, the major algorithm used is that developed in the Framingham Heart Study. The risk factors included in the Framingham calculation of 10-year risk are age, total cholesterol, HDL cholesterol, systolic blood pressure, treatment for hypertension, and cigarette smoking. Diabetes is not listed because it has been designated as a CHD risk equivalent, qualifying by itself as a high-risk condition. To complicate matters, in other Framingham algorithms, diabetes is counted as a risk factor and included in the risk assessment. The 10-year risk for myocardial infarction and coronary death is then estimated from the total points obtained from the number of risk factors. Another risk assessment tool originates from the PROspective Cardiovascular Munster (PROCAM) Study performed in men in Munster, Germany. The risk factors included in this algorithm are cigarette smoking, blood pressure, LDL cholesterol, HDL cholesterol, triglycerides, a family history of myocardial infarction, diabetes, and age. The risk estimate is again calculated using the number of points obtained after the addition of each risk-factor level. A third algorithm has been developed specifically for type 2 diabetic patients and derived from the United Kingdom Prospective Diabetes Study (UKPDS). The UKPDS risk engine calculates the absolute CHD risk in patients with type 2 diabetes mellitus from nine risk factors: age at diagnosis, duration of diabetes, sex, ethnicity, smoking habits, systolic blood pressure, HbA1C, and total and HDL cholesterol. The major difference between this and the Framingham model is the recognition by the UKPDS model of glycemic control as a continuous risk factor rather than a simple variable, such as absence or presence of diabetes. Indeed, age at diagnosis and duration of diabetes are added, as well as ethnicity. A recent study has compared the performance of the UKPDS and Framingham risk engines. If we evaluate statin treatment for type 2 diabetic patients at a 10-year CHD risk of more than 15%, the two methods are comparable in identifying at-risk patients, but the UKPDS risk engine calculated a significantly higher mean 10-year CHD risk. What are the limitations of these calculations? Current risk assessment guidelines for physicians, generally provided by national and international societies, are numerous, confusing, impractical, and time-consuming to apply. Furthermore, although their diagnostic specificity is high overall (around 90%), their sensitivity is low: less than 40% with a positive predictive value of 20% to 30%. The other major deficiency in the risk assessments is that they are highly dependent on age and presented as risk over the coming 10 years. This approach has clear limitations in clinical practice. If we consider, for example, a 35-year-old, overweight, sedentary woman who smokes two packs of cigarettes daily, has stage II hypertension, glucose intolerance, and severe dyslipidemia, her 10-year risk of CHD as estimated by the Framingham equation is 2%. However, most physicians would recognize that this person has a high lifetime vascular risk and would benefit from lifestyle and therapeutic interventions. It would therefore be much more appropriate to calculate lifetime risk rather than the 10-year risk. A simple solution to this problem would be to eliminate time dependency in the algorithm and to calculate age-specific relative risks rather than 10-year absolute risks. The concept of lifetime risk would reinforce the notion that it is not only necessary to reduce cardiovascular risk factors, such as LDL cholesterol, blood pressure, and blood glucose, but also to emphasize the long-term benefit of such reductions. An additional limitation is that most algorithms do not include all of the risk factors that have now been clearly identified in the INTERHEART study. Although INTERHEART is a case control study in patients with acute myocardial infarction and is not a cohort study, the data have the merit of being derived from 30,000 patients in 52 countries. The nine identified risk factors are smoking, raised apoB/apoA1 ratio, hypertension, diabetes, abdominal obesity, and psychosocial factors including stress. Three of the variables were actually protective: daily consumption of fruits and vegetables, regular alcohol consumption, and regular physical activity. Very significantly, there was a clear relationship between risk and the number of cigarettes smoked per day, as well as the apoB/apoA1 ratio, findings that are similar to what was observed for HbA1C in UKPDS. Collectively, these nine risk factors accounted for 90% of the population attributable risk in men and 94% in women. These results clearly suggest that for a good CV assessment, it is necessary to include not only adverse but also favorable risk factors, and to quantify them. What about risk assessment in diabetic patients? It is well known that the rate of fatal CHD is higher in patients with diabetes than in those without. A recent meta-analysis estimated this increase as 3.2-fold. Furthermore, the relative risk for fatal CHD is 50% higher in women than in men. More importantly, a population-based
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The early identification of patients at high risk of cardiovascular disease (CVD) is essential for its prevention. Several studies have clearly shown a high prevalence of adverse lifestyles and modifiable risk factors among both diabetic and nondiabetic patients.\(^1\) Undertreatment of patients at risk can be avoided by increasing physician adherence to guideline recommendations and by increasing patient compliance with medication.\(^2\) Risk of cardiovascular (CV) complications in type 2 diabetes is associated independently and additively with hyperglycemia and hypertension.\(^3\) Thus, intensive treatment of both these risk factors is required to minimize the incidence of complications. A recent study by Booth et al has shown that diabetes confers a risk that is equivalent to that of aging 15 years.\(^4\) It was found that the transition to a high-risk category occurred at a younger age for men and women with diabetes than for those without (mean difference of almost 15 years). Diabetic men and women entered the high-risk category for the outcomes of acute myocardial infarction, stroke, or death from any cause, at the early ages of 48 and 54 years, respectively. Patients with type 2 diabetes are at the highest CV risk and consequently have the most to gain from treatment. Therefore, absolute CV risk should be evaluated precisely in all diabetic patients in order to determine optimal care. Risk calculators based on equations taken from the Framingham Heart Study tend to underestimate risks for patients with diabetes. The United Kingdom Prospective Diabetes Study (UKPDS) risk engine is the first type 2 diabetes-specific risk calculator based on 53,000 patient-years of data from UKPDS.\(^5,6\) It provides risk estimates and 95% confidence intervals in individuals with type 2 diabetes not known to have heart disease, for combined nonfatal and fatal coronary heart disease (CHD), fatal CHD, combined nonfatal and fatal stroke, and fatal stroke.\(^7\) These can be calculated for any given duration of type 2 diabetes based on the patient’s current age, sex, ethnicity, smoking status, presence or absence of atrial fibrillation, HbA\(_1c\) level, systolic blood pressure, total cholesterol and HDL cholesterol.\(^8\) The model is provided as a software package including the risk engine, and is distributed free of charge to nonprofit organizations (http://www.dhltol.dx.ac.uk/). The UKPDS model was shown to be of use to health care providers, insurers, planners, industry and algorithms are cumbersome for the clinician, have low sensitivity, do not take into account all adverse and favorable risk factors, and do not quantify them. In addition, the age factor is much too important in the risk assessment and not enough credit is given to lifestyle prevention at younger ages. It is thus sound to consider type 2 diabetic patients as high-risk patients, particularly when diabetes or other risk factors are not well controlled. The clear message to primary care physicians is that they need not bother with risk estimates of no added value. ⚫

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Is it possible to optimize cardiovascular risk assessment in diabetic patients?
government figures, in addition to clinicians and patients. Other risk calculators, like the Finnish Diabetes Risk Score (FINDRISC), were recently developed to estimate the future risk of diabetes and to identify individuals at high risk of CHD and stroke, and total mortality. So, we have appropriate tools to assess CV risk in patients with impaired glucose tolerance, but what about their implementation? Most physicians believe they adhere to guidelines, but the majority of patients nonetheless remain undertreated, and medical professionals in fact overestimate the extent to which guidelines are implemented in clinical practice. Physicians often underestimate patients’ CV risk and overestimate patients’ awareness of CV risk. Hobbs and Erhardt have shown that 43% of physicians rarely or never use any risk calculator charts that accompany guidelines. Only 13% of physicians always use risk charts to assess a patient’s CV risk. Consequently, having appropriate risk calculators for diabetic patients may not necessarily translate into bridging the gap between guidelines and daily practice. Self-perception of CV risk is insufficient in many diabetic patients. Patients’ knowledge of their own CHD risk factors has been shown to correlate with lifestyle changes, reaching defined treatment goals, and adhering to treatment with prescribed drugs. Consequently, broader use of risk calculators by diabetics may lead not only to better awareness of CV risk, but also to reduced CV morbidity and mortality in this group of patients.

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Diabetic risk in type 2 diabetes mellitus

According to the most recent estimates, the worldwide prevalence of DM for all age groups is set to increase from 2.8% in 2000 to 4.4% in 2030. This would represent a staggering 366 million diabetics worldwide in 2030. More alarmingly, these predictions do not account for the projected increase in type 2 diabetes mellitus (T2DM) is a metabolic disease characterized by disorders of insulin action and insulin secretion, and it represents between 85% and 90% of all cases of diabetes mellitus (DM). Although autoimmune destruction of β cells does not occur, patients with T2DM have abnormal β-cell functioning that leads to defective insulin secretion. Because the hyperglycemia in T2DM increases gradually, this form of DM may go undiagnosed for many years, increasing the rate and severity of complications.

Most of the complications of T2DM result from its microvascular and macrovascular effects, which translate into retinopathy, neuropathy, nephropathy, coronary heart disease (CHD), and stroke. Diabetics have two to four times the age-adjusted CHD mortality rates of nondiabetics, and are twice as likely to suffer from stroke. Indeed, it has been reported that 80% of diabetics die from cardiovascular complications. This implies that any supplementary cardiovascular protection that can be obtained from a therapy whose main aim is to reduce blood glucose levels would be beneficial, even in diabetics not at obvious risk of cardiovascular complications. The objective of this short review is to examine the possibility of achieving such cardioprotection from oral antidiabetic treatment with a sulfonylurea.

The United Kingdom Prospective Diabetes Study (UKPDS) recently showed that in patients with type 2 diabetes mellitus, any reduction in glycated hemoglobin is linked to a reduction in the risk of complications of the disease, and that the lowest level of risk is found in individuals with values in the normal range. This underlines the importance of good blood glucose control for the prevention of diabetic complications, including those of a cardiovascular nature. The prevalence of cardiovascular disease is increased in patients with diabetes mellitus because of the acceleration of coronary atherosclerosis and the increased risk of arterial thrombosis. Any supplementary cardiovascular protection that can be obtained from hypoglycemic therapy, over and above the general positive effects of blood glucose control, would therefore be beneficial and should be an important consideration when deciding which strategy to use in a particular patient. Recent results from a large scale, population based, case-control study in Denmark indicate that prescription of a newer sulfonylurea (such as gliclazide) in type 2 diabetes mellitus reduces the risk of myocardial infarction and increases the probability of surviving such an episode. These beneficial cardioprotective effects have been linked to the results of in vitro and in vivo studies showing antiatherogenic, antiplatelet, and antioxidant properties for gliclazide, in addition to a neutral effect on ischemic preconditioning, which can be explained by the selectivity of the drug for pancreatic sulfonylurea receptors.

Keywords: type 2 diabetes mellitus; cardiovascular complications; sulfonylureas; cardioprotective effects

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obesity—a known risk factor for T2DM—in the western world, and may thus even underestimate the size of this so-called “diabetes epidemic.”

The increased prevalence of cardiovascular disease in patients with DM has been attributed to the acceleration of coronary atherosclerosis, which occurs at an earlier age in this patient population and progresses more rapidly to clinical cardiovascular events than in nondiabetic individuals. Moreover, diabetics are also prone to arterial thrombosis because of persistently activated thrombogenic pathways and impaired fibrinolysis. The situation is aggravated by the presence of autonomic neuropathy, which can reduce the symptoms of CHD, delay its detection, and worsen its prognosis.

The risk of microvascular and macrovascular complications in DM is strongly associated with the degree of hyperglycemia. The United Kingdom Prospective Diabetes Study (UKPDS) recently showed that in patients with T2DM, any reduction in glycated hemoglobin (HbA1C) is linked to a reduction in the risk of complications, and that the lowest risk is found in those with values in the normal range. In this prospective, observational study, 3642 patients with T2DM were included in the analyses of risk. Each 1% reduction in mean HbA1C was associated with a 14% reduction in the risk of myocardial infarction (MI) (95% confidence interval [CI], 8% to 21%, P<0.0001) and a 37% reduction in microvascular events (95% CI, 33% to 41%, P<0.0001) (Figure 1). The lack of any threshold in the HbA1C value underlines the importance of tight blood glucose control in the management of patients with T2DM.

Figure 1. Adjusted incidence rates per 1000 person-years and 95% confidence intervals for myocardial infarction (red squares) and microvascular disease (green circles) according to mean glycated hemoglobin (HbA1C) concentrations in the United Kingdom Prospective Diabetes Study (UKPDS); adjusted for age, sex, and ethnic group.


Treatment in diabetes mellitus

Recommended blood glucose target levels have dropped over the last decade in line with the above observations. The latest International Diabetes Federation (IDF) guidelines recommend achieving HbA1C values <6.5%, and even suggest that if a target level less than this can be achieved easily, this will further reduce complications.

The basis of any therapy in T2DM is to promote diet and lifestyle modification in order to decrease blood glucose levels by reducing calorie intake and achieving weight loss. It is also important to address any risk factors for cardiovascular disease by controlling lipids and hypertension.

If lifestyle modification fails, the physician has a number of choices regarding oral antidiabetic treatment, which include the sulfonylureas and metformin. Sulfonylureas are insulin secretagogues that address β-cell defects and stimulate the secretion of insulin by causing the closure of the adenosine triphosphate (ATP)-sensitive potassium (K_ATP) channels in the plasma membrane of the β cell. K_ATP channels are also present in many other tissues, most notably the myocardium and vascular smooth muscle cells, where they play a role in the cardioprotective mechanisms of ischemic preconditioning and vasodilation. This may account for the variation in the pharmacological and side effect profiles of the antidiabetics within the sulfonylurea class, which have differing interactions with the various types of K_ATP channels. By choosing a sulfonylurea that selectively targets the pancreatic K_ATP channels, it is possible, therefore, to obtain effective blood glucose control without hampering the endogenous cardioprotective mechanisms.

The administration of metformin (a biguanide) to patients with T2DM results in a decrease in hepatic insulin resistance, leading to a reduction in glucose production with no direct effect on fasting plasma insulin levels. This is because metformin has no action on pancreatic insulin secretion. The result is an effective reduction in hyperglycemia of comparable extent to that achieved with a sulfonylurea, but via a totally different mechanism of action.

How well the strategies of diet, insulin, sulfonylurea, or metformin work in long-term monotherapy has also been assessed in UKPDS. After 3 years on monotherapy, 50% of diabetic patients no longer met the UKPDS blood glucose targets (HbA1C <7%) and required combination therapy to meet these targets. Because the biguanides (metformin) and sulfonylureas have completely different mechanisms of action, but bring about a similar reduction in hyperglycemia, they constitute the classic combination treatment, with additive effects and an acceptable side-effect profile.

Clearly, a good antidiabetic treatment needs to thoroughly address two target factors as early as possible in treatment: insulin secretion and insulin resistance. The additional impact of the various classes of antidiabetic agents on cardiovascular risk factors has been investigated, and is an important consideration in deciding which strategy to use in a particular patient.
Clinical data for cardioprotective effects of oral antidiabetic agents

Although evidence from observational studies suggests a link between hyperglycemia and cardiovascular disease, UKPDS was unable to directly demonstrate a statistically significant reduction in macrovascular events with intensive blood glucose control. The one exception to this involved the use of metformin in overweight type 2 diabetic subjects.12 Use of metformin in 342 overweight patients was associated with a greater risk reduction than in any of the other intensive treatment groups of overweight patients (265 patients receiving chlorpropamide, 277 patients receiving glibenclamide, and 409 patients receiving insulin) for any diabetes-related end point (P=0.0034), all-cause mortality (P=0.021), and stroke (P=0.032). Moreover, the metformin group had a 39% lower risk of MI compared with the conventional treatment group (overweight patients on diet alone; n=411) and a 30% lower risk of all cardiovascular outcomes taken together (MI, sudden death, angina, stroke, and peripheral diseases).12 This effect cannot be explained by the improved blood glucose control alone, which led to speculation that other actions, such as improved fibrinolysis, might be involved.

Treatment with metformin for overweight patients with T2DM was also associated with less weight gain and fewer hypoglycemic attacks than the other intensive treatment groups. For all these reasons, metformin is widely regarded as the drug of choice in overweight or obese patients with T2DM, provided they can tolerate the drug’s side effects (most notably gastrointestinal) and do not have any contraindications for its use (such as impaired renal function).

There are few clinical data on the relationship between treatment with a sulfonylurea, cardiovascular risk, and the prognosis of T2DM, and many of the results from clinical studies remain controversial. Although UKPDS showed that glibenclamide and chlorpropamide did not cause excess cardiovascular morbidity and mortality,3 there is evidence that the "older" sulfonylureas (ie, glibenclamide, glipizide, and tolbutamide) inhibit ischemic preconditioning, a process by which the myocardium becomes accustomed to ischemia via repetitive episodes of transient mild ischemia.13-15 This inhibition may contribute to an increased risk of MI and a poorer prognosis after MI with the use of these agents.

A recent study in Denmark by Johnsen et al14 has attempted to address this controversy by investigating the risk of first-time hospitalization for MI among diabetics receiving various sulfonylureas, other oral antidiabetic medications, or insulin, compared with nondiabetic subjects.15 This population-based trial comprised a case-control study and a follow-up study; and was conducted within about 9% of the total Danish population between 1994 and 2002 using data from the Hospital Discharge Registry and the Civil Registration System.

A total of 6738 cases of first-time hospitalization for MI were identified, of which 867 (12.9%) were diabetic. The prescriptions for antidiabetic drugs prior to hospitalization were analyzed.15 The oral antidiabetic treatments were classified as follows: (i) new sulfonylureas (gliclazide and glimepiride); (ii) old sulfonylureas (glibenclamide, glipizide, and tolbutamide); and (iii) nonsulfonylurea antidiabetic drugs (metformin [78%], acarbose [19%], and repaglinide [3%]). The study calculated odds ratios (ORs) of MI (case-control study) and the 30-day case fatality rates (CFR; follow-up study) associated with antidiabetic drug use, adjusted for possible confounding factors (Table I), and used nondiabetic subjects as a reference group (10 controls for each case). The ORs for MI calculated in the case-control study are presented in Table I according to the different prescriptions of the various antidiabetic drugs.15 After adjustment for possible confounding factors, it was found that the use of any antidiabetic drug was associated with an increased risk for MI, irrespective of the pharmacological treatment used. However, because the risk was lower than that of diabetics receiving no drug therapy, we can safely assume that drug treatment of DM lowers cardiovascular risk. There were, however, significant differences in the ORs between the various antidiabetic drugs administered prior to hospitalization. The risk estimates for users of the old sulfonylureas (OR=2.07; 95% CI, 1.81-2.37) were higher (P=0.01) than for the newer sulfonylureas (OR=1.36; 95% CI, 1.01-1.84) and for the nonsulfonylurea antidiabetic drugs (OR=1.39; 95% CI, 0.90-2.11). The 30-day CFRs calculated in the follow-up part of the study are presented in Figure 2 (page 258). The lowest CFRs were found for users of the new sulfonylurea glimepiride (9.5%; adjusted OR=0.34; 95% CI, 0.08-1.44) and for the nonsulfonylurea antidiabetic drugs (mainly metformin) (22.6%; adjusted OR=0.69; 95% CI, 0.27-1.76). Despite the fact that these results are statistically nonsignificant, these findings point to a strong trend in favor of glimepiride and metformin.

<table>
<thead>
<tr>
<th>Antidiabetic medication</th>
<th>Cases (n=6636)</th>
<th>Controls (n=66 839)</th>
<th>OR (95% CI)* for myocardial infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td>New sulfonylureas</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glimepiride</td>
<td>56</td>
<td>322</td>
<td>1.36 (1.01-1.84)</td>
</tr>
<tr>
<td>Gliclazide</td>
<td>35</td>
<td>205</td>
<td>1.36 (0.93-1.99)</td>
</tr>
<tr>
<td>Glibenclamide</td>
<td>21</td>
<td>117</td>
<td>1.37 (0.84-2.22)</td>
</tr>
<tr>
<td>Old sulfonylureas</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glibenclamide</td>
<td>305</td>
<td>1306</td>
<td>2.07 (1.81-2.37)**</td>
</tr>
<tr>
<td>Glipizide</td>
<td>206</td>
<td>889</td>
<td>2.08 (1.77-2.45)</td>
</tr>
<tr>
<td>Tolbutamide</td>
<td>72</td>
<td>317</td>
<td>1.97 (1.50-2.58)</td>
</tr>
<tr>
<td>Nonsulfonylurea oral antidiabetic drugs</td>
<td>27</td>
<td>100</td>
<td>2.32 (1.48-3.64)</td>
</tr>
<tr>
<td>Diabetics without pharmacotherapy</td>
<td>189</td>
<td>423</td>
<td>3.51 (2.92-4.22)</td>
</tr>
</tbody>
</table>

* Adjusted for confounding factors such as hypertension, chronic bronchitis, and emphysema, alcoholism and liver cirrhosis, prescription for antihypertensive drugs, lipid-lowering agents, high-dose aspirin, platelet inhibitors, oral anticoagulants, hormone replacement therapy, and nitrates prior to the date of hospitalization for myocardial infarction.

** P<0.01 versus new sulfonylureas.
Studies on cloned sarcolemmal KATP channels show effects on ischemic preconditioning. Abbreviation: SU, sulfonylurea.

These results indicate that the risk of MI in type 2 diabetics can be reduced by selecting treatment with a newer sulfonylurea (gliclazide or glimepiride). This is consistent with the data on ischemic preconditioning. Furthermore, it appears that only the patients receiving gliclazide or metformin—and surprisingly not glimepiride—had a reduced CFR, and thus an increased probability of surviving an MI. It is possible that the low CFR values for gliclazide and metformin were a random finding caused by the small numbers of patients involved. However, these findings are consistent with other results for metformin, the use of which has previously been associated with reduced cardiovascular mortality. Moreover, with regard to glazide, Johnsen et al suggest that their results are in line with its known free radical-scavenging activity and antiplatelet activity, in addition to its neutral effect on ischemic preconditioning.

Preclinical evidence for cardioprotection with selected sulfonylureas

The Danish study described above has provided preliminary clinical evidence of differences between the sulfonylureas in terms of cardiovascular effects. Although the clinical evidence remains sparse, there are a number of preclinical studies that support the cardioprotective advantage of the newer sulfonylureas over their older counterparts. In addition to studies into the effects on ischemic preconditioning, this includes investigations into antiatherogenic effects, antioxidant effects, and antiplatelet activity.

**Effects on ischemic preconditioning**

Studies on cloned sarcolemmal KATP channels show that the newer sulfonylureas, in contrast to the older sulfonylureas, have a high affinity for the pancreatic sulfonylurea receptor (SUR)-1, but a low affinity for cardiac and vascular receptors SUR2A and SUR2B. The effects of treatment with glibenclamide or gliclazide on ischemic preconditioning and the protection induced by the antianginal drug nicorandil have been studied in vivo in rats in an open chest model of MI. In this model, the rats underwent regional ischemia for 25 minutes followed by reperfusion for 2 hours, after which the ratio of the size of infarct to the size of the zone at risk was calculated. At the beginning of the experiment, the animals were randomly assigned to receive saline (control), gliclazide, or glibenclamide as an intravenous bolus. Each rat was then also randomly assigned to a control group, ischemic preconditioning group (two periods of 5 minutes' ischemia and 5 minutes' reperfusion), or nicorandil-induced protection group. Infarct size was significantly reduced with ischemic preconditioning (15.0 ±1.1%) and nicorandil (25.5±4.2%) versus control (44.1±3.2%) (P<0.005), confirming the validity of the model. Glibenclamide completely abolished the protective effects of ischemic preconditioning (40.8 ±4.6%) and nicorandil (39.5±5.1%), while glazide had no adverse effects on ischemic preconditioning (20.4±1.9%) or nicorandil-induced protection (23.6±2.2%) (P<0.005).

These results in animals were recently confirmed in a study of human myocardium using right atrial appendages from cardiac surgery patients. In the study, glibenclamide (0.1, 1, 3, or 10 μmol/L) and gliclazide (1, 10, 30, or 100 μmol/L) were added for 10 minutes prior to ischemic preconditioning. The cardioprotection was abolished by glibenclamide at all the concentrations tested, whereas it was lost with gliclazide only at the supratherapeutic concentrations of 30 and 100 μmol/L. This confirms the differential effects of the two sulfonylureas on ischemic preconditioning, and implies that diabetic patients with ischemic heart disease can be safely prescribed glazide without the risk of losing the cardioprotective effects of ischemic preconditioning.

**Antiplatelet and fibrinolytic activity**

A number of hemobiological abnormalities are often observed in DM, including increased platelet adhesiveness, platelet hyperaggregability, decreased platelet half-life, hemorrhheological abnormalities, and altered fibrinolysis, which may contribute to a procoagulative state. This abnormal platelet reactivity in DM depends on the prothrombin imbalance, ie, an increase in the proaggregant, vasoconstrictor thromboxane A2 (TXA2) and a decrease in the antiaggregant, vasodilator prostacyclin (PGI2, prostaglandin I2). The effect of the new sulfonylurea glazide on the TXA2/PGI2 ratio, and hence its antiplatelet activity, was studied in 25 type 2 diabetic patients. The patients in this study were previously treated with gliclazide or with a gliclazide/phenformin combination, and were switched to receive glazide (80 mg/day [n=21], 160 mg/day [n=21], or 240 mg/day [n=2]) for 3 months. All drugs affecting PGI2 synthesis and lipid metabolism were discontinued 3 weeks prior to the start of the study. The patients were assessed for fasting blood glucose, lipids, insulin, TXB2 (a metabolite of TXA2), and 6-ketoprostaglandin F1 (6-KPGF1, a metabolite of PGI2).
After 3 months of treatment with gliclazide, TXA2 decreased by almost 50%, while 6-KPGF1 increased by approximately 50%. This change in the calculated TXA2/PGI2 ratio from 4.6 to 1.6, which indicates that switching from the older sulfonylurea (ie, glibenclamide) to the newer sulfonylurea (ie, gliclazide) improves the prostaglandin imbalance, thereby correcting the platelet hyperadhesiveness and hyperaggregation in diabetes, and reducing cardiovascular risk. These changes were observed despite the fact that neither fasting plasma glucose nor plasma insulin levels changed with therapy. Similar results have been found in animals, but this was the first time that gliclazide had been shown to improve the prostaglandin balance in humans.

Another important factor for delayed tissue repair and progression of atherosclerotic disease in DM is dysfunction of the endothelial cell–dependent fibrinolytic system. Studies in type 1 diabetic patients without residual β-cell function have demonstrated that gliclazide increases endothelial cell tissue plasminogen activator (t-PA) and has an effect on the fibrinolytic variables in the liver, as histidine-rich glycoprotein concentrations significantly decreased during gliclazide administration. These effects were independent of the positive effect on the metabolic state of the patients. Other studies have shown that gliclazide can increase blood t-PA in type 2 diabetic patients with abnormally low blood t-PA activity, which is an indicator of increased risk for MI in patients with ischemic heart disease. These results indicate that gliclazide could be beneficial in patients with defective endothelial cell–dependent fibrinolysis. The pharmacological explanation for the fibrinolysis-enhancing properties of gliclazide remains unclear, although it has been postulated that it is an indirect effect of the benefits of heparin on the endothelial cell–dependent t-PA system, as gliclazide reportedly increases tissue synthesis and decreases the degradation of glucosaminoglycans in diabetic mice.

**Antioxidant effect**
DM increases oxidative stress through a number of mechanisms. First, glucose catalyzes lipid peroxidation. Moreover, there is evidence that an acute glucose load can decrease antioxidant defenses in humans. Second, advanced glycation end-products (AGEs) can generate free radicals, meaning that antioxidants such as glutathione, vitamin E, vitamin C, and the carotenoids are reduced in patients with DM.

The antioxidant effects of various sulfonylureas have been investigated in vitro. Blood samples were collected from type 2 diabetics and control subjects. The antioxidant effects of supplementation with 1 μmol gliclazide, glimepiride, glibenclamide, tolbutamide, or glipizide were assessed by measuring total plasma antioxidant capacity (TPAC) using a colorimetric assay, and the susceptibility of low-density lipoprotein (LDL) to oxidation was measured using a technique based on copper-based LDL oxidation lag-time. The results for the LDL oxidation are presented in Figure 3. They show clearly that differences exist between the sulfonylureas in terms of their antioxidant effects, even at their maximal equivalent therapeutic dosages. Only gliclazide significantly increased the resistance of LDL to oxidation. Similar results were found for TPAC; only gliclazide significantly improved plasma antioxidant defenses from 1.09±0.11 mmol/L to 1.23±0.11 mmol/L (P<0.01), thus reducing oxidative stress.
**Antiatherogenic effect**

Increased oxidative stress and glycation strongly contribute to the physiological basis of the pathogenesis of cardiovascular disease in DM. Gliclazide not only lowers blood glucose, but is also a free radical scavenger, indicating that it may have additional advantages in preventing cardiovascular complications. This has been investigated in type 2 diabetic patients using ultrasonographic assessment of the carotid artery intima-media thickness at both the beginning and end of a 3-year observation period.

![Table II. Progression in carotid artery intima-media thickness from the beginning to the end of a 3-year observation period in type 2 diabetic patients using ultrasonographic assessment.](image)

Table II. Progression in carotid artery intima-media thickness from the beginning to the end of a 3-year observation period in type 2 diabetic patients using ultrasonographic assessment.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Glibenclamide (n=59)</th>
<th>Glibenclamide and metformin (n=29)</th>
<th>Gliclazide (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Annual change in average intima-media thickness (mm)</strong></td>
<td>0.004±0.045</td>
<td>0.003±0.048**</td>
<td>0.032±0.036*</td>
</tr>
<tr>
<td><strong>Annual change in maximum intima-media thickness (mm)</strong></td>
<td>0.114±0.131</td>
<td>0.041±0.105*</td>
<td>0.044±0.106*</td>
</tr>
</tbody>
</table>

*Significantly different from glibenclamide, P<0.05.
**Significantly different from gliclazide, P=0.043.

On entry into the study, patients were already receiving antidiabetic treatments: glibenclamide (n=59), gliclazide (n=30), or glibenclamide and metformin combination (n=29). The results indicating the changes in carotid artery intima-media thickness at the end of the study are presented in Table II. A multivariate regression analysis was performed to adjust these results for other factors, such as changes in HbA1C value, lipid profile, and blood pressure. This analysis showed that the administration of gliclazide or metformin significantly (P<0.05) and independently reduced the progression of average intima-media thickness compared with glibenclamide therapy.

The authors conclude that administration of metformin or gliclazide can attenuate the progression of atherosclerosis in human carotid arteries in patients with T2DM. They suggest that the antiatherogenic effect of metformin is a result of its fibrinolytic effect and its ability to modulate the generation of reactive oxygen species. They explain the antiatherogenic effect of gliclazide as being caused by its free radical-scavenging properties, its restorative action on endothelial function, and its reduction in platelet reactivity.

**Conclusion**

UKPD5 has shown that good blood glucose control can protect patients with T2DM against cardiovascular disease. However, there appear to be differences between the various available antidiabetic treatments in terms of their cardioprotective effects, and above their hypoglycemic efficacy. Recent clinical studies have highlighted significant differences between sulfonylureas in terms of their impact on cardiovascular disease, and provided evidence that some of the newer generation sulfonylureas provide an added advantage of cardiovascular protection for type 2 diabetics. These effects have been specifically linked to the antiatherogenic, antiplatelet, and antioxidant properties of gliclazide, as well as the neutral effect of the new sulfonylureas on ischemic preconditioning.

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Diamicron MR : un antidiabétique qui permet des bénéfices cardiovasculaires et un contrôle efficace de la glycémie

L’étude UKPDS (United Kingdom Prospective Diabetes Study) a montré récemment que chez les diabétiques de type 2, toute diminution de l’hémoglobine glyquée (HbA1C) est liée à une diminution du risque de complications de la maladie et que les plus faibles niveaux de risque se retrouvent chez les sujets dont les valeurs sont dans la normale. Voilà qui souligne l’importance du contrôle glycémique dans la prévention des complications diabétiques, y compris les complications cardiovasculaires. L’accélération de l’athérosclérose coronaire et l’augmentation du risque de thrombose artérielle majorent la prévalence de la maladie cardiovasculaire chez les diabétiques. Toute protection cardiovasculaire supplémentaire générée par un traitement hypoglycémique, en plus des gains généraux positifs du contrôle glycémique, sera donc bénéfique et jouera un rôle important dans le choix de la stratégie à adopter selon les patients. Une vaste étude de population danoise récente, cas-témoins, a montré que la prescription d’une sulfonylurée de nouvelle génération (comme le gliclazide) chez les diabétiques de type 2 réduit le risque d’infarctus du myocarde et augmente la probabilité de survie après un tel événement. La sélectivité du gliclazide pour les récepteurs pancréatiques aux sulfonylurées peut expliquer ces effets cardioprotecteurs associés aux résultats in vivo et in vitro d’études ayant démontré ses propriétés antioxydantes, antiplaquetaires et antiathérogènes, associées à un effet neutre sur le préconditionnement ischémique.
Can you describe the background to the ADVANCE trial?

It has long been recognized that type 2 diabetes carries an increased cardiovascular (CV) risk. This was well quantified in the Framingham study, which indicated a two- to fivefold increase in relative risk for all types of CV events in type 2 diabetes, compared with controls. Given the long-term epidemiological evidence of a linear relation between blood glucose and CV risk, trials were soon set up to test whether reducing high blood glucose would lower the associated risk. The first large-scale trial was the University Group Diabetes Program (UGDP) in the USA during the late 1960s. The linear relation between high blood pressure (BP) and CV risk in type 2 diabetes was also highlighted in the “Mister Fit” study published in 1993 (Multiple Risk Factor Intervention Trial; MRFIT).

Microvascular disorders are typical of diabetes, with quasi-specific anatomical lesions like microaneurysms. Two risk factors are well established for microangiopathy: high blood glucose and high BP. Microangiopathy impairs the function of organs like the retina (causing blindness) and kidneys (glomerulopathy causing proteinuria and leading to end-stage renal failure), and also of the target organs of atherosclerosis, namely the heart and brain. Myocardial and cerebral microvessels can be affected by microangiopathy, leading to heart failure and dementia (as described many years ago byBinswanger). Microangiopathy also impairs large vessel function. Maneuvers like percutaneous coronary intervention and coronary artery bypass grafting, which are used to widen blood vessels narrowed...
by atherosclerotic plaque or thrombi, will only be successful if the downstream capillary network is operative. This is why revascularization procedures were formerly not easy to perform in diabetics. Also, microcirculatory disorders in type 2 diabetes and its accompanying neuropathy are the likely explanations for CV events occurring without typical symptoms, like silent myocardial infarction. Lastly, high BP and blood glucose can alter arterial wall composition, which modifies hemodynamic conditions, typically manifesting as isolated systolic hypertension, with all its deleterious CV consequences. However, in contrast to their effects on microvessels, high blood glucose and BP cannot by themselves modify the nature of atherosclerotic plaque.

**What is the current evidence concerning blood pressure lowering and the risks of microangiopathy and cardiovascular disease in type 2 diabetes?**

The most prominent finding of the United Kingdom Prospective Diabetes Study (UKPDS) was the spectacular beneficial effect on microangiopathy of lowering systolic blood pressure (SBP) by 10 mm Hg and diastolic blood pressure (DBP) by 5 mm Hg, in diabetics with hypertension (SPB/DBP >160/90 mm Hg). Epidemiological analysis of UKPDS suggested a linear benefit, i.e., the lower the BP, the greater the benefit, consistent with the large meta-analysis published by the Oxford group. Also, the Hypertension Optimal Treatment (HOT) and the SYSTolic hypertension in EUROpe (Syst-Eur) trials suggested that hypertensives with type 2 diabetes benefit from BP lowering to 140/80 mm Hg. There is a need for proof to support the current recommendations of BP <130/80 mm Hg (<120/75 mm Hg if proteinuria present) for normotensive patients with type 2 diabetes, and this is one of the main objectives of the ADVANCE trial (Action in Diabetes and Vascular disease: PreterAx and DiamicroN Controlled Evaluation). The ability of angiotensin-converting enzyme (ACE) inhibitors to reduce microalbuminuria independently of their BP-lowering effect was first shown in normotensives with type 1 diabetes, versus placebo and thiazide. These findings were consistent with the concept that, in diabetic nephropathy, BP elevation is secondary to glomerular disease whose progression is blocked by specifically reducing intraglomerular hypertension. But this may not be the case for a majority of people with type 2 diabetes.

**What is the current evidence concerning blood pressure lowering and the risks of microangiopathy and cardiovascular disease in type 2 diabetes?**

The causal relationship between high blood glucose and microangiopathy has been examined in follow-up studies, experiments in animal models, and clinical trials, like those of Eschwege et al in 1976; the Diabetes Control and Complications Trial (DCCT) in type 1 diabetes, and UKPDS in type 2 diabetes. Type 1 diabetes is certainly the best model to ascertain the effect of glucose-lowering strategies on the microcirculation, because people with type 1 diabetes are normotensives initially, unlike type 2 diabetics, many of whom also have hypertension. In DCCT, a reduction in glycylated hemoglobin (HbA1c) from 9% to 7% reduced the risk of renal disease by 60% to 70%, and UKPDS data were consistent with the magnitude of this benefit. However, DCCT concerned primary prevention of microangiopathy, and the benefit of glucose lowering in secondary prevention is less clear-cut. In DCCT, renal status worsened during the first 3 years in participants on intensive treatment, with initial background retinopathy, compared with participants with the same renal status on conventional treatment. Feldt-Rasmussen and coworkers showed that 2 years of strict blood glucose control reduced progression from microalbuminuria to proteinuria, but did not induce regression. Tesfaye and coworkers showed that rapid transition from uncontrolled diabetes to strict blood glucose control can provoke acute neuritis through ischemia of the vasa nervorum. These data are consistent with the finding of Fiorett et al that 10 years of normoglycemia are required to normalize kidney morphology, and with the observation by Engerman et al that dogs made diabetic with streptozotocin developed retinopathy when normoglycemia was a secondary intervention, in contrast to the effectiveness of primary intervention.

Thus, although UKPDS showed that reduction of HbA1c from 7.9% to 7% afforded a 25% benefit in retinal and renal diseases in subjects with recently diagnosed type 2 diabetes, two questions remain unanswered and will be examined in ADVANCE: (i) does the benefit of glucose lowering for microangiopathy risk go beyond the evidence-based HbA1c <7% target? (ii) in people who have had type 2 diabetes for 10 or more years, does strict blood glucose control provide benefit for microvascular (and macrovascular) disease, in spite of the long-term “glucose memory” effect well illustrated in type 1 diabetes (see also data on CV disease from the DCCt/ Epidemiology of Diabetes Interventions and Complications (EDIC) study)? Historically, UKPDS was set up to check the validity of data from UGDP; which was controversial because of methodological concerns, during which no benefit for CV risk—and even some harm—was reported for the use of oral antidiabetic drugs. Okhnb et al were the first to report a global benefit in people with type 2 diabetes, but the patients were Japanese and their type 2 diabetes may differ in nature from that affecting other ethnicities. While epidemiological
analysis of UKPDS data suggested that \( \text{HbA1C} \) reduction had a dose-dependent benefit in type 2 diabetes,\(^9\) it showed little benefit regarding risk of myocardial infarction and no benefit at all for stroke, and no protection regarding diabetes-related death.\(^22\) Interestingly, the blood glucose threshold below which CV disease risk starts is below that of the microangiopathy risk (the latter is used to define diabetes).\(^20\) As shown in a metaregression analysis by Coutinho et al,\(^{30}\) fasting blood glucose of 110 mg/dL (6 mmol/L) corresponds to a relative CV risk of 1.33, and blood glucose of 140 mg/dL (7.8 mmol/L) 2 hours after a 75-g oral glucose load corresponds to a relative CV risk of 1.40. So, there are two unresolved questions, which can be adequately answered by ADVANCE:\(^3\)

(i) is reducing blood glucose effective in lowering the CV risk of people with type 2 diabetes? (ii) in lowering CV risk, should blood glucose targets be below those defining type 2 diabetes and even dysglycemia, ie, \( \text{HbA1C} < 6.5\% \) and fasting blood glucose <6 mmol/L?

ADVANCE will also yield valuable data on the safety of intensive blood glucose–lowering treatments. What, for instance, is the frequency of severe hypoglycemia in these conditions? And what about weight gain? Does it occur, does it increase with time, as suggested by UKPDS, is it harmful because of consequent increases in other CV risk factors like BP, lipids, hemostasis?

Can you outline the design, recruitment, and objectives of ADVANCE?

ADVANCE is perhaps the largest ongoing randomized trial to address the issue of microvascular and CV disease in type 2 diabetes. With its two-by-two factorial design,\(^7\) ADVANCE is comparing, on the one hand, Preterax with its matched placebo in a double-blind fashion, and, on the other hand, an open, randomized strategy of lowering \( \text{HbA1C} \) below 6.5% and fasting blood glucose below 6.1 mmol/L, using gliclazide 30 mg MR first-line, with locally recommended strategies (in the latter arm, only sulfonylureas other than gliclazide are authorized). If the investigators consider that treatment with ACE inhibitors is necessary, they are free to prescribe perindopril (2 mg or 4 mg daily).

The main selection criteria for participants were age ≥55 years, hypertensive or normotensive, together with ≥1 of the following risk factors: age ≥65 years; history of major microvascular events; type 2 diabetes diagnosed ≥10 years before; other major risk factors.\(^23\) Recruitment started in November 2001 and lasted until April 2003, by when 12 878 participants had been registered, 11 140 of whom were randomized after a 6-week run-in period. During this period, mean SBP decreased by 8 mm Hg, suggesting that the study conditions are adequate.

The primary objectives of ADVANCE in both normotensive and hypertensive subjects with type 2 diabetes and high CV risk are to answer the following questions: (i) does reducing BP using a fixed combination of perindopril (2 mg then 4 mg) and indapamide (0.625 mg then 1.25 mg) lower the risk of CV events (defined as the first occurrence of nonfatal myocardial infarction or stroke, or CV death)? (ii) does reducing BP using a fixed combination of perindopril (2 mg then 4 mg) and indapamide (0.625 mg then 1.25 mg) lower the risk of CV events compared to placebo regarding microangiopathy (retinopathy, nephropathy)? (iii) does reducing \( \text{HbA1C} \) to below 6.5% and fasting blood glucose to below 6.1 mmol/L, versus using an intensive gliclazide (30 mg/day)-based strategy, versus locally recommended objectives, reduce the risk of onset or worsening of microangiopathy (retinopathy, nephropathy)? (iv) does reducing \( \text{HbA1C} \) to below 6.5% and fasting blood glucose to below 6.1 mmol/L, versus using an intensive gliclazide (30 mg/day)-based strategy, versus locally recommended objectives, reduce CV events (as defined above)? (v) does reducing \( \text{HbA1C} \) to below 6.5% and fasting blood glucose to below 6.1 mmol/L, versus using an intensive gliclazide (30 mg/day)-based strategy, versus locally recommended objectives, improve the combined outcome of microangiopathic and CV events as defined above? (vi) does reducing \( \text{HbA1C} \) to below 6.5% and fasting blood glucose to below 6.1 mmol/L, versus using an intensive gliclazide (30 mg/day)-based strategy, versus locally recommended objectives, improve the combined outcome of microangiopathic and CV events as defined above? (vii) are the benefits of intensive BP–lowering and blood glucose–lowering treatments independent, additive, or synergistic?

How are the ADVANCE results likely to impact on diabetes care?

The data of the BP arm of ADVANCE will be presented at the next European Society of Cardiology meeting in Vienna, in September 2007. The findings of the glucose arm will be available during 2008. It is almost certain that these results will modify the rules of type 2 diabetes care. In terms of blood pressure lowering, if Preterax has a greater effect than placebo on both microvascular and CV outcomes, it will be recommended that BP be lowered to the values attained during ADVANCE, including when used in addition to angiotensin receptor blockers. All type 2 diabetics over 65 years of age will be advised to follow this strategy. If Preterax is better than placebo regarding microvascular outcome alone or CV outcome alone, the aforementioned options would not be modified, since renal and renal diseases are of as much concern as CV diseases in type 2 diabetes. It is unlikely that Preterax will be neither better nor worse than placebo, but if this were so the currently recommended (but not evidence-based) BP target of <130/80 mm Hg in type 2 diabetics would have to be reconsidered seriously. As for blood glucose lowering, if a gliclazide-based glucose-lowering strategy is better than a standard strategy in terms of both microvascular and CV outcomes, then this would be evidence that \( \text{HbA1C} < 6.5\% \) and fasting blood glucose <6.1 mM are efficacious (and realistic) objectives (once again, this is not yet proven). Also, oral antidiabetic treatment strategies should be reconsidered, with gliclazide as first-line therapy in a strategy based on intensive multidrug regimens, including insulin treatment.

If the gliclazide-based strategy is better than the standard strategy in terms of CV outcomes, but not for microvascular disease, this would be the first demonstration of a causal effect of moderate hyperglycemia on CV risk, and demonstration of a feasible option for this purpose. By contrast, it would also demonstrate that CV risk starts at blood glucose increases lower than those provoking microvascular risk. Also, it has long been claimed that some sulfonylureas increase CV risk, and this would be a clear argument for the preferential use of gliclazide as insulin secretagogue.

If the gliclazide-based strategy is not better than the standard strategy in terms of microvascular and CV outcomes, this would confirm that \( \text{HbA1C} < 7\% \) is a reasonable objective, and would provide a means of making it realistic. It would also provide a basis for quantifying the cost (if any) of this objective in terms of severe hypoglycemic events and weight gain.

Many important issues for diabetes care are pending on the results of ADVANCE. It is anticipated that the size of this trial, and therefore its power, will be large enough to provide clear-cut answers to the questions raised. □
REFERENCES

ADVANCE : LA PLUS IMPORTANT ÉTUDE EN COURS RANDOMISÉE, CONTRÔLÉE, DE LA MALADIE CARDIO-VASCULAIRE DANS LE DIABÈTE DE TYPE 2

L'étude ADVANCE (Action in Diabetes and Vascular disease : Preterax and Diamicron MR Control Evaluation) est une étude de conception factorielle deux fois deux chez des patients diabétiques de type 2 à haut risque cardio-vasculaire. Elle a pour but d’expérimenter deux types d’actions sur les risques microvasculaires et cardio-vasculaires : la réduction de la pression artérielle (chez les hypertendus comme chez les normotendus) avec une association fixe de perindopril et d’indapamide dans une étude en double aveugle contrôlée contre placebo et la diminution de l’hémoglobine glyquée en dessous de 6,5 % et de la glycémie à jeun en dessous de 6,1 mmol/l grâce au glicazide LM (libération modifiée) 30 mg en première intention, face à des stratégies recommandées localement et de façon ouverte et contrôlée. Ces interventions s’ajoutent aux traitements actuellement recommandés par les investigateurs, comme l’utilisation d’un inhibiteur de l’enzyme de conversion (perindopril 2 mg/jour à 4 mg/jour). Cet article présente l’argumentaire de cette étude (y compris l’incertitude actuelle quant aux avantages de la normalisation de la pression artérielle et de la glycémie chez les diabétiques de type 2) et ses résultats anticipés.
Reducing CVD risk in type 2 diabetes: Mission possible

by O. Pedersen, Denmark

Intervention in type 2 diabetes: from a glucocentric approach toward global vascular protection

For a long time, type 2 diabetes mellitus (T2DM) was believed, at least in the elderly, to be a relatively benign disorder. Insights into the disease have, however, become deeper. In epidemiological surveys, it is well documented that the age-adjusted prevalence of coronary heart disease in white adults who have diabetes mellitus is about 45% compared with about 25% in individuals without diabetes mellitus. Cardiovascular disease (CVD; coronary heart disease, stroke, and peripheral vascular disease) may account for about 70% of all deaths in people with diabetes mellitus, and all manifestations of CVD are also substantially more common in patients with T2DM than in nondiabetic individuals. Therefore, T2DM is not “just another risk factor” for a poor cardiovascular prognosis; at the population level, it defines maximal risk per se for target organ damage, primarily within the cardiovascular system.

During recent years, numerous prospective studies have identified several modifiable risk factors for CVD in patients with T2DM. In addition to hyperglycemia, these factors include hypertension, dyslipidemia, microalbuminuria, a prothrombotic state, visceral fat accumulation, chronic low-grade inflammation, smoking, diets rich in saturated or trans fatty acids, and lack of physical activity.

Even though there are no data from controlled long-term clinical trials to provide definite answers to the impact on CVD outcome of each of the individual lifestyle factors, there is overwhelming epidemiological evidence that a healthy life performance helps prevent CVD in patients with diabetes mellitus. Importantly, crucial information has been gained from individual risk factor intervention trials in both diabetic and nondiabetic subjects. On the basis of the results of interventions in diabetic patients (for a review, see references 10-13), the degree of CVD relative risk reduction with each individual risk factor target ranges from small (eg, nonsignificant for hyperglycemia lowering using insulin or a sulfonylurea in the United Kingdom Prospective Diabetes Study [UKPDS]), to moderate (eg, about 10% with aspirin therapy), to substantial (eg, 25% to 40% with blood pressure [BP] reduction or statin in-

Type 2 diabetes mellitus (T2DM) is a major risk factor for premature cardiovascular disease (CVD) that is the equivalent of existing ischemic coronary disease. The reason appears to be that besides hyperglycemia, a clustering of other known but modifiable and interactive risk factors for CVD coexists in patients with T2DM more often than would be expected by chance alone. During the last 5 to 10 years, however, several successful randomized individual risk factor intervention trials have been performed, punching the nihilistic attitude previously taken by many physicians and diabetes educators regarding improving the CVD prognosis of T2DM. Thus, to prevent or postpone premature vasculopathy in T2DM, evidence indicates that, in all age groups, a structured and intensified long-term approach is required that is far more than just glucocentric—an approach addressing more CVD risk factors, including hypertension, dyslipidemia, platelet aggregation, sedentary behavior, smoking, and dietary habits. The application of such an integrated and aggressive therapy for almost 8 years to high-risk type 2 diabetic patients cuts the relative risk of CVD by half. It is time to take these health benefits of global CVD interventions aimed at all validated targets in controlled clinical trials, to the community level, where it has been documented that a major gap exists between evidence-based diabetology and daily clinical practice.

Medicographia. 2007;29:266-272. (see French abstract on page 272)

Keywords: diabetes; cardiovascular disease; risk factor; health behavior; polypharmacy; drug concordance; education

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duced lipid lowering). Also, treatment with angiotensin-converting enzyme (ACE) inhibitors as secondary prevention of CVD has been convincingly demonstrated. Based upon the indisputable results from clinical end point trials, the pharmacotherapy for T2DM, as reflected in national guidelines, has changed from the glucocentric traditional approach, toward an approach involving more global vascular protection. The outcome of this intensive and integrated vascular treatment approach aimed at multiple sources of risk has, however, only been evaluated in a few studies of patients with T2DM (for a review see references 11-13). By targeting several risk factors simultaneously using treatment goals in many respects comparable with current guidelines from the American Diabetes Association, the Steno-2 study, which was initiated 15 years ago, demonstrated an overall 50% CVD relative risk reduction in a high risk population of type 2 diabetic patients with microalbuminuria (a marker of a generalized vasculopathy), thus underscoring the benefits of an intensified intervention integrating both a target-driven polypharmacological therapy and a focused behavior modification.14,15

Steno-2 demonstrates that an intensive and multi-targeted intervention makes a major difference

The Steno-2 study14,15 was the first long-term T2DM trial to compare the impact of an intensified multi-targeted intervention with that of conventional multifactorial treatment on risk factors for CVD. In a randomized, open, parallel trial, 80 patients with T2DM and microalbuminuria were randomized to receive conventional treatment in accordance with national guidelines, while another 80 patients with T2DM were assigned to receive an intensified, integrated treatment targeting a series of modifiable risk factors. The primary composite end point was death from CVD, nonfatal MI, nonfatal stroke, percutaneous coronary intervention, coronary artery bypass grafting, revascularization, and amputation. At a mean follow-up of 7.8 years, patients receiving the intensive therapy had a 53% (95% confidence interval [CI], 27% to 76%) lower relative risk of CVD. More detailed information on the impact of intensified interventions on the various components of the primary CVD end point is given in Figure 1.

Figure 1. Data regarding the intensive therapy and conventional therapy groups of the Steno–2 study. Panel A shows the distribution of the total number of cardiovascular events in the Steno-2 Study14 in the intensive therapy group (red) and conventional therapy group (green). Panel B shows Kaplan-Meier estimates of time to first stroke in the intensive therapy and conventional therapy groups. Panel C shows Kaplan-Meier estimates of time to first percutaneous intervention or coronary artery bypass grafting, revascularization, and amputation. Panel D shows Kaplan-Meier estimates of time to first myocardial infarction in the intensive therapy and conventional therapy groups.


Abbreviations: CABG, coronary artery bypass graft; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; PCI, percutaneous intervention.
The secondary end points of microvascular complications were also markedly altered: 61% (CI: 13% to 83%) lower relative risk of nephropathy, 58% (CI: 14% to 79%) lower risk of retinopathy, and 63% (CI: 21% to 82%) lower risk of autonomic neuropathy. For the primary CVD end point, risk reductions were seen for all of the different components except for mortality. It may be added that this trial was not statistically powered to evaluate the interventional impact on mortality.

Compared with the majority of individual risk factor intervention trials, the absolute risk reduction in the Steno-2 study was considerable. The absolute risk reduction for the primary end point was 20%, meaning that one CVD event was prevented for every 5 patients treated intensively for 7.8 years. In comparison, the absolute risk reductions for most of the other intervention studies have typically been about 5%, giving a number needed to treat of 20. The outcome of the Steno-2 study may have implications for T2DM care generally, adding to the accumulating knowledge and practical experiences that the integration of several different now evidence-based interventions cuts the risk of macro- and microangiopathy by half—at least in high-risk patients.

**How were the CVD risk reductions achieved in the Steno-2 study?**

In the Steno-2 study, patients randomized to intensive therapy were followed by a diabetes team consisting of a nurse, a clinical dietician, and a physician. In this group, each patient paid a visit to the clinic at least every third month. Individual risk assessments and prioritizations of risk factor targeting were made at the start of the trial and whenever appropriate, but as a minimum, annually throughout the trial period. At each consultation, measurements of clinical (BP, body mass index, waist and hip circumference, smoking status), and biochemical variables (HbA1C, fasting serum levels of total cholesterol, HDL-cholesterol and triglycerides, as well as urinary albumin excretion rate) were performed and the treatment was adjusted accordingly.

The intensive intervention involved a stepwise introduction of lifestyle and pharmacological interventions aimed at keeping HbA1C (<6.5%), BP (<130/80 mm Hg), total fasting serum cholesterol (<175 mg/dL), and fasting serum triglycerides (<150 mg/dL) at strict targets. It should be emphasized that the treatment goals in the intensive arm were made more ambitious as the study progressed, concomitantly with the gain of novel insights from published single risk factor intervention studies. A stepwise introduction of the pharmacotherapeutic package was chosen to facilitate concordance. The details of the treatment algorithms have previously been reported.6-11

To keep up the long-term motivation for this integrated and aggressive approach, at each consultation, the patients were educated about the rationale for the prescribed polypharmacy and the behavior modification.

A diet interview was performed annually or whenever patients or the diabetes team found it necessary. In this way, continuity in diet education was maintained. The dietary intervention was concentrated on qualitative changes of the diet, including a reduction in the intake of animal fat, an increase in omega-3 fatty acid–rich food items, and an increase in daily intake of vegetables and fruits. At each consultation, patients were encouraged to stop smoking. Structured stop-smoking courses for smoking patients and their spouses in the intensive therapy group were organized throughout the follow-up period. Nicotine substitution was offered for free. The patients were continuously inspired to increase the level of leisure-time physical activity. Otherwise, treatment goals for smoking and exercise were similar in the two treatment arms.

**Steno-2—strengths and shortcomings**

In evidence-based medicine, that which seems to be common sense still has to be documented. The Steno-2 study proved what many clinicians and diabetologists for years had thought to be obvious: that T2DM is a treatable disorder and that the CVD prognosis of patients with the disease can be dramatically improved if the intervention is aggressively directed against a series of modifiable risk factors and if the patients are offered continuous education and motivation.

A major strength of the Steno-2 study is the pragmatic treatment approach to the everyday clinical challenges that patients with T2DM present. Although the protocol was limited to patients who had microalbuminuria, this subgroup of patients may constitute up to one third of all patients with T2DM. It may be reasonable, however, to expect lower absolute risk reductions for type 2 diabetic patients at lower risk than the patients included in the Steno-2 study.

Even in a clinical setting such as the Steno-2 study, it is rather thought-provoking that the treatment goals were not obtained to a greater extent in the intensive therapy group. Only 15% of patients in this group achieved an HbA1C value below 6.5% and only about half achieved the target for systolic BP (Figure 2).14 It also turned out to be extremely difficult in the long-term perspective to change health behavior in middle-aged and elderly overweight people, despite the investment of relatively many educational resources.15

**Should every type 2 diabetic patient be offered a Steno-2-like treatment protocol?**

An ongoing trial with a treatment concept and clinical end points similar to those of the Steno-2 protocol is examining the treatment effect in a low risk population of screen-detected type 2 diabetic patients.16 If significant CVD risk reductions are demonstrated in these low-risk patients, the intensified multi-targeted approach could be offered to all patients with T2DM. Until then, however, it seems reasonable to confine the intensified approach pri-
majorly to type 2 diabetic patients with elevated levels of albumin excretion rate or known CVD. Such patients may well comprise more than half of the T2DM population.

**The current gap between the reality and the guidelines recommending the multi-targeted therapeutic package**

A recent Swedish survey involving more than 40,000 patients with T2DM from both primary care units and diabetes clinics reported that the new European treatment targets of HbA1C < or = 6.1%, BP <130/80 mm Hg, and total serum cholesterol <4.5 mmol/L were attained by 16%, 13%, and 28% of patients in 2003, respectively. Aspirin was prescribed in 36% of cases. These findings are compatible with reports from the US calling for a reduction of CVD risk.

Reducing CVD risk in type 2 diabetes – Pedersen

It is the experience of the Steno-2 investigators that repetitive teaching about the rationale for the individual interventions and their expected health benefits is of utmost significance for the long-term motivation and therapy adherence of patients. A similar experience was recently reported by Dr Ravid and coworkers, who examined whether motivating patients to gain expertise in closely following their risk factors would attenuate the course of the vascular sequelae of diabetes. A randomized, prospective study was conducted in 165 patients with T2DM, hypertension, and hyperlipidemia, who were referred for consultation to a diabetes clinic in an academic hospital. Patients were randomly allocated to standard consultation (SC) or a patient participation (PP) program. Both groups were followed by their primary care physicians. The mean follow-up time was 7.7 years, a period similar to that of the Steno-2 study. The SC group attended eight annual consultations. The PP patients initiated on average one additional consultation per year. There were 80 cardiovascular events (8 deaths) in the SC group versus 47 events (5 deaths) in the PP group (P=0.001). The relative risk over 8 years for a cardiovascular event in the intervention (PP) versus the control (SC) group was 0.65 (95% CI, 0.89-0.41). There were 17 and 8 cases of stroke in the SC and PP groups, respectively (P=0.05). The relative risk for stroke was 0.47 (95% CI, 0.85-0.32). In the SC group, 14 patients developed overt nephropathy (4 end-stage renal disease) versus 7 (1 end-stage renal disease) in the PP group (P=0.05; Figure 3, page 279).}

The critical role of continued motivation and education of the diabetic patient at high risk of CVD

Reducing CVD risk in type 2 diabetes – Pedersen

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<tr>
<th>Intensive group</th>
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<td>Hemoglobin A1C &lt;6.5%</td>
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<td>Cholesterol &lt;175 mg/dL</td>
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<td>Triglycerides &lt;150 mg/dL</td>
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<td>Systolic BP &lt;130 mm Hg</td>
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<td>Diastolic BP &lt;80 mm Hg</td>
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Many of the therapies given in an intensified multifactorial intervention approach are given as preventive treatments irrespective of the presence of symptoms, and therefore patients without symptoms may find that the treatment interferes more with their quality of life than the disease itself. In this respect, it is worth noting that patients may find that a change in lifestyle and diet can lead to a large reduction in their quality of life and thus be a more severe barrier to the adherence to treatment than taking drugs.25 Even in the case of symptomatic patients, the start of a treatment may not relieve the symptoms, thereby in itself being a risk factor for nonadherence to treatment.26

Whether the prescription of a single polypill per day containing many of the ingredients needed for the prevention of CVD, thereby diminishing the complexity of the drug regimen, will increase the adherence to polypharmacy is an intriguing question that deserves to be pursued.27 Of course, side effects including drug interactions will also influence drug adherence, and finally, cost of treatment may be of significance.28,29 From the professional perspective, it has been shown that barriers from professionals in following guidelines are related to their knowledge of the disease and its rational treatment approach. Many of the therapies given in an intensified multifactorial intervention approach are given as preventive treatments irrespective of the presence of symptoms, and therefore patients without symptoms may find that the treatment interferes more with their quality of life than the disease itself. In this respect, it is worth noting that patients may find that a change in lifestyle and diet can lead to a large reduction in their quality of life and thus be a more severe barrier to the adherence to treatment than taking drugs.25 Even in the case of symptomatic patients, the start of a treatment may not relieve the symptoms, thereby in itself being a risk factor for nonadherence to treatment.26

Removing the barriers

The success of a treatment strategy depends both on the patient’s ability or will to adhere to the treatment prescribed, as well as possible barriers of the health professional against the treatment. A recent investigation of the adherence to prescribed oral medications in type 2 diabetic patients following a multifactorial approach in a primary care setting demonstrated that only 1 in 3 patients had adequate adherence.24 Factors associated with nonadherence included diabetes duration, complexity of drug regimen, and inadequate control of CVD risk factors.

Many of the therapies given in an intensified multifactorial intervention approach are given as preventive treatments irrespective of the presence of symptoms, and therefore patients without symptoms may find that the treatment interferes more with their quality of life than the disease itself. In this respect, it is worth noting that patients may find that a change in lifestyle and diet can lead to a large reduction in their quality of life and thus be a more severe barrier to the adherence to treatment than taking drugs.25 Even in the case of symptomatic patients, the start of a treatment may not relieve the symptoms, thereby in itself being a risk factor for nonadherence to treatment.26

Whether the prescription of a single polypill per day containing many of the ingredients needed for the prevention of CVD, thereby diminishing the complexity of the drug regimen, will increase the adherence to polypharmacy is an intriguing question that deserves to be pursued.27 Of course, side effects including drug interactions will also influence drug adherence, and finally, cost of treatment may be of significance.28,29 From the professional perspective, it has been shown that barriers from professionals in following guidelines are related to their knowledge of the disease and its rational treatment approach.
Reducing CVD risk in type 2 diabetes – Pedersen

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The matched background population, leaving much fied multifactorial intervention cut this event rate ical study of 510 patients. The kidney in maturity onset diabetes mellitus: a clin-

Further improvements by an intensified, multi-targeted intervention in type 2 diabetes

The cardiovascular complications are by far the most threatening for the long term prognosis in patients with overt T2DM, and the high-risk mi- croalbuminuric patients participating in the standard multi-targeted intervention in the Steno-2 study showed an event rate of the combined CVD end point of 7% per year.3 Although the intensi- fied multifactorial intervention cut this event rate by half, it is still more than three times as high as in the matched background population, leaving much room for improvement. A target for major improve- ment is the treatment resistant hyperglycemia of type 2 diabetic patients. UKPDS showed a steady decline in pancreatic β-cell function with diabetes duration, most likely caused by an accelerated apo- tosis induced by numerous factors, including chronic exposure to elevated levels of free fatty acids, glu- cose, and proinflammatory cytokines.4 Any future intervention that might prevent reduction of β-cell mass or function (eg, glucagon-like peptide–1 ana- logues, DPP4 inhibitors, and exenatide) is expected to improve glycemic regulation.

Treatment targets for circulating levels of LDL cholesterol and triglycerides can in most cases rather easily be achieved with statins and fibrates. In contrast, it is much more difficult to improve the low serum level of HDL cholesterol as a CVD risk factor. Some hope is given to several novel drug candidates that have shown their ability to increase serum levels of HDL cholesterol substantially.

Finally, it is anticipated that progress within the field of pharmacogenomics identifying those pa- tients by genotype who are responders and lesser responders to a given drug treatment of hyper- glycemia, dyslipidemia, or hypertension, will greatly contribute to efficacious “personalized” interven- tions improving the risk marker profile and thereby enhancing the health of patients suffering from T2DM.
Réduire le risque cardiovasculaire chez les diabétiques de type 2 : mission possible

L'e diabète de type 2 (DT2) est un facteur de risque majeur de maladie cardiovasculaire prématurée (MCV) c'est-à-dire l'équivalent d'une maladie coronaire ischemique existante. Il semble que ce soit à cause de la coexistence plus fréquente que s'ils avaient été seuls, à côté de l'hyperglycémie, d'un groupe de facteurs de risque de MCV connus, interactifs et modifiables, chez des patients DT2. Au cours des 5 à 10 dernières années, plusieurs études randomisées réussies d'intervention sur les facteurs de risque individuel ont cependant été menées, mettant à mal l'attitude nihiliste précédemment adoptée par de nombreux médecins et éducateurs du diabète en ce qui concerne l'amélioration du pronostic cardiovasculaire du DT2. Ainsi, pour prévenir ou retarder la vasculopathie prématurée du DT2, il est prouvé que dans tous les groupes d'âge, une approche à long terme intensive et structurée est nécessaire, bien loin de la seule approche centrée sur le glucose, s'intéressant plus aux facteurs de risque cardiovasculaire, y compris l'hypertension, la dyslipidémie, l'agréation plaquettaire, la sédentarité, le tabagisme et les habitudes diététiques. Le risque relatif de MCV chez des diabétiques de type 2 à risque élevé est divisé par 2 grâce à cette prise en charge globale et agressive pendant presque 8 ans. Le fossé important qui existe entre la diabétologie basée sur les preuves et la pratique clinique quotidienne montre qu’il est temps d’adopter au niveau communautaire ces effets bénéfiques des actions CV globales, menées sur toutes les cibles validées dans des études cliniques contrôlées.
The aim of treatment for type 2 diabetes mellitus (T2DM), over and above the achievement of normoglycemia, is the primary and secondary prevention of both cardiovascular complications—in particular coronary artery disease—and microangiopathy. However, the various classes of antidiabetics appear to differ in their impact on cardiovascular complications, independent of their antihyperglycemic efficacy.

### Sulfonylureas

Sulfonylureas (SUs) are classified by generation: first generation (carbutamide, tolbutamide, chlorpropamide, acetohexamide, and tolazamide), second generation (glibenclamide, glipizide, gliclazide, and glipizide), and third generation (gliclazide modified release [MR], glimepiride, glipizide extended release). In 1970, the University Group Diabetes Program (UGDP) reported that tolbutamide was associated with increased cardiovascular morbidity and mortality. This study was, however, the first of its type and was subject to bias and methodological error. In 1998, the United Kingdom Prospective Diabetes Study (UKPDS) published robust evidence on the efficacy of SUs in the prevention of cardiovascular complications: 3867 newly diagnosed type 2 diabetic patients were randomized to either an intensive group, in which blood glucose control was optimized using SUs (chlorpropamide, glibenclamide) and/or insulin, or a conventionally treated group who initially received dietary advice alone. The results at 10 years showed a 12% decrease in diabetes-related end points in the intensive group, with a clear trend ($P=0.052$) toward a decreased incidence of myocardial infarction (MI); no difference was reported between the effect of SUs and insulin in this regard.

The Steno2 study compared the complication rates for intensive multifactorial intervention comprising gliclazide as the insulin secretagogue, and conventional intervention. The study reported a 53% reduction in major cardiovascular events in the intensive group after 8 years of follow-up.

Two recent studies have examined the influence of previous oral antidiabetic treatment on the incidence of cardiovascular complications: PROactive and MICRODIADE. The PROactive study reported a 23% reduction in major cardiovascular events in the intensive group after 6 years of follow-up. The MICRODIADE study showed a 34% reduction in major cardiovascular events in the intensive group after 3 years of follow-up.

### Differential Cardiovascular Impact of Long-term Antidiabetic Treatments

The different molecular modes of action of antidiabetic therapies account for their differing positive and negative effects on cardiovascular complications in type 2 diabetes mellitus (T2DM). Although Steno2 and the United Kingdom Prospective Diabetes Study (UKPDS) confirmed the efficacy of insulin secretagogues (sulfonylureas [SUs] and glinides) in the long-term prevention of diabetic complications, the drugs belonging to that class differ in their impact on coronary and vascular prevention, especially due to differences in molecular specificity. Insulin secretagogues close KATP channels by binding to SU receptors (SURs) and the most effective SUs for prevention of cardiovascular complications are those that bind specifically to the SUR1 receptor isofoms found on pancreatic $\beta$ cells. At therapeutic concentrations, they will only close KATP channels. As they have no effect on the coronary SUR2 isofom, they do not impair ischemic myocardial preconditioning, unlike their non-$\beta$-cell-specific counterparts. This has been confirmed both experimentally and epidemiologically through studies investigating the impact of previous antidiabetic treatment on the incidence of myocardial infarction and the prognosis in T2DM. With the second- and third-generation (“new”) SU-specific insulin secretagogue antidiabetic drugs, in particular gliclazide and glimepiride MR, the risk of infarction in diabetic patients is no greater than in nondiabetics, while postinfarction mortality rates are lower than those associated with the first-generation (“old”) antidiabetics. The specificity of pancreatic receptor binding is thus a key criterion in the selection of an insulin secretagogue. Major clinical trials have found no difference in the degree of cardiovascular protection conferred by intensive insulin therapy or SUs. Information on other drug classes is currently unavailable or has failed to show any significant benefit, as with glitazone in the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive), the sole secondary prevention trial of this drug, which yielded negative results with respect to the primary study end point. Overall, the present state of our knowledge enables a rational choice to be made between the drugs available for the management of type 2 diabetic patients.

### MedicoGraphia

MedicoGraphia. 2007;29:273-276. (see French abstract on page 276)

Keywords: cardiovascular complication; coronary complication; death; glinide; glitazone; heart failure; insulin; intestinal a-glucosidase inhibitor; metformin; sulfonylurea receptor; sulfonylurea; treatment; type 2 diabetes

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**Differential cardiovascular impact of long-term antidiabetic treatments**

by P.-J. Guillausseau, France


dence and prognosis of MI in patients with T2DM,6,5 in 2005, a French study investigated 2320 patients hospitalized with acute MI, of whom 487 were diabetic, with 215 of these receiving SUs. The HbA1c values and the type, location, and severity of MI did not differ between those receiving SUs, and those receiving other oral antidiabetics and insulin. Inpatient mortality in SU patients was 30% lower than in those receiving other oral antidiabetics (10.2% vs 16.9%, P<0.035), with a trend toward less frequent ventricular fibrillation (2.3% vs 5.9%, P<0.052). Multivariate analysis showed a significant association between previous SU treatment and decreased inpatient mortality (relative risk [RR], 0.44; P<0.012).5 A 2006 Danish study investigated 6738 patients, including 867 patients with T2DM, who were hospitalized for first-time MI. Patients were compared with 67 374 age- and sex-matched controls, including 3148 patients with T2DM. In diabetic patients receiving a new SU (gliclazide or glimepiride), the risk of first MI did not differ from that in nondiabetics, while those receiving an old SU at higher risk (Figure 1).6

**SELECTED ABBREVIATIONS AND ACRONYMS**

| AGI | α-glucosidase inhibitor |
| DPP-IV | dipeptidyl peptidase–IV |
| GLP-1 | glucagon-like peptide–1 |
| PPAR | peroxisome proliferator-activated receptor |
| SUR | sulfonylurea |
| T2DM | type 2 diabetes mellitus |
| UKPDS | United Kingdom Prospective Diabetes Study |

The fatality rate at 30 days after admission did not differ from that observed in nondiabetics, was lower with glimepiride than with glipizide, and was higher with old SUs (Figure 2).6 SUs differ in their effects on coronary events and mortality, because they have different molecular modes of action.7 Insulin secretagogues bind to the SU receptor (SUR) expressed on the β cell membrane and regulatory subunit of the K_ATP potassium channel. Binding to the receptor closes the channel, and is beneficial in that it leads to insulin release. By contrast, activation of myocardial K_ATP channels by non–β-cell-specific insulin secretagogues has potentially adverse effects. Non–β-cell specificity derives from the fact that different SUR isoforms are expressed in different tissues; for example, SUR1 is expressed in β cells, and SUR2A in the myocardium. At therapeutic concentrations, insulin secretagogues have different binding affinities for SUR1 and SUR2, enabling them to be classified as β-selective (tolbutamide, gliclazide, nateglinide)7,9 and non–β-selective (glibenclamide, glimepiride, repaglinide). Non–β-selective SUs bind to myocardial SUR2 receptors with high affinity at therapeutic concentrations.7 The resulting myocardial K_ATP channel blockade may impair the potent anti-ischemic tissue protection mechanism known as myocardial preconditioning.

The difference in the effects of β-selective and non–β-selective SUs has been demonstrated in vivo.10 Rats were randomized to three pretreatment groups; controls (saline control), glibenclamide (0.3 mg/kg IV), or glimepiride (1 mg/kg IV), and were then further randomized into three subgroups: controls, ischemic preconditioning, or myocardial protection with the K_ATP channel opener nicorandil. Regional myocardial ischemia of 25 minutes’ duration was then induced. In saline controls, ischemic preconditioning and nicorandil significantly reduced the infarct size compared with controls (15.0%±1.1% and 25.5%±4.2% vs 44.1%±3.2%; P<0.005). Glibenclamide abolished the effect of both ischemic preconditioning (40.8±4.6%) and nicorandil (39.5±5.1%), while glimepiride had no adverse effect on either (ischemia: 20.4%±1.9%; nicorandil: 23.6%±2.2%).

A study in patients with T2DM confirmed the adverse myocardial effect of non–β-selective SUs. In patients with coronary artery disease treated with glibenclamide, myocardial dysfunction occurred during dipyridamole-induced ischemia, and was reversed after glibenclamide withdrawal.11 The use of non–β-selective insulin secretagogues may block K_ATP channels and suppress myocardial defense mechanisms against ischemia, as well as inhibit cardioprotective drugs.12 The results of the two recent epidemiological studies presented above tend to support this conclusion. These data are thus most important for achieving an informed choice regarding SUs.

**Figure 1.** The relative risk of first myocardial infarction in patients with type 2 diabetes, as a function of the anti-diabetic treatment received over the 60 days preceding admission to hospital; comparison is made with matched nondiabetic patients after adjustment for comorbidity and concomitant treatments. Based on data from reference 6.

**Figure 2.** Relative risk of death by 30 days after admission to hospital for a first myocardial infarction in type 2 diabetes, as a function of the antidiabetic treatment received over the 60 days preceding admission; comparison is made with matched nondiabetic patients after adjustment for comorbidity and concomitant treatments. Based on data from reference 6. Abbreviations: SUs, sulfonylureas.
**Glinides**

Glinides (repaglinide, nateglinide) are nonsulfonylurea insulin secretagogues introduced in the late 1990s. No cardiovascular complications data are currently available.

**Glucagon-like peptide-1 analogs and dipeptidyl peptidase-IV inhibitors**

Glucagon-like peptide 1 (GLP-1) analogs and dipeptidyl peptidase IV (DPP-IV) inhibitors are currently only in development or, in the case of two drugs, have only just entered clinical practice. No complications data are available to date.

**Metformin**

Metformin, a biguanide, has been used as an antidiabetic treatment for 30 years. In UKPDS, secondary randomization in 753 overweight patients (mean body mass index 31.4 ± 4.6 kg/m²) yielded a group of 342 patients who were receiving metformin. After a mean 10.7 years, diabetes-related mortality was significantly reduced in the metformin group compared with conventionally treated overweight patients (n=411), but not compared with those on intensive SU and/or insulin treatment (n=951). Similarly, while the incidence of MI was lower in overweight patients on metformin than in the conventional treatment group, it did not differ from that in the intensively treated group.12

**Peroxisome proliferator-activated receptor agonists**

◆ **Glitazones**

Glitazones and thiazolidinediones (pioglitazone and rosiglitazone) bind to nuclear peroxisome proliferator–activated receptor–γ (PPARγ), expressed mainly in adipocytes. The 2005 PROspective pioglitAzone Clinical Trial in macroVascular Events (PROactive) compared the effect on macrovascular complications and mortality of adding pioglitazone versus placebo to previous oral antidiabetic and/or insulin treatment in 5238 type 2 diabetics with evidence of macrovascular disease.13 The primary end point after a mean 34.5 months was a predefined composite of all-cause mortality, nonfatal MI (including silent MI), stroke, acute coronary syndrome, amputation above the ankle, and endovascular or surgical intervention in the coronary or leg arteries. For this primary end point, the relative risk of events with pioglitazone versus placebo was 0.904 (non-significant); 514 events were recorded in 2605 pioglitazone patients, and 572 events in 2633 placebo patients.

No difference was observed in the individual components of the composite end point or in cardiovascular mortality, even without adjusting for differences in HbA1c of 0.5% and in systolic blood pressure of 3 mm Hg. Analysis of a main secondary end point, however, a composite of all-cause mortality, nonfatal MI, and stroke, showed that at 3 years, pioglitazone significantly reduced the risk by 16% compared with placebo (P=0.027).13,14 The relevance of this end point, which was not predefined in the protocol, has been challenged.15-17

More recently, a meta-analysis of the rosiglitazone trials was suggestive of an increased risk of MI and cardiovascular death in patients treated with rosiglitazone compared with controls.18

The glitazones have adverse cardiac effects—primarily heart failure—which at worst can cause pulmonary edema19,20 even in patients with no relevant medical history. As a consequence, although heart failure was a PROactive exclusion criterion, an increased incidence of heart failure was observed in the pioglitazone group compared with placebo (10.8% vs 7.5%, RR 1.44).13,14 Cumulative clinical trial safety data show that heart failure caused hospitalization in 5.7% of pioglitazone patients compared with 4.1% of placebo patients (RR, 1.40).21 An Oregon Medicaid database study22 reported similar results: the odds ratio for hospitalization for heart failure was 1.71 with exposure to glitazone over the past 60 days (1.81 for combined glitazone and insulin exposure).

◆ **Muraglitazar**

In September 2005, a US Food and Drug Administration advisory committee review of phase 2 or 3 prospective double-blind randomized studies concluded that muraglitazar, a dual PPAR-α and γ agonist, was associated with an increased incidence of death, nonfatal MI, and nonfatal stroke compared with placebo or pioglitazone (RR, 2.23; 95% confidence interval [CI], 1.07-4.66; P=0.03).23 These results suggest that one should be wary of dual PPAR agonists, and perhaps of the combination of glitazones with fibrates, given that fenofibrate has not been proven to be effective in reducing coronary complications in T2DM.24

**Intestinal α-glucosidase inhibitors**

Two competitive and reversible intestinal α-glucosidase inhibitors (AGIs) are currently available: acarbose and miglitol. A meta-analysis of seven studies (two unpublished) that occurred over a minimum duration of 52 weeks concluded that acarbose reduced cardiovascular events in type 2 diabetics by 35% compared with placebo.25 This result is questionable in that another meta-analysis found no evidence for an effect on mortality or morbidity.26

**Insulin**

UKPDS showed that insulin was effective in preventing complications in T2DM, but no more so than SUs.27 The long-term results of the Diabetes mellitus Insulin Glucose infusion in Acute Myocardial Infarction 1 (DIGAMI 1) study showed a 25% reduction in mortality in the immediate and late sequelae of MI (mean 3.4 years) in type 2 diabetics receiving initial intensive insulin IV therapy for at least 24 hours compared with conventional treatment (mainly SUs).27,28 DIGAMI 2 failed to confirm these results: early intensive insulin therapy after MI, with or without subsequent long-term insulin,
did not decrease short- or long-term mortality versus an SU alone, or combined with other oral anti-diabetics. On the other hand, the study confirmed the adverse effect of hyperglycemia.\(^{29}\) Robust data are thus available for guiding treatment choice in T2DM, in particular toward β-cell-specific third-generation SUs, and metformin. With the other classes of antidiabetics (PPAR agonists, intestinal AGIs, and glinides), the benefit is much less apparent, either because the necessary studies do not yet exist, or because of negative or unconfirmed cardiovascular protection data.

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**IMPACT CARDIOVASCULAIRE DIFFÉRENTIEL DES TRAITEMENTS ANTI-DIABÉTIQUES À LONG-TERME**

Les différentes classes thérapeutiques qui visent à traiter l’hyperglycémie et les médicaments qu’elles comportent, possèdent une influence différente, favorable ou non, vis à vis des complications cardiovasculaires et coronaires des diabétiques de type 2. Si les sulfonylurées ont fait la preuve de leur efficacité dans la prévention des complications à long terme (études UKPDS et Steno 2), les différents médicaments de la classe des insulino-sécrétagogues, sulfonylurées et glinides, n’ont pas le même impact en termes de prévention coronarique et vasculaire. Ces différences sont en rapport avec leur spécificité moléculaire. Les insulino-sécrétagogues agissent en fermentant les canaux K_ATP en se fixant à un récepteur appelé SUR. Les sulfonylurées les plus intéressantes en terme de prévention cardiovasculaires sont les dérivés spécifiques des récepteurs SUR1, isomère de SUR des cellules β du pancréas. Ils ferment aux concentrations thérapeutiques les seuls canaux K_ATP des cellules β. En absence d’effet sur les récepteurs SUR2 coronaires, ils respectent le préconditionnement myocardique à l’ischémie, inhibé par les insulino-sécrétagogues non spécifiques des cellules β du pancréas. Ces données ont été confirmées par des études expérimentales et par des études épidémiologiques qui apportent des précisions sur l’influence du traitement hypoglycémiant ancière sur la fréquence et le pronostic des infarctus du myocarde chez les diabétiques de type 2. Les dérivés « récents » (de seconde et troisième génération), gliclazide et glitazide MR notamment, insulino-sécrétagogue spécifique du pancréas, sont associés à un risque d’infarctus non différent de celui des non dia-bétiques et à un taux de décès après infarctus plus faible que les dérivés « anciens ». La spécificité de liaison aux récepteurs pancréatiques est donc l’un des critères de choix d’un insulino-sécré-tagogue. La preuve de l’efficacité de l’insuline et de la metfor-mine en prévention des complications cardiovasculaires est aussi fondée sur les résultats de l’UKPDS et de Steno 2. L’UKPDS et DIGAMI 2 n’ont pas mis en évidence de différence entre insulino-thérapie intensive et sulfonylurées. Les données concernant les autres classes médicamenteuses sont absentes ou négatives. La seule étude de prévention secondaire menée avec une gliptazone, l’étude Proactive, s’est avérée négative sur le critère principal. L’ensemble de ces données permet un choix rationnel parmi les outils thérapeutiques actuellement disponibles pour l’équilibrage glyémique du diabète de type 2.
A marriage certificate survives for a printer from Mareuil-sur-le-Lay (Vendée) by the name of Jehan Clemenceau, dated January 12, 1498. Subsequently, from the 17th century onwards in this region of Western France, the Clemenceaus formed a dynasty of doctors who dabbled in politics. One such was the Honorable (Sieur) Clemenceau who practiced in Nantes between 1623 and 1629, and was granted a coat of arms, although not ennobled, by Louis XIII. More prominent in the family tradition was Pierre Paul Clemenceau (1749-1825), who practiced in Nantes and was Mayor of Mouchamps during the Vendée uprising, before becoming physician to the army in Western France during the Consulate.

Political affiliations in the well-to-do traditionalist Clemenceau family were sharply divided between blue (republican) and white (royalist). Benjamin Clemenceau (1810-1897), Georges’ father, practiced in Nantes, but was also a politician, sculptor, model-maker, and painter. On March 27, 1835, he successfully defended his doctor of medicine thesis, Proposals on bronchitis and pneumonia (Propositions sur la bronchite et la pneumonie), based on the recent groundwork on auscultation of the lungs by Laennec (1781-1826). He took part in the 1848 uprising in Nantes, protested the accession of the prince-president Napoleon III (1808-1873), was arrested in 1858 after Felice Orsini’s attempted assassination of the Emperor, and sentenced to deportation to Algeria (although this was never carried out). As a strong-minded

The Clemenceaus were a long-established medical family with revolutionary inclinations who were from the Vendée region in Western France, and who had been more or less ennobled under Louis XIII. Georges’ father, Benjamin, was a forceful character who inspired his son’s professional and political career. Georges Clemenceau (1841-1929) is one of medicine’s more unusual deserters in that he was actually a practicing physician for 20 years, from 1865 to 1885, in the provinces and in Paris. He began his political career in 1871 after the Commune and after staying for several years in Britain and the United States. Mayor of Montmartre, deputy (1871-1893), senator (1902-1920), and head of government (1906-1909 and 1917-1920), Clemenceau was a virulent polemicist and redoubtable journalist. The “Tiger” founded a number of newspapers, eg, Le Travail (1861), Le Matin (1862), La Justice (1880), L’Homme Libre (1913), and L’Homme Enchaîné (1914). Patriotic, authoritarian, and intransigent, he led France and her allies to victory in the First World War by controlling the power of the military and securing the support of the poilus and the people, earning the title of “Father Victory.” Clemenceau then played a critical if nonexclusive role in the peace negotiations, being one of those who advocated the harshest terms against Germany, with consequences that became apparent only later. Defeated in the 1920 presidential elections, Clemenceau returned to his true passion—writing. Uninhibited, positivist, and atheist, he remains a symbolic figure of the Third Republic and the radical movement; despite his intransigence and contradictions, he has left his mark on the history of 20th century Europe.

and ferociously republican atheist, Benjamin Clemenceau refused to baptize any of his six children; he was fond of saying, glancing heavenwards: “we’ll see which of us gives in first.” On the opposite pole of the political spectrum, Georges’ uncle, his father’s brother, was a royalist who lived at L'Aubraie, the family estate bought by their paternal grandfather.1,2

Georges Clemenceau was born on September 28, 1841 at Mouilleron-en-Pareds, in the heart of the distinctive hedged farmland of the Vendée, the **bocage**, in an old and modest bourgeois home that had belonged to his mother’s Protestant forebears. He always maintained a deep respect for his birthplace and its inhabitants: “I like Vendée people. They have an ideal and, to fight for it, they have something narrow, pig-headed, and untamed about them that I like.”3

Medical school and political revolt: the youthful years

As a student, Georges Clemenceau was not top of the class, but he excelled in philosophy, Latin, and French. Following the family tradition, he entered medical school in 1858 in Nantes, becoming an extern in 1861 before being sent down for indiscipline. In November of that year, his father took him to complete his studies at the Paris Faculty of Medicine, a hotbed of atheism and opposition to the imperial regime. For Georges he secured the patronage of his friend, the playwright Étienne Arago (1802-1892), a veteran of the 1848 revolution. Within weeks—by December 22—Georges brought out the first issue of his first paper *Le Travail* (Labor), a revolutionary weekly closely monitored by the police, while still finding the time, on December 24, to come 10th out of 198 in his extern exam. The revolutionary medical student befriended writers, philosophers, militants, and his counterparts in the arts faculties. He made contact with staunch republicans strongly opposed to the imperial regime, such as the writers Émile Zola (1840-1902) and Camille Pelletan (1846-1915) and the future industrialist and politician Auguste Scheurer-Kestner (1833-1899). They shared a common oath: “The undersigned hereby swear to break with all doctrines whose principles they reject and never to receive a sacrament from any religion: no priest at birth, no priest at marriage, and no priest at death. You must know what you want; when you want it, you must say so, and you must have the courage to persist until you succeed; defeat only comes to those who give up the struggle.” On February 23, 1862, with two of his comrades, Clemenceau was arrested for flyposting the workers and people of Paris to commemorate the 14th anniversary of the proclamation of the Second Republic in 1848. He spent 77 days in Mazas Prison, near the Gare de Lyon, much like his father 4 years previously. Shortly after his release, he published a new newspaper, *Le Matin*, bringing out eight issues between June 29 and August 31.1,3,4

After being appointed a provisional intern at La Pitié Hospital in 1863, he often visited political friends in the neighboring Sainte Pélagie Prison, even meeting regularly with the revolutionary Auguste Blanqui (1805-1881) whom his father had hidden in Nantes in 1848. From the courtyard of La Pitié, he could see Blanqui’s cell window and used to communicate with him via sign language.

On May 13, 1865, Georges Clemenceau obtained his medical degree after defending his thesis: *Notions of anatomy and general physiology. On the generation of anatomical elements (Notions d’anatomie et de physiologie générale. De la génération des éléments anatomiques)*, published by Jean-Baptiste Baillière in 1867. In this curious study, he maintained, following his master and the chairman of his thesis examiners, Charles Robin (1821-1885), that cells generate spontaneously in connective tissue or “blastema.” Inspired by the naturalist philosophy of Charles François de Mirbel (1776-1854), Clemenceau wrote: “cells are so many living individuals, each enjoying the ability to grow, multiply, and, within certain limits, transform themselves—they are materials that make up plants, or ‘collective’ living forms.” These theories reducing man to a simply biological collection of cells contrasted with the uniqueness of tissue groups described by the German histologist, Rudolf Virchow (1821-1902). At a time when contro-
versy raged over positivism, which rejected divine intervention in the creation of man. Clemenceau provided a stormy defense of his thesis. As a journalist, he for a while rejected the germ theory of Louis Pasteur (1822-1895), before duly making amends after it had been confirmed.2-4

On July 25, 1865, he left for Britain and the US to learn how their political and social systems functioned, with the idea of possibly transposing them to France. He lived in the US for 3 years, even practicing medicine on 12th Street in Greenwich Village. He also taught French literature and horse-riding in a girls’ school at Stamford, Connecticut; it was there that he met Mary Plummer, a pupil he married on June 20, 1869. The lessons he drew from his American experience were the value of institutional freedoms, the political power of the press, the dynamism of entrepreneurs, and a distaste for racial segregation.2,3,5,6

Georges Clemenceau the physician
Returning to France on June 26, 1869, Clemenceau went to Vendée to practice medicine, taking over his father’s rural clientele. “I did what he himself did there. I practiced medicine, traveling through the countryside on horseback.” He recorded his visits in a 142-page notebook, mentioning his patients’ names and addresses, the date, and payment where made (some visits were free). The notebook was presented to the Academy of Medicine on July 31, 1934, by the gynecologist Félix Jayle who noted: “Our great colleague Clemenceau was a man of order, precise and even meticulous. He had a fairly wide understanding of medicine, carrying out minor surgery and using electrical stimulation. From early 1870 onwards, Clemenceau made frequent trips to Paris to meet up with his political friends, Arago in particular. It was not long before he left Vendée for good, making his last patient visit on October 18, 1871.3,4

Since he had always been able to marry politics with medicine, Georges Clemenceau opened a small dispensary in Montmartre at 23 rue des Trois-Frères, near the Place des Abbesses. He practiced there for 11 years, from 1874 to 1885, when he was elected deputy of the Var region in the South of France. The dispensary was modest, comprising an office and waiting room. According to a journalist: “You enter the first room off a narrow corridor. It’s the waiting room. It would be a tight fit for 5 children, but over 30 people are piled inside it. Sick women are crammed onto the chairs and deal table. Men perch on the mantelpiece.” An unending procession of patients with tuberculosis took up much of his time. The buildings on the hill of Montmartre were unhealthy; despite the altitude, the air was particularly humid. Clemenceau’s own description of practicing medicine in Montmartre is evidence not only of the powerlessness of late 19th century physicians to provide effective therapy, but also of his depth of feeling: “A sorry spectacle, a pathetic procession of every kind of human misery, suffering at the bottom of the social scale.” His medical training and humanist convictions transformed these feelings into veritable statements of political faith, especially when recalling the home visits he paid his patients: “These were wretched assignments—brief forays into the worst sectors of the Butte Montmartre into the unhealthy cells of stinking hives packed, beneath the poisonous vapors seeping from every kind of refuse, by so many laboring families whose infection-laden lodgings provided their only respite from the deadly germs of the sweatshop… The rich would find their hearts going out to them if they could see this misery with their own eyes or touch it with their fingers. But they live among themselves.”4-7

From mayor of Montmartre to Paris deputy
Georges Clemenceau was in Paris from the start of the Franco-Prussian War. After the French capitulation at Sedan and the proclamation two days later of the Third Republic on September 4, 1870, the mayor of Paris, Clemenceau’s protector, Étienne Arago, appointed him mayor of the 18th arrondissement, which includes Montmartre. Paris was about to be besieged by the Prussians, and Arago wanted men around him whom he could trust. Clemenceau’s appointment was confirmed by the ballot held on November 9, 1870. He introduced mandatory nonreligious schooling forthwith. For the first time, he was able to put his political ideas into practice, in particular the principles of separation between Church and State and abso-

Georges Clemenceau: physician of the poor, “Father Victory,” and patron of Monet – Régnier

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Clemenceau became mayor of Montmartre in 1870, during the Franco-Prussian war, in which France was defeated, after heavy loss of life. An armistice was signed on 28 January 1871. Some French cannons were kept in the rue des Rosiers, in Clemenceau’s precinct, and the French government, anxious to avoid their falling into the hands of the Prussians, sent two generals, Lecomte and Thomas, to secure them. This worried the Parisians who believed it would trigger retaliation from the Prussian army. Clemenceau tried to stave off the fury of the populace, and warned Lecomte that an insurrection was under way (this is the scene depicted in the painting, dated 1871 and kept in the Montmartre Museum). His warning went unheeded, and the very same day both generals were shot. © AKG-images.
named the “slayer of ministries” or the “Tiger,” he brought about the collapse of the Gambetta and Ferry cabinets (in 1882, and 1881 & 1885, respectively). His friend Camille Pelletan described “this familiar energetic figure with his bushy moustache, close-cropped hair, prominent forehead, and dark eyes. His movements suggest a certain brusque impatience, but controlled by an iron will and ever-alert composure. His voice is clear, lively and resolute, forcing his audience’s attention.” Clemenceau obtained an amnesty for the Communards and became the defender of workers’ interests and democratic freedoms. As a renowned orator and virulent polemicist, he was also feared for the power of his pen, notable for its cruel wit. His portrait of Aristide Briand (1862-1932) was that of “the soul of a rabbit inside a drum skin,” while Marshal Joffre (1852-1931) was “a cobblestone, but a cogitating cobblestone.” His enemies, not to be outdone, replied in kind, describing him as an “evil scatterbrain” (Léon Gambetta, 1838-1882) and as “capable of the worst, in both good and evil, but most of all in evil, because he’s evilly intentioned” (Ferry).

From reflection to action

In September 1893, Clemenceau was defeated in the legislative elections. He had been criticized for his dealings with the doctor and controversial businessman Cornelius Herz, who had been accused of buying deputy votes to secure the credits needed for building the Panama Canal. He began to write *La Mêlée Sociale* (The Social Fray), a compendium of articles from *La Justice*, his new newspaper. Two other books followed: *Le Grand Pan* (The Great Pan) and *Au Fil des Jours* (Day After Day) in which he advocated action as the solution to life’s torments and social injustice. “Pan orders us: Into action! Action is the principle, action is the means, action is the end. Obstinate action by everyone for everyone, selfless action, action that is superior to puerile vainglory, the rewards of a nebulous Eternity, the despair of lost battles or of inevitable death. Action in the pursuit of an ideal, as a unique force and total virtue.” Clemenceau also wrote *Aux Embuscades de la Vie* (Ambushes of Life) in which he described man’s struggles—against illusory beliefs, the ideas and facts that make up the tissue of society, and the feelings, passions, and unrealizable dreams of men themselves. On January 13, 1898, he returned to the fore by publishing in his newspaper *L’Aurore* (Dawn) Émile Zola’s famous *J’accuse*, which denounced the acquittal of the officer responsible for Alfred Dreyfus’ sentence to a penal colony in 1894. Dreyfus, the son of a Jewish manufacturer and an artillery captain, had been, at a time of rampant anti-Semitism, unjustly accused of delivering documents connected with the national defense to a foreign government, and had been court-martialed, degraded, and transported.
Throughout his political career, Clemenceau refused to live in the “furnished quarters” of grace and favor palaces. In Paris, from 1895 to his death in 1929, he lived at 8 rue Franklin in the 16th arrondissement. The apartment was designed for work, rest, and the “company of friends.” It was where he felt comfortable among “any number of books and, along the walls, souvenirs of family, travel, and friendship,” while the garden catered for his “love of fresh air, flowers, the company of his dogs and poultry” (it included a chicken run). After the “Tiger” died, his friend and admirer, James Stuart Douglas (1868-1949), a wealthy Canadian entrepreneur who owned the building at 8 rue Franklin, donated Clemenceau’s apartment to the foundation recently set up to perpetuate the great man’s memory. It became a museum open to the public in 1931, furnished with objects and souvenirs donated by his three children, Michel, Thérèse, and Madeleine.

Three years after the death of Georges Clemenceau, on November 24, 1932, at the intersection of the Petit Palais and the Champs-Élysées, President Edouard Herriot (1872-1957) unveiled a statue of the Tiger by François Cogné. Every year, the President of the Republic—after rekindling the flame of the Unknown Soldier under the Arc de Triomphe—lays a wreath at the foot of Clemenceau’s statue.

As the fiefdom of his family, Vendée was always “home” for Clemenceau. In 1906, as Minister of the Interior, he went to La Roche-sur-Yon to take part in a Republican banquet with 3000 guests. From the 18th century, the cradle of the Clemenceau family was Mouchamps, where his father was mayor in 1793. The family lived in the Manoir du Colombier (Dovecote Manor). The Tiger is buried nearby, together with his father, in untamed ground bordering the River Lay, beneath a cedar planted by his father. There is no tombstone or commemorative plaque, just a stele commissioned in 1923 from the sculptor Sicard representing the helmeted Greek god Pallas Athena (Minerva in Roman mythology), resting on her spear. In the house where he was born in Mouilleron-en-Pareds, the National Museum of the Two Victories (Musée National des Deux Victoires) gives an idea of Clemenceau the man by exhibiting a number of personal items and documents relating to the signing of the Treaty of Versailles; the Museum combines his memory with that of another child of Mouilleron, Marshal Jean de Lattre de Tassigny (1889-1952), who signed the armistice of May 8, 1945, in Berlin on behalf of France. A plaque was affixed to the house on January 12, 1919, to commemorate the birth of the village’s famous son and “the gratitude of France which grows more ardent by the day towards the organizer of victory and liberator of the country.”

The Tiger retired to Saint-Vincent-sur-Jard on the Atlantic coast of Vendée where he rented a single-storey fisherman’s house between sky, earth, and sea; he referred to this refuge as his “horizontal country house.” His friend, the painter Claude Monet (1840-1926), designed a suitably wild garden for him. The house has been kept intact and can be visited; it contains a collection of prints and personal souvenirs.
for life to Devil’s Island, in French Guiana. From this moment onwards, to right-wing fury, Clemenceau never ceased to speak out in defense of Dreyfus. In 1906, the verdict was finally reversed and Dreyfus was restored to his army rank and fought in World War I and was awarded the Legion of Honor. It was in 1906 that Georges Clemenceau showed his real face, his talents as a ruler and also his political authoritarianism. On his appointment as Minister of the Interior in March 1906, he modernized the police force by supplying it with motorized mobile brigades (“Tiger Brigades”) and introducing scientific identification techniques, such as the anthropometric system devised by Alphonse Bertillon (1853-1914) and fingerprinting. He proved merciless in his repression of miners in the Pas-de-Calais, winegrowers in the South, and teachers and civil servants, ordering the troops to open fire on demonstrators, and incurring the enmity of the Socialists and Jean Jaurès (1859-1914) in particular. Yet at the same time, as the head of government, he created the Ministry of Labor and Public Health, established the weekly day of rest, a pension for railroad workers, and introduced the law that finally separated Church from State.

Political error forced his resignation in July 1909. The Clemenceau cabinet had held for 33 months—a longevity record for the Third Republic. On the very day that his government fell, a law was promulgated banning the use of white lead (also known as ceruse or basic lead carbonate) in paint; since 1904, Clemenceau had led the campaign against the lead poisoning that was decimating construction workers. Many of his editorials for L’Aurore had denounced the use of lead: “It’s quite simply a matter of preventing men from killing men.” He also led a relentless campaign against the dangers of alcoholism, thus continuing to display the reflexes of a doctor whose practice was anchored among the poor. During his political career, he helped to establish a Public Welfare (Assistance Publique) histology laboratory and a Mental Illness Chair at the Paris Faculty of Medicine. On his election to the Academy of Medicine, he declared, perhaps more demagogue than doctor: “We have doctors here, and pharmacists, chemists, public health experts, and veterinarians—I represent patients, the biggest and most important group.” His newspaper L’Homme Libre (The Free Man), which in October 1914, in protest against press censorship, he renamed L’Homme Enchaîné (The Man in Chains), was one of the first to denounce shortcomings in the organization of medical care for the troops after the first three months of war. 1917 saw the Russian withdrawal from the war, mutiny in the French Army, and heavy losses in the offensives: French morale fell lower than at any stage in the war. On November 16, 1917, Clemenceau was recalled to head the government by his political enemy, the President of the Republic, Raymond Poincaré (1860-1934). Clemenceau had no desire to take up the appointment, confiding to his secretary Martet: “I’m afraid of power. It scares me stiff! I’d give anything to avoid it! Just look at me: you can tell I’m done for, I’m rotten with diabetes.” A strong man was needed to push through unpopular measures and
The painter of light, Claude Monet (1840–1926), was virtually the same age as Clemenceau. The two men became friends around 1890, when both were 50 years old and shared a similar taste for things Japanese, food, and gardens. Clemenceau used to address his friend with such endearments as “My Poor Old Fool,” “Dear Man of the Woods,” “My Old Heart,” “Dear Old Brother,” “Poor Old Crustacean,” and “Diamond Lens.” In May 1911, on the death of Monet’s wife, Alice Hoschedé (whom he had married in July 1892), it was Clemenceau who provided him with support and friendship.

In 1907, the diagnosis of cataract on returning from Venice made Monet depressed; he was afraid that he would be unable to use color properly. By 1912, he was blind in the left eye. Clemenceau encouraged him to continue his research into light and the disappearance of the object. The letters between them became striking in their intensity and sincerity.

On admiring a recently finished canvas in the Water Lily (Nymphéas) series in 1914, Clemenceau told Monet: “You bombard me with a monstrous rock of light.” The painting inspired him to write: “What is seeing, if not understanding? All there is to seeing is learning to look: looking outwards, looking inwards, looking on all sides, in order to exalt man’s perception of the shimmerings of the universe. (…) This is where the miracle of the Water Lilies actually resides. It represents a different order of things from that which we have observed till now. (…) That is what Monet discovered by viewing the sky in the water of his garden. And that is what, in turn, seeks to show us.”

In a letter written to Clemenceau on November 12, 1918 (the day after the Armistice), Monet donated a series of eight Water Lily canvases to France to symbolize military peace, but above all, the return to man’s inner peace. “I’m just about to finish two decorative panels that I’d like to sign with the Day of Victory and I’m asking if I can donate them to the State via yourself. It isn’t much, but it’s the only way I can join in the general celebration.” The donation was as much a personal thank-you for the unfailing support and encouragement of his friend Clemenceau as homage to “Father Victory.”

On September 7, 1922, Monet’s eyesight was found to be seriously impaired: he was virtually blind in the right eye and had only one tenth of his vision in the left. He was afraid that surgery would leave him totally blind, as it had his fellow painter Honoré Daumier (1808–1879) after his disastrous cataract operation. Clemenceau managed to change his mind, referring him to Dr Charles Coutela, who operated on his right eye in January and July 1923, at the clinic in Neuilly. Monet recovered three tenths of his vision, but found the sequelae so distressing that he refused surgery on the left eye. Referring to his “semi-vision,” Clemenceau again tried to change his mind, but in vain. The ophthalmologist Jacques Mawas met Monet in Giverny in September 1923, and prescribed color lenses. He reported Monet as saying: “I see blue, but not red any more, nor yellow; this is terribly annoying because I know these colors exist, because I know that I have red, yellow, a special green and a particular shade of purple on my palette, but I can’t see them any more in the way I used to, although I have a very clear memory of the colors they produced.”

Monet died on December 5, 1926, probably from lung cancer. Clemenceau was with him: “Are you in pain?” “No,” replied Monet, before dying a few moments later in the house in Giverny where he had lived for 43 years. Clemenceau objected to the black sheet about to be draped over the painter’s coffin: “No! No! No black on Monet. Black is not a color.” He draped him in a multicolored tissue instead. In 1928, a year before his death, Georges Clemenceau published a biography of Claude Monet.
He played an active role in the negotiations culminating in the Treaty of Versailles (signed on June 28, 1919). Because he was against setting up the League of Nations, he disagreed with the British and Americans in insisting on the disarmament and occupation of Germany, and on the imposition of punitive reparations. The US Senate refused to ratify the Treaty of Versailles, and Britain withdrew its moral guarantee if Germany rearmed the left bank of the Rhine. Clemenceau’s defeat by the British and Americans in the peace negotiations brought “Father Victory” a punning new nickname in France: “Father Vanquished” (Perd la Victoire— the homophonous “perd” meaning “lose”). Many contemporary historians hold Clemenceau partly responsible for the errors in the Treaty of Versailles that carried in it the seeds of the Second World War.\(^3\)\(^8\)

On February 19, 1919, Clemenceau survived ten shots from a revolver in a botched assassination by a 23-year-old anarchist Émile Cottin. It left him with a bullet in the right shoulder blade and his popularity healthier than ever. Cottin’s initial sentence to the guillotine was commuted, with Clemenceau’s endorsement, to five years in prison. In January 1920, parliamentarians chose to elect Paul Deschanel as President of the Republic, many of them being wary of Clemenceau’s authoritarianism. In September 1920, Clemenceau traveled to India, South-East Asia, Sudan, and Egypt. He then retired to a fisherman’s house in Vendée at Saint-Vincent-sur-Jard to write a number of books, including Au Soir de la Pensée (The Evening of my Thought) (1927) and Grandeurs et Misères d’une Victoire (Grandeur and Misery of Victory) (1930).\(^7\)\(^8\) He died on November 24, 1929, at his Paris home, 8 rue Franklin, aged 88 years.

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GEORGES CLEMENCEAU : MÉDECIN DES PAUVRES, « PÈRE LA VICTOIRE » ET AMI DE MONET

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Monet and the Orangerie Museum
Songs without words
by I. Spaak, France

“My dear good friend,” wrote Claude Monet to Georges Clemenceau on September 18, 1926, “I’m better… even well enough to consider getting my palettes and brushes ready for returning to work… I’ve been busy on some big changes in my studio and on putting things right in the garden. All of which goes to show you that I’m getting the upper hand… Let me tell you that if I don’t recover enough of my strength to do what I’d like with my panels, I’ve decided to donate them as they are or at least in part. Yours more than ever.”

The panels to which Monet was referring were the now-famous Water Lilies (Nymphéas), a series of 22 canvases, each between 2 and 6 meters long, arranged side by side in a continuum of 8 vast flower-and-water compositions. The Orangerie Museum began exhibiting this masterly ensemble—the artist’s obsessive final project—a few months after his death on December 5, 1926.

Completion of this vast work drove Monet forward in the last two decades of his life, despite major health problems, in particular failing eyesight, and the death of his second wife, Alice. He painted some 300 water lily studies between the ages of 55 and 80; over 40 of these were large-scale. Perseverance bordered on obsession. Despite his fame, the father of Impressionism never ceased to question his own work. To his death he worked like a man driven by despair. Every now and then, he would slash or burn his canvases when they failed to meet his standards. He could be irritable and even unbearable for his family and friends.

After six years spent relocating the Walter-Guillaume collection of modern art, the Orangerie Museum in the Tuileries Gardens reopened in May 2006, presenting Claude Monet’s Water Lilies (Nymphéas) in a revamped setting of light and tranquility in the heart of Paris. Monet, the founder of Impressionism, donated this major work—a vast flower-and-water composition inspired by his water garden in Giverny—to the French nation the day after the 1918 armistice via his friend Georges Clemenceau, who had led the country to victory. The Water Lily series was the painter’s final obsession, occupying the two decades preceding his death on December 5, 1926. This picture-poem without beginning or end fills 22 consecutive panels each over 2 meters high arranged in 8 compositions totaling 91 meters in length. As a celebration of Nature at its most sacred, the huge mural is a monument to peace. Devoid of all visible detail, unbounded by horizon or perspective, and without identifiable figures, the Water Lily panorama is the precursor of abstract art.


(see French abstract on page 292)
The painter and the head of state: the making of a masterpiece

The most faithful of his friends, Georges Clemenceau, described Monet’s doubts in a study published in 1928. “Far from being seduced by his first brush stroke, Monet was forever revising his initial inspirations. He would always find a way of vilifying his alleged shortcomings. He had no qualms about violent self-criticism, swearing that his life was a failure, and that there was nothing left but for him to destroy all his canvases before departing this world. Studies of the first magnitude perished in these attacks of rage.”

Monet’s donation of the Water Lily series to the nation was effected through Clemenceau. It was also on Clemenceau’s initiative that the paintings were hung in the Orangerie Museum. It all started in 1914, when Monet, despite fading eyesight, had been devoting himself exclusively for some years to large canvases inspired in each case by the same motif: water lilies. Clemenceau, as an unconditional admirer and chairman of the Armed Forces Committee, encouraged Monet to develop a large-scale project suitable for decorating a public building. Monet became so enthusiastic about the idea that he built a new studio in which he worked flat-out through the War with the support not only of Clemenceau, who had become head of the government, but also that of Étienne Clémentel, Minister of Trade and Industry, who provided materials and paint, as well as coal, and gas for his automobile.

When victory was proclaimed, Monet was keen to join in the patriotic enthusiasm. No sooner than the day after the Armistice, on November 12, 1918, he wrote to Clemenceau: “I’m just about to finish two decorative panels that I’d like to sign with the Day of Victory… It isn’t much, but it’s the only way I can join in the general celebration… I’d be happy if it was you who chose them.” Instead of the two panels that Monet was hoping to see exhibited in the Museum of Decorative Arts, France’s “Tiger” persuaded him to donate the totality of the Water Lily series to the nation as a monument to peace.
The project took over ten years to come to fruition. Discouraged by his fading eyesight and the slow pace of the donation procedure, which failed to be completed in his lifetime, Monet was a difficult person to deal with. However, despite hesitation, equivocation, and multiple vicissitudes, the result is now on display in this monument built beside the Seine in 1852 as the orangery to the Tuileries Palace. Bathed in natural light, it appears to have been expressly designed to house large-scale works of art. The building’s rectangular shape readily accommodates the successive display of the Water Lily panorama “in a circle, then an oval, and finally in a double ellipse embodying the mathematical sign for infinity,” as the father of Impressionism had wished.

In addition, the building’s orientation to the rising and setting sun along the main east-west axis of Paris integrates it into the cosmic order. This is emphasized by hanging the two compositions, Reflections of Trees and Setting Sun, at the west end of the building. Meanwhile, the parallel flow of the Seine symbolizes the passing of time. The entire site, on the relatively tranquil terrace of the Tuileries in the heart of Paris, is an invitation to contemplation. Everything conspires to make the Orangerie an enclave in which city dwellers can recharge their batteries.

Monet explained his intention as early as 1909. “Overworked nerves should be able to relax there and follow the soothing example of these tranquil waters; anyone living in this room should find it a haven of peaceful meditation in the midst of a flower-laden aquarium.”

The new Orangerie: a vision restored
Since May 2006, after six years of work in which the Museum was restored to its 1927 configuration, visitors have been able to float in the tranquility of Monet’s Nature, bathe in the pleasure of contemplation, while oblivious to the world in and around them, personal concerns, or the city hubbub. The near-monochrome compositions devoid of distinctive features are an invitation to inner peace. The fusion of air, water, and vegetation produces a colored fog in which visitors are no longer sure where they are. “You can barely make out, here and there,” says the art historian, Michel Hoog, “and even then only by looking closely, a dangling branch or floating petals, and in the second room only, the trunks of willow trees.” For the critic Louis Gillet, the long aquatic poem is “astonishing painting, without pattern or borders.” Unbounded by perspective or horizon, devoid of figures or details, these are “songs without words” about Nature as sacred. The color panorama continues essentially unbroken through the communicating doors. Visitors follow their senses rather than individual pictures hung on the walls. The oblong rooms of the Orangerie Museum remind Hoog “more of a Romanesque cloister than of an Impressionist gallery.” Sitting on a bench seat in the middle of either room bathed in natural light, it’s easy to imagine communing with the elements, like Monet himself, sitting for hours in front of the water garden in Giverny.

Water lily pond and Nymphéas: mental landscapes both
Monet created the pond himself, out of nothing, using a brook—the Ru, a diversion of the Epte—that ran across his land. From 1893, once he had overcome the opposition of some jealous neighbors who feared that his plan to grow aquatic plants would “poison the water,” until his death in 1926, Monet never ceased enlarging and developing this pond which was to become his principal source of inspiration.
Bordered by weeping willows, azaleas, poplars, and ferns, and carpeted by waterlilies, the pond was Japanese in inspiration, complete with elegantly arched wooden bridge trailing wisteria. The water reflected the changes of Nature with time of day, sky, and season. The pond was a painting come to life. Its interdigitating liquid shapes echoed Monet’s obsessions. For the poet Michel Butor, “in the real pond of Giverny, it was as if water had reversed the world… to force us to reverse ourselves.” For Monet it was less a matter of representing reality than of timelessly transposing its elements. “Monet used water,” said Paul Claudel, “to make himself the indirect painter of what we fail to see.”

**History of the Orangerie**

On May 25, 1852, a new orangery was decreed to replace the late 16th-century building sited on the city’s third wall, the “yellow ditch,” so named from the color of its soil. The new structure was a large rectangle comprising a south (Seine)-facing glass wall, providing light to the plants, and a north (Tuileries Garden)-facing blank wall, accessed via two doors at the east and west ends. However, as time went by, orange cultivation gradually lost out to a variety of other functions: science and art exhibitions, patriotic get-togethers, dog shows, and sports events. During the First World War, the building housed military equipment and billeted soldiers.

In 1921, the Orangerie was handed over to the Fine Arts Council, which, via Georges Clemenceau, then offered it to Monet as a receptacle for the huge *Water Lily* series that he had donated to the nation. The Museum duly opened to the public in May 1927, after Monet’s death, to no general enthusiasm, although the panels were hung as the painter had wished, in a bath of natural light. Until 1959, the Orangerie was a key element in the Paris art scene thanks to a series of major exhibitions. Following a period of indifference bordering on contempt by contemporary artists toward the “dated” *Water Lilies*, abstract expressionists discovered the modernity of Monet’s final work.

In 1959 and 1960, in a two-stage process, Juliette “Domenica” Walter sold most of the magnificent art collection assembled by her husband Paul Guillaume (1892-1934), including 144 Cézannes and works by Renoir, Matisse, Picasso, Douanier Rousseau, Modigliani, and Soutine. Her condition was that the collection be exhibited permanently and in its entirety in the Orangerie. From 1959 to 1965, the building was transformed. The glass wall over the *Water Lilies* was covered to build a first floor reached by a central staircase in the lobby, depriving the *Water Lilies* of their dedicated access. The Walter-Guillaume collection opened in 1966. Thirty years later, in 1996, it was decided to redevelop the Museum a second time and restore natural light to the *Water Lilies*. The Orangerie remained closed from January 2000 to May 2006, when the *Water Lilies* were once again exhibited as Monet had intended.

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[www.musee-orangerie.fr](http://www.musee-orangerie.fr)
Open daily except Tuesdays from 9 AM to 7 PM, and to 9 PM on Fridays.
In their to and fro between direct observation and memory, the *Water Lilies* marked a clear departure from the open-air “paintings-of,” i.e., with recognizable subject matter, that Monet himself had inaugurated as founder of the Impressionist movement. In fine weather, Monet painted outside, often on large canvases spread between trees.

During the rest of the year, he withdrew into the studio he had built in 1916. A visitor reported: “The panels are set lengthwise, almost reaching the ground, on heavy easels on rollers that the artist moves around like a laborer.”

“An artist of the floating world”

Although he denied being a precursor of abstract art, Monet invented a totally new language between the walls of his studio. “To a great extent Monet’s later painting is a decidedly mental affair,” wrote Butor. “Once he’d

Located approximately 5 km east of Vernon at the confluence of the rivers Seine and Epte, Giverny is a tranquil little town welcoming Parisians to Normandy. It was here that the painter Claude Monet, the founder of the Impressionist movement, lived for 43 years. The gardens, village, and surrounding area that were his models continue to draw half a million visitors each year from all over the world, along with painters attracted by the special light of the Seine valley. Bequeathed in 1966 by his son Michel to the Academy of Fine Arts, the house with pink render where the painter lived from 1883 to 1926 was restored thanks to generous donations, largely from the United States, before opening to the public in 1980. The property has been restored to its former charm and colors, with its attractive yellow-painted dining room decorated with the artist’s collection of Japanese prints and its huge studio built specially for the *Water Lily* panels.

But the gardens are the main attraction: the *clos normand* occupying over two acres in front of the house, an explosion of color with its borders of hollyhocks, nasturtiums, poppies, marigolds, dahlias, asters, and bellflowers, but also its rows of fruit trees and the arch entwined with climbing roses over its center path; and on the other side of the road, reached via an underground passage, the *jardin d’eau* or water garden, where all is symmetry and curves, with a pond crossed by a Japanese-style wooden bridge. Designed by Monet from 1893 onwards, this pond of around 100 square meters bordered by weeping willows and bamboo thickets is a work of art in its own right: the famous water lilies still flourish in its midst.
thought his composition out, it never occurred to him to reproduce it sitting in front of his pond; instead he called in a builder to come and make him a new studio: one with blank walls, no opening other than the door, and a roof made two-thirds of glass.” Although a master of landscape, Monet abandoned it, turning away from representation and reversing the roles. It was no longer Nature inspiring the artist, but the artist fashioning Nature as he wanted to see it. “The real pond was no longer there as model but as master,” wrote Butor. Monet arranged reality to avoid yielding to pure abstraction.

CLAUDE MONET: THE KEY DATES

1840 Birth in Paris.
1845 His parents move to Le Havre.
1856 Meets the painter Eugène Boudin, and begins to paint on the Normandy coast.
1857 Death of his mother, Louise. Meets Pissarro and Courbet at the Suisse Académie (a pre-Beaux Arts facility in Paris).
1863 Discovers Manet and outdoor painting in the forest of Fontainebleau.
1867 Birth of Jean, his first child, with his future wife, Camille Doncieux.
1868 Attempts suicide in financial despair. Paints on the Normandy coast (Fécamp and Étretat).
1870 Marries Camille Doncieux. Takes refuge with Pissarro in London during the Franco-Prussian War.
1874 First exhibition (in Nadar’s studio): it includes Impression, Sunrise, inspiring the name “Impressionism.”
1878 Birth of Michel, his second son. Settles in Vétheuil, near Giverny.
1879 Death of Camille. Alice Hoschedé, a friend, looks after the Monet family, in addition to her own six children.
1883 Settles in Giverny.
1890 Buys house in Giverny and begins building the water lily pond.
1891 Produces the Haystack and Poplar series of paintings.
1892 Cathedral series. Marries Alice Hoschedé.
1899 Begins Water Lily series.
1907 First symptoms of cataract.
1911 Alice dies.
1914 Death of son Jean. Blanche, his daughter-in-law, comes to look after him in Giverny.
1916 Builds a dedicated Water Lily studio, and works on the series for the next ten years.
1923 Undergoes unilateral eye surgery for near-blindness.
1926 Dies December 5. Clemenceau attends funeral in Giverny.
Monet may have been operating a revolution within art, but his contemporaries ignored him. He was also a prey to self-doubt. Negotiations with the State were interminable. Monet was a difficult old master. While being demanding when it came to the exhibition of his work, he was forever overrunning the delivery deadline, eventually set for 1924. It was not until 1927 that the *Water Lilies* were installed in the two elliptical rooms of the Orangerie Museum, forming an aquatic landscape over 2 meters in height and almost 100 meters in length—in Monet’s words “an illusion of an unboundaried whole, water without horizon or shore.”

But perhaps it was too early rather than too late. Clemenceau always claimed that Monet “could only paint what he saw.” It was not what people expected. The Orangerie Museum had few visitors up until 1950. People wanted something new. The opening years of the 20th century had already seen Picasso’s *Demoiselles d’Avignon*, Cubism, Surrealism, and the plastic experiments of Kandinsky and Mondrian. Monet’s spiritual painting attracted virulent criticism. The painter André Lhote spoke of “plastic suicide,” others of “neurasthenia” or “square yards of daubing” fit for “transatlantic liner interiors.”

The era of incomprehension is long past. Generations of abstract painters have recognized their master. In this setting so strikingly restored, it is the view of the Surrealist painter André Masson that now rings true. “Only Monet gave painting a new twist. He dissolved barriers, he conjured away the very idea of form that had been dominating us for millennia.” The grand old man has found no finer homage.
Instructions for authors

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