Ischemic Heart Disease in Type 2 Diabetes

Irina Otel, François Ledru, and Nicolas Danchin

Type 2 diabetes has reached epidemic proportions and an increasing proportion of patients with coronary artery disease (CAD) are diabetics. CAD in diabetics has specificities and, in particular, more extensive atherosclerosis; diabetic patients are also more frequently asymptomatic, with silent myocardial ischemia, which makes the diagnosis of CAD more difficult. In addition, diabetic patients with CAD have poorer outcomes than nondiabetics. The management of diabetic patients with CAD is based on intensive intervention on lifestyle and risk factors, together with the mandatory use of medications of proven benefit as regards secondary prevention in coronary patients: antiplatelet agents, statins, β-blockers, and angiotensin-converting enzyme (ACE) inhibitors. Glycemic control is also essential; although the use of sulfonylureas has been controversial, there is now a vast amount of data suggesting a beneficial effect, in particular when agents more specific for the pancreatic adenosine triphosphate–dependent potassium (K_{ATP}) channels are used. At the acute stage of myocardial infarction, the Diabetes mellitus, Insulin Glucose infusion in Acute Myocardial Infarction (DIGAMI) trial suggested a beneficial effect of insulin therapy prolonged for 3 months after hospital discharge; these data will have to be confirmed by larger intervention trials. Finally, the respective roles of coronary angioplasty and coronary surgery in diabetics are debated; a post hoc analysis of the Bypass Angioplasty Revascularization Investigation (BARI) trial data showed increased mortality in diabetics with multivessel CAD treated with angioplasty compared with surgery, but the results of the more recent trials using intracoronary stents appear more balanced; in this regard, the effects of drug-eluting stents, which dramatically decrease the incidence of re-stenosis, seem promising.

DIABETES MELLITUS is one of the main risk factors for coronary artery disease (CAD), and an increasing proportion of CAD patients have diabetes. In France, the percentage of patients hospitalized for acute myocardial infarction who had diabetes increased from 17% to 21% (a 24 % increase) between 1995 and 2000,[1] and 23% of the patients enrolled in the recent Euro-Heart Survey of acute coronary syndromes (ACS) have diabetes.[2] Conversely, the outcome of CAD patients with diabetes is worse than that of their nondiabetic counterparts. In the present review, we will summarize the evidence currently available regarding the specificity of the anatomy of CAD in diabetic patients, the specific outcome of coronary patients with diabetes, and the optimal management of diabetic patients with CAD.

ANATOMY OF CAD IN DIABETES MELLITUS

A number of angiographic studies have analyzed the specificity of CAD in diabetic patients. In a study of 466 patients without myocardial infarction or previous revascularization procedures undergoing diagnostic coronary angiography, Ledru et al[3] found that type 2 diabetic patients were more likely to have coronary artery narrowings than nondiabetics, and that both the severity score and the extent score were higher in diabetic patients. In addition, distal lesions were significantly more frequent in diabetics and both severe and mild lesions were found to be more common. These findings reinforced previous data showing that mild or moderate stenoses were significantly more frequently observed on coronary angiography in diabetic patients.[4]

CARDIOVASCULAR OUTCOME OF DIABETICS

In a much-publicized survey, Haffner et al showed that diabetic patients without known CAD had a 7-year risk of death or acute myocardial infarction similar to that of CAD patients with a history of myocardial infarction.[5] More recent studies are somewhat less pessimistic, but all show that the cardiovascular outcome of diabetic patients is definitely worse than that of nondiabetics without known CAD, although slightly better than that of patients with documented CAD. Thus, in the Framingham study, the risk of coronary heart disease death or myocardial infarction at 2 years in men increases from 1.8% in subjects without diabetes mellitus or CAD to 3.1% in diabetic patients without CAD, and 9.4% in coronary patients without diabetes mellitus.[6] Likewise, in the Heart Protection Study, the risk of major vascular events was low in diabetic patients without additional risk factors, but nearly similar to that of coronary patients without diabetes in diabetic patients with at least one additional risk factor[7] (Fig 1). In all of these studies, CAD patients with diabetes mellitus fared less well than nondiabetics with CAD.

DETECTION OF CAD IN TYPE 2 DIABETIC PATIENTS

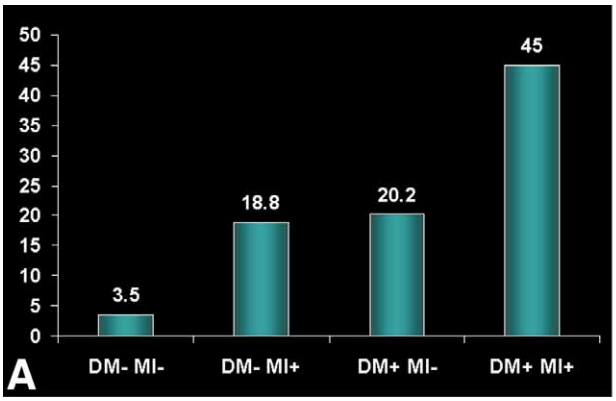
Myocardial ischemia is more often asymptomatic in diabetic patients. The inference is that specific screening may be needed even in asymptomatic patients, although there is no definite evidence that such a policy improves prognosis. Current guidelines, however, recommend that exercise testing be performed in asymptomatic patients with 2 or more risk factors, electrocardiographic (ECG) abnormalities, or a history of peripheral or carotid artery disease.[8] Thallium single-photon emission computed tomography or stress echocardiography may constitute alternative methods to detect the presence of CAD, particularly in patients who are unable to perform an exercise test. Imaging techniques, such as radionuclide studies or stress echocardiography, have the advantage of allowing both the positive

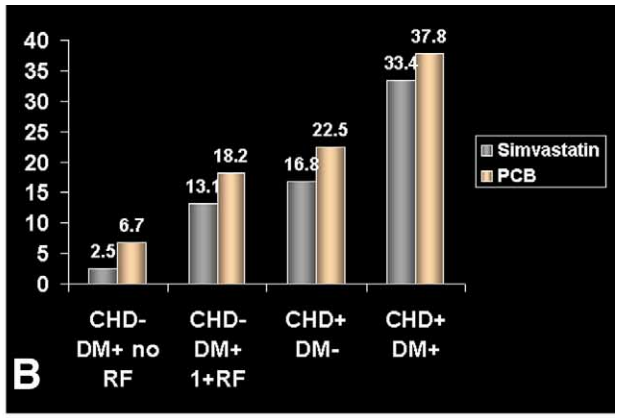
From the Department of Cardiology, Hôpital Européen Georges Pompidou, Paris, France.

Address reprint requests to Nicolas Danchin, MD, Cardiologie, Hôpital Européen Georges Pompidou, 20 rue Leblanc, 75015, Paris, France.

0026-0495/03/5208-1006$30.00/0

doi:10.1016/S0026-0495(03)00216-6





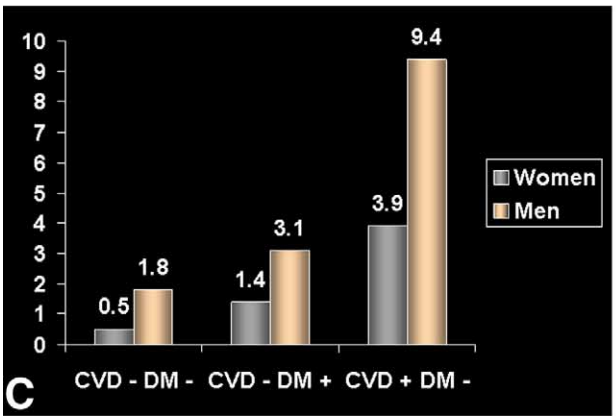


Fig 1. Long-term outcome of patients with diabetes mellitus, compared with patients with CAD. (A) Risk of myocardial infarction at 7 years in the study from Haffner et al[5]; (B) risk of major vascular events in the Heart Protection Study[7]; (C) risk of coronary heart disease death or myocardial infarction at 2 years in the Framingham cohort.[6] Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; DM, diabetes mellitus; MI, myocardial infarction; RF, risk factor.

diagnosis and quantification of the extent of myocardial ischemia, which have documented prognostic significance[9] and are useful criteria to discuss the legitimacy of performing a coronary angiogram or a revascularization procedure.

THERAPEUTIC MANAGEMENT OF DIABETIC PATIENTS WITH DOCUMENTED CAD

Risk Factor Modification and Secondary Prevention Medications

Particular attention should be given to associated risk factors, which are extensively discussed elsewhere in this supplement.

Smoking is associated with an increased risk of microvascular and macrovascular complications in diabetic patients and smoking cessation should therefore be strongly encouraged. Blood pressure control is also an absolute necessity in patients with CAD and diabetes mellitus, as shown, for example, in the United Kingdom Prospective Diabetes Study (UKPDS),[10] where tighter blood pressure control was accompanied by a significant reduction in diabetes-related deaths, stroke, and microvascular complications.

Four classes of medications have demonstrated a beneficial effect in secondary prevention in patients with CAD: antiplatelet agents, β-blockers, statins, and angiotensin-converting enzyme (ACE) inhibitors.

Antiplatelet agents, and particularly aspirin, have been extensively studied in patients with CAD. In the most recent meta-analysis,[11] which involved more than 200,000 diabetic and nondiabetic patients, antiplatelet agents reduced the risk of severe cardiovascular events by about one quarter, with a 34% reduction in nonfatal myocardial infarction and a 26% reduction in nonfatal myocardial infarction or coronary heart disease death. In the Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial,[12] which compared the efficacy of clopidogrel and aspirin on the outcome of patients with coronary artery, peripheral artery, or cerebrovascular disease, 3,866 patients had diabetes mellitus. The reduction in event (vascular death, myocardial infarction, stroke, or hospitalization for ischemia or bleeding) rates with clopidogrel was 21% in diabetics, compared with 9% in nondiabetics, suggesting a more pronounced effect of clopidogrel in this population. Conversely, in the Clopidogrel Reduction of Events During extended Observation (CREDO) trial,[13] which assessed the efficacy of prolonged (1 year) treatment with clopidogrel on top of aspirin in patients undergoing percutaneous coronary interventions (PCI), the risk reduction for prolonged treatment was 11% in diabetics, compared with 33% in nondiabetics. Overall, diabetic patients with CAD seem to benefit from antiplatelet therapy at least as much as nondiabetics.

β-Blockers are beneficial in post–myocardial infarction patients. The specific outcome in diabetics with myocardial infarction has not been assessed in the most recent meta-analysis.[14] In the Carvedilol Postinfarct Survival Controlled Evaluation (CAPRICORN) trial,[15] which found a 23% reduction in mortality with carvedilol in patients with large myocardial infarctions, 22% of the population had diabetes mellitus; there is no indication that the diabetic patients benefited less

than the nondiabetics from the β-blocking agent. In the Cleveland Clinic cohort of 4,553 patients who had undergone PCI, of whom 2,056 received β-blockers, the adjusted odds ratio for 1-year mortality in patients on β-blockers was 0.63 (95% confidence interval, 0.46 to 0.87) and the benefit was similar in diabetic and nondiabetic patients.[16]

Serum lipid abnormalities are frequent in patients with diabetes mellitus. In CAD patients, numerous trials have shown that 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors reduce cardiovascular mortality and morbidity, with survival curves increasingly diverging after 12 to 18 months of follow-up.[7,17-20] The beneficial effects of statins have been documented in patients with stable CAD, previous myocardial infarction, ACS, or following percutaneous transluminal coronary interventions, irrespective of the initial level of low-density lipoprotein (LDL) cholesterol and triglycerides, although patients with very severe hypertriglyceridemia were excluded from the trials. In most of these studies, subgroup analyses showed that the benefit was of a similar magnitude in diabetic patients.[7,18-20] The evidence is less compelling with fibrates, although some trials have found reductions in cardiovascular events, particularly with fenofibrate and gemfibrozil.

A number of clinical trials have demonstrated the major beneficial effect of ACE inhibitors in patients with myocardial infarction and symptomatic or asymptomatic left ventricular dysfunction. In the most recent meta-analysis of trials carried out in this setting, mortality reduction was 23% in patients receiving ACE inhibitors with a similar beneficial effect being suggested for diabetic and nondiabetic patients.[21] The Heart Outcomes Prevention Evaluation (HOPE) trial assessed 9,297 patients aged ≥ 55 years with documented CAD or diabetes mellitus combined with at least one other risk factor.[22,23] The primary outcome (cardiovascular death, acute myocardial infarction, or stroke) at the end of the 5-year follow-up period was significantly lower in patients treated with high-dose (10 mg) ramipril, compared with placebo. The risk reduction in diabetic patients (n = 3,577) was 25% for the primary outcome and 37% for cardiovascular death, with similar rates for the primary outcome being observed in nondiabetic patients. There is evidence, however, that only high doses of ACE inhibitors have direct effects on arterial atherosclerosis: in the Study to Evaluate Carotid Ultrasound changes in patients treated with Ramipril and vitamin E (SECURE),[24] which included 35% of diabetic patients without left ventricular dysfunction, the 2.5-mg ramipril dose failed to significantly reduce carotid artery atherosclerosis progression, while the 10-mg dose nearly halved it. At the end of this year, the EUropean trial on Reduction Of cardiac events with Perindopril is stable coronary Artery disease (EUROPA), which compared high-dose (8 mg) perindopril versus placebo in patients with documented CAD and no left ventricular dysfunction, will bring the final answer to the question of systematic treatment with ACE inhibition in all CAD patients, irrespective of the presence of left ventricular dysfunction.

In addition to the associated risk factors for CAD, it has by now been well established that hyperglycemia is an important determinant of cardiovascular disease in type 2 diabetic patients. However, the beneficial effect of tight blood glucose control on macrovascular outcomes has never been convincingly shown, as discussed in detail elsewhere in this supplement. Large intervention studies, such as the Action in Diabetes and Vascular disease: preterAx and DiamicroN MR Controlled Evaluation (ADVANCE) program, are currently under way to provide definitive evidence about the value of intensive blood glucose control in type 2 diabetes patients at high risk for cardiovascular disease.

Myocardial Revascularization in Stable Patients

In patients with chronic stable CAD, randomized trials performed in the 1970s and 1980s showed that coronary artery surgery was more efficacious than medical therapy alone on anginal symptoms, and that it improved long-term outcome in specific anatomic subsets, such as tight stenosis of the left main coronary artery, proximal left anterior descending artery stenosis, or triple-vessel disease, especially in the presence of left ventricular dysfunction. More recently, the Asymptomatic Cardiac Ischemia Pilot (ACIP) trial[25] showed that myocardial revascularization was superior to medical therapy alone in stable patients with documented silent myocardial ischemia. Perioperative mortality, however, is increased by more than 20% in diabetics, and PCI might therefore appear particularly attractive in diabetics. Unfortunately, a post hoc analysis of the subset of diabetic patients in the Bypass Angioplasty Revascularization Investigation (BARI) trial, which was designed as a randomized comparison of PCI and coronary artery surgery in stable patients with multivessel CAD, showed that 5-year survival was significantly lower in patients assigned PCI (65.5% *v* 81%), casting doubt on the appropriateness of using PCI in diabetic patients.[26] More reassuring data, however, have been collected from large registries, such as the one from Emory University, in which PCI and coronary artery surgery yielded similar results in type 2 diabetics, while surgery was superior to PCI in type 1 diabetics.[27] More recently, the recent results of the Angina With Extremely Serious Operative Mortality Evaluation (AWESOME) trial,[28] in high-risk patients with refractory angina enrolled from 1995 to 2000, showed no difference in 3-year survival in diabetic patients randomized to PCI or coronary bypass surgery. Likewise, the Arterial Revascularization Therapies Study (ARTS),[29] comparing coronary surgery and PCI using coronary stents, found nonsignificantly higher mortality and myocardial infarction rates at 1 year in diabetics treated with PCI, but a lower risk of stroke. The reintervention rate remained significantly higher in PCI-treated patients, emphasizing the increased risk of re-stenosis in diabetic patients. In this regard, the results of the RAndomized study with the sirolimus-eluting Bx Velocity balloon ExpandabLe stent (RAVEL),[30] which compared the re-stenosis rate in patients receiving conventional stents versus stents coated with the immunosuppressive agent sirolimus, are extremely encouraging: in the diabetic patients, the re-stenosis rate was 0% with sirolimus-eluting stents, compared with 42% with conventional stents. However, the question of re-stenosis and its prevention is unlikely to erase the whole difference between surgery and angioplasty; indeed, surgical grafts bypass an entire coronary artery segment and not only the most severe narrowing,

whereas angioplasty provides treatment of single narrowings and therefore does not provide any protection in the case of subsequent rupture of mild coronary plaques leading to thrombotic occlusions.

Invasive Versus Noninvasive Management of Acute Coronary Syndromes

There are 2 types of ACS, both resulting from plaque rupture or erosion. In all instances, diabetic patients are at increased risk, when developing ACS. ACS with ST-segment elevation on the ECG correspond to a persistent, complete, acute coronary occlusion and require emergency reperfusion. In this regard, both intravenous thrombolysis and primary coronary angioplasty can be used, the latter having yielded better results in randomized trials carried out in highly specialized centers. Both methods can be used with similar efficacy in diabetics and nondiabetics. In the Global Utilization of Streptokinase and TPA for Occluded arteries (GUSTO) trial,[31] 90-minute coronary artery patency was similar after thrombolysis in diabetic and nondiabetic patients, although the reocclusion rate tended to be higher in diabetics. In the Global Use of Strategies To open Occluded arteries in acute coronary syndromes (GUSTO IIb) trial,[32] which was the largest trial comparing intravenous thrombolysis and primary PCI, the magnitude of PCI superiority was similar in diabetics and nondiabetics. ACS without ST-segment elevation are caused by incomplete or intermittent coronary artery occlusion. Several trials have evidenced the beneficial effect of intensive antithrombotic therapy with antiplatelet agents (glycoprotein IIb/IIIa inhibitors, clopidogrel) or heparin, and particularly the low-molecular-weight heparin enoxaparin. In the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial,[33] testing the effect of clopidogrel in non–ST-segment elevation ACS, as well as in the meta-analysis of trials using glycoprotein IIb/IIIa inhibitors in the same setting,[34] the efficacy of the antiplatelet agents was similar in diabetic and nondiabetic patients. The benefit of an invasive strategy with rapid coronary angiography followed by myocardial revascularization was assessed in the Second Fragmin and fast Revascularization during InStability in Coronary artery disease (FRISC-2), Treat angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy– Thrombolysis In Myocardial Infarction (TACTICS-TIMI 18), and Randomized Intervention Treatment of Angina (RITA-3) trials.[35-37] All 3 trials showed the superiority of the invasive strategy, particularly in patients with the most severe forms (especially those with increased troponin levels). In the FRISC-2 trial, the risk of death or myocardial infarction at 6 months was decreased by 23% in nondiabetics, compared with 25% in diabetics, when the invasive strategy was used. In the TACTICS-TIMI 18 trial, where all patients were treated with the glycoprotein IIb/IIIa inhibitor tirofiban, the absolute risk reduction for death, myocardial infarction, or hospitalization for ACS at 6 months was 7.6% in diabetics, compared with a nonsignificant absolute reduction of 2.2% in nondiabetics.

THE SULFONYLUREA CONTROVERSY

Oral antidiabetic agents of the sulfonylurea family have been used successfully for the treatment of type 2 diabetes for more than 4 decades. However, 30 years ago, the University Group Diabetes Program (UGDP) raised questions about the potential cardiovascular deleterious effect of sulfonylurea therapy, although the methodology was heavily criticized and tolbutamide was the only sulfonylurea used.[38] Indeed, sulfonylureas act on the adenosine triphosphate–dependent potassium (K_{ATP}) channels of the pancreatic β cells, and the closure of these ionic channels results in increased insulin secretion.[39] However, K_{ATP} channels are also present in other organs and in particular in myocardial cells and vascular smooth muscle cells. In the heart, activation of the K_{ATP} is responsible for the so-called "ischemic preconditioning effect." This effect, which results in a better tolerance to ischemia after a first ischemic episode has "prepared" ("preconditioned") the myocardium, has been evidenced in many animal experimental models, as well as in certain experimental models in man.[40] Because of this background, some have recommended that sulfonylureas be avoided in patients with CAD.[41] The clinical importance of ischemic preconditioning in man, though, had not been clearly demonstrated until the results of the Impact Of Nicorandil in Angina (IONA) trial were known.[42] In this trial, nicorandil, an antianginal medication that acts both as a nitric oxide (NO) donor and an activator of myocardial K_{ATP} channels,[43] on top of conventional antianginal therapy in stable coronary patients, resulted in a decreased risk of cardiovascular events (death, myocardial infarction, or severe angina), suggesting the clinical relevance of ischemic preconditioning in coronary patients.

Table 1. Cardiovascular Events at 8 Years in the Steno-2 Trial Comparing a Policy of Intensive, Multifactorial Intervention Including Gliclazide and/or Metformin Therapy With Conventional Management in Type 2 Diabetic Patients[45]

	Relative Risk	95% Confidence Interval
All cardiovascular events	Unadjusted: 0.47	0.24-0.73
	Adjusted: 0.47	0.22-0.74
Cardiovascular events excluding revascularizations	Unadjusted: 0.45	0.23-0.91
Nephropathy	Unadjusted: 0.39	0.17-0.87

However, regarding sulfonylureas as a whole, there is no clinical evidence of any potent deleterious cardiovascular effect. In the UKPDS,[44] intensive glycemic control, which was based on first-line use of sulfonylureas (glibenclamide, chlorpropamide, and glipizide), was associated with a significant 25% reduction in microvascular events, and a nonsignificant 16% reduction in myocardial infarction, and 12% reduction in any diabetes-related endpoint. More recently, the Steno-2 study[45] showed that intensive management of type 2 diabetics with microalbuminuria, based on dietary intervention, increased physical activity, and medication (gliclazide and/or metformin) reduced cardiovascular risk at 8 years by 53% (Table 1). Conceptually, however, not all sulfonylureas have the same effects on the myocardium; it has been recently shown that pancreatic and myocardial K_{ATP} channels are different and have different receptors to sulfonylureas (SUR 1 *v* SUR 2) and

that the action of sulfonylureas on these 2 types of receptors differs according to the medication used.[46] Experimentally, glibenclamide acts on both receptors and is used to block ischemic preconditioning in experimental models (this effect explaining why patients on sulfonylureas were excluded from the IONA trial),[47,48] while gliclazide acts specifically on the pancreatic receptors, and glimepiride has intermediate effects. In nondiabetic patients with coronary disease, glibenclamide, but not glimepiride, has been shown to block ischemic preconditioning in a classic model with repeated balloon inflation during percutaneous coronary angioplasty.[49] Discrepant results have been reported in models using repeated exercise tests at short intervals of time, glibenclamide suppressing the effects of ischemic preconditioning in 2 studies[50-53]; recently, a study comparing the effects of insulin and glibenclamide in coronary patients undergoing stress echocardiography showed that glibenclamide treatment resulted in a decrease in ejection fraction and a worsening of regional contractility during stress, whereas insulin therapy had no effect.[54]

At the acute stage of myocardial infarction, hyperglycemia at entry is associated with a poorer outcome.[55] The open-design randomized Diabetes mellitus, Insulin Glucose infusion in Acute Myocardial Infarction (DIGAMI) trial[56] showed that insulin therapy continued for at least 3 months after hospital discharge reduced cardiovascular mortality. Conversely, a small cohort of patients from the Mayo Clinic undergoing primary PCI at the acute stage of myocardial infarction showed an increased risk of death in patients treated with the sulfonylureas available in the United States (mainly glibenclamide, glipizide, and glimepiride).[57] However, there is no evidence from large databases of diabetic patients with acute myocardial infarction that the use of sulfonylureas is associated with increased risk at the acute stage. In the large Medicare database, the use of sulfonylureas was even associated with a slight reduction in the risk of complications.[58] Likewise, in the French USIC (Unités de Soins Intensifs Cardiologiques) 2000 database, diabetic patients receiving sulfonylureas at the time of their infarction had a decreased risk of in-hospital mortality, even after adjustment with other predictors of outcome (personal data on file). Although the type of medication prescribed in this database was not recorded, it is noteworthy that gliclazide, which has no effect on myocardial K_{ATP} channels, was the most prescribed sulfonylurea in France at the time the survey was performed and these data are in keeping with the results of the Steno-2 trial.[45]

CONCLUSION

Ischemic heart disease represents one of the main challenges in type 2 diabetic patients. The disease is more extensive than the disease observed in nondiabetics, its diagnosis is often more difficult because of the frequent presence of clinically silent myocardial ischemia, and the short-term and long-term outcomes of diabetic patients is poorer than that of nondiabetics. Therapeutic management is based on intensive intervention for associated risk factors and the use of secondary prevention medications with a documented efficacy in patients with CAD; in particular, antiplatelet agents, statins, β-blockers, and ACE inhibitors should be used extensively. Glycemic control is also an important part of the therapeutic strategy. In this regard, there is no convincing evidence that sulfonylureas have a deleterious effect in the clinical setting, and the availability of medications with no or limited action on the myocardial K_{ATP} channels, such as gliclazide or glimepiride, is further reassuring. When necessary, myocardial revascularization can be used, with coronary bypass surgery being the reference technique in patients with multivessel disease; drug-eluting stents, however, which considerably reduce the risk of re-stenosis, are likely to have a profound impact on the use of angioplasty in diabetic patients.

REFERENCES

1. Danchin N, Hanania G, Grenier O, et al: Evolution du traitement de sortie après hospitalisation pour syndrome coronaire aigu en France entre 1995 et 2000: données des études USIK 1995, Prévenir 1 et 2 et USIC 2000. Ann Cardiol Angeiol 52:1-6, 2003

2. Hasdai D, Behar S, Wallentin L, et al: A prospective survey of the characteristics, treatments and outcomes of patients with acute coronary syndromes in Europe and the Mediterranean basin. The Euro Heart Survey of acute coronary syndromes (Euro Heart Survey ACS). Eur Heart J 23:1190-1121, 2002

3. Ledru F, Ducimetière P, Battaglia S, et al: New diagnostic criteria for diabetes and coronary artery disease: insights from an angiographic study. J Am Coll Cardiol 37:1543-1550, 2001

4. Henry P, Makowski S, Richard P, et al: Increased incidence of moderate stenosis among patients with diabetes: Substrate for myocardial infarction? Am Heart J 134:1037-1043, 1997

5. Haffner SM, Lehto S, Ronnemaa T, et al: Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 339:229-234, 1998

6. Wilson PW, D'Agostino RB, Sullivan L, et al: CHD risk in persons with diabetes mellitus or with known coronary heart disease. Circulation 106:II-509, 2002 (suppl, abstr 2514)

7. Heart Protection Study Collaborative Group: MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: A randomized placebo-controlled trial. Lancet 360:7-22, 2002

8. American Diabetes Association: Standards of medical care for patients with diabetes mellitus. Diabetes Care 26 1):S33-S50, 2003 (suppl 1)

9. Giri S, Shaw LJ, Murthy DR, et al: Impact of diabetes on the risk stratification using stress single-photon emission computed tomography myocardial perfusion imaging in patients with symptoms suggestive of coronary artery disease. Circulation 105:32-40, 2002

10. UK Prospective Diabetes Study (UKPDS) Group: Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes (UKPDS) 38. BMJ 317:713-720, 1998

11. Antithrombotic Trialists Collaboration: Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 324:71-86, 2002

12. Cannon CP, on behalf of the CAPRIE Investigators: Effectiveness of clopidogrel versus aspirin in preventing acute myocardial infarction in patients with symptomatic atherothrombosis (CAPRIE trial). Am J Cardiol 90:760-762, 2002

13. Steinbuhl SR, Berger PB, Mann JT III, et al: For the CREDO investigators. Early and sustained dual oral antiplatelet therapy follow-

ing percutaneous coronary intervention. A randomized controlled trial. JAMA 288:2411-2420, 2002

14. Freemantle N, Cleland J, Young P, et al: β Blockade after myocardial infarction: Systematic review and meta-regression analysis. BMJ 318:1730-1737, 1999

15. The CAPRICORN Investigators: Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: The CAPRICORN randomised trial. Lancet 357:1385-1390, 2001

16. Chan AW, Quinn MJ, Bhatt DL, et al: Mortality benefit of beta-blockade after successful elective percutaneous coronary intervention. J Am Coll Cardiol 40:669-675, 2002

17. The Scandinavian Simvastatin Survival Study Group: Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study (4S). Lancet 344:1383-1389, 1994

18. Sacks FM, Pfeffer MA, Moye LA, et al: The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol And Recurrent Events Trial investigators. N Engl J Med 335:1001-1009, 1996

19. The Long-Term Intervention With Pravastatin in Ischaemic Disease (LIPID) Study Group: Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med 339:1349-1357, 1998

20. Serruys PWJC, de Feyter P, Macaya C, et al: Fluvastatin for prevention of cardiac events following successful first percutaneous coronary intervention: A randomized controlled trial. JAMA 287:3215-3222, 2002

21. Flather MD, Yusuf S, Køber L, et al: Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: A systematic overview of data from individual patients. Lancet 355:1575-1581, 2000

22. The Heart Outcomes Prevention Evaluation Study Investigators: Effects of an angiotensin-converting enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. N Engl J Med 342:145-153, 2000

23. Heart Outcomes Prevention Evaluation (HOPE) Study Investigators: Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: Results of the HOPE study and micro-HOPE substudy. Lancet 355:253-259, 2000

24. Lonn EM, Yusuf S, Dzavik V, et al: Effects of ramipril and vitamin E on atherosclerosis. The Study to Evaluate Carotid Ultrasound changes in patients treated with Ramipril and vitamin E (SECURE). Circulation 103:919-925, 2001

25. Davies RF, Goldberg AD, Forman S, et al: Asymptomatic Cardiac Ischemia Pilot (ACIP) study two-year follow-up: Outcomes of patients randomized to initial strategies of medical therapy versus revascularization. Circulation 95:2037-2043, 1997

26. The BARI Investigators: Seven-year outcome in the Bypass Angioplasty Revascularization Investigation (BARI) by treatment and diabetic status. J Am Coll Cardiol 35:1122-1129, 2000

27. Weintraub WS, King SB, Douglas JS, et al: Percutaneous transluminal coronary angioplasty as a first revascularization procedure in single-, double-, and triple-vessel coronary artery disease. J Am Coll Cardiol 26:143-151, 1995

28. Sedlis SP, Morrison DA, Lorin JD, et al: Percutaneous coronary intervention versus coronary bypass graft surgery for diabetic patients with unstable angina and risk factors for adverse outcomes with bypass. Outcome of diabetic patients in the AWESOME randomized trial and registry. J Am Coll Cardiol 40:1555-1566, 2002

29. Serruys PW, Unger F, Sousa E, et al: for the Arterial Revascularization Therapies Study Group: Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. N Engl J Med 344:1117-1124, 2001

30. Morice MC, Serruys PW, Sousa EJ, et al, for the RAVEL study Group: A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med 346:1773-1180, 2002

31. The GUSTO Investigators: An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med 329:673-682, 1993

32. The GUSTO IIb Angioplasty Substudy Investigators: A clinical trial comparing primary coronary angioplasty with tissue plasminogen activator for acute myocardial infarction. N Engl J Med 336:1621-1628, 1997

33. The Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators: Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 345:494-502, 2001

34. Boersma E, Harrington RA, Moliterno DJ, et al: Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: A meta-analysis of all major randomised clinical trials. Lancet 359:189-198, 2002

35. Fragmin and Fast Revascularisation During Instability in Coronary Artery Disease Investigators: Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. Lancet 354:708-715, 1999

36. Cannon CP, Weintraub WS, Demopoulos LA, et al: Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. N Engl J Med 344:1879-1887, 2001

37. Fox KAA, Poole-Wilson PA, Henderson RA, et al, for the RITA investigators: Interventional versus conservative treatment for patients with unstable angina or non-ST-elevation myocardial infarction: the British Heart Foundation RITA 3 randomised trial. Lancet 360:743-751, 2002

38. Seltzer HS: A summary of criticisms of the findings and conclusions of the University Group Diabetes Program (UGDP). Diabetes 21:976-979, 1972

39. Gribble FM, Tucker SJ, Seino S, et al: Tissue specificity of sulfonylureas: studies on cloned cardiac and beta- cell K_{ATP} channels. Diabetes 47:1412-1418, 1998

40. Gross GJ, Auchampach JA: Blockade of ATP-sensitive potassium channels prevents myocardial preconditioning in dogs. Circ Res 70:223-233, 1992

41. Engler RL, Yellon DM: Sulfonylurea KATP blockade in type II diabetes and preconditioning in cardiovascular disease. Time for reconsideration. Circulation 94:2297-2301, 1996

42. The IONA Study Group: Effect of nicorandil on coronary events in patients with stable angina: The Impact Of Nicorandil in Angina (IONA) randomised trial. Lancet 359:1269-1275, 2002

43. Auchampach JA, Cavero I, Gross GJ: Nicorandil attenuates myocardial dysfunction associated with transient ischemia by opening ATP-dependent potassium channels. J Cardiovasc Pharmacol 20:765-771, 1992

44. UK Prospective Diabetes Study (UKPDS) Group: Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 352:837-853, 1998

45. Gaede P, Vedel P, Larsen N, et al: Multifactorial intervention and cardiovascular risk in patients with type 2 diabetes. N Engl J Med 348:383-393, 2003

46. Inagaki N, Gonoi T, Clement JP, et al: A family of sulfonylurea receptors determines the pharmacological properties of ATP-sensitive K+ channels. Neuron 16:1011-1017, 1996

47. Reimann F, Ashcroft FM, Gribble FM: Structural basis for the interference between nicorandil and sulfonylurea action. Diabetes 50: 2253-2259, 2001

48. Cleveland JC, Meldrum DR, Cain BS, et al: Oral sulfonylurea hypoglycaemic agents prevent ischemic preconditioning in human myocardium. Two paradoxes revisited. Circulation 96:29-32, 1997

49. Klepzig H, Kober G, Matter C, et al: Sulfonylureas and ischaemic preconditioning. A double-blind, placebo-controlled evaluation of glimepiride and glibenclamide. Eur Heart J 20:439-446, 1999

50. Tomai F, Danesi A, Ghini AS, et al: Effects of K_{ATP} channel blockade by glibenclamide on the warm-up phenomenon. Eur Heart J 20:196-202, 1999

51. Correa SD, Schaefer S: Blockade of K_{ATP} channels with glibenclamide does not abolish preconditioning during demand ischemia. Am J Cardiol 79:75-78, 1997

52. Ovunc K: Effects of glibenclamide a K_{ATP} channel blocker, on warm-up phenomenon in type II diabetic patients with chronic stable angina pectoris. Clin Cardiol 23:535-539, 2000

53. Bogaty P, Kingma JG, Robitaille NM, et al: Attenuation of myocardial ischemia with repeated exercise in subjects with chronic stable angina. Relation to myocardial contractility, intensity of exercise and the adenosine triphosphate-sensitive potassium channel. J Am Coll Cardiol 32:1665-1671, 1998

54. Scognamiglio R, Avogaro A, De Kreutzenberg SV, et al: Effects of treatment with sulfonylurea drugs or insulin on ischemia-induced myocardial dysfunction in type 2 diabetes. Diabetes 51:808-812, 2002

55. Capes SE, Hunt D, Malmberg K, et al: Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: A systematic overview. Lancet 355:773-778, 2000

56. Malmberg K, for the DIGAMI (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction) Study Group: Prospective randomised study of intensive insulin treatment on long term survival after acute myocardial infarction in patients with diabetes mellitus. BMJ 314:1512-1515, 1997

57. Garratt KN, Brady PA, Hassinger NL, et al: Sulfonylurea drugs increase early mortality in patients with diabetes mellitus after direct angioplasty for acute myocardial infarction. J Am Coll Cardiol 33:119-124, 1999

58. Jollis JG, Simpson RJ Jr, Cascio WE, et al: Relation between sulfonylurea therapy, complications, and outcome for elderly patients with acute myocardial infarction. Am Heart J 138:S376-5380, 1999