

REVIEW ARTICLES

Coronary Artery Disease in Diabetes Patients: Prevention and Management

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Abstract

Diabetes mellitus (DM) increases the risk of cardiovascular events in patients with cardiovascular disease as well as in patients without any previous history of ischemic heart disease (IHD). This inordinate increase in the risk of coronary events in diabetic patients is attributed to multiple factors, including glycation and oxidation of proteins and increased prevalence of classic risk factors of coronary disease, such as hypertension, obesity, and dyslipidemia. Despite advances in the management of cardiovascular disease, a large proportion of diabetic subjects continue to have uncontrolled hyperglycemia, hypertension, and dyslipidemia. Patients with CAD and pre-diabetic states should undergo lifestyle modifications aimed at preventing DM. In patients with CAD and DM, routine use of aspirin and an angiotensin-converting enzyme inhibitor (ACE-I)—unless contraindicated or not tolerated—and strict glycemic, blood pressure, and lipid control are strongly suggested. The results after revascularization in diabetic patients are usually worse compared with non-diabetic patients. Advances in PCI include the use of drug-eluting stents and adjunctive drug therapies, such as GpIIb/IIIa antagonists. Glycemic control is an important determinant of outcome after revascularization in diabetic patients. In this review, some of these landmark studies are reviewed and some practical guidelines of management are suggested.

Key words : Angiotensin-converting enzyme inhibitor, Coronary artery disease, diabetes mellitus, dyslipidemia.

Introduction

Existence of the global epidemic of diabetes mellitus is well known since over 150 million people worldwide suffer from the disease and a conservative estimate is that this number will be doubled by the year 2025¹. Type 2 diabetes accounts for most of the current and the predicted figures, and its close association with cardiovascular disease seems to emerge from a common soil, insulin resistance. Hence, it is believed that in the near future this global epidemic of type 2 diabetes will be closely associated with an epidemic of cardiovascular disease. Furthermore, diabetes mellitus increases mortality risk and reduces life expectancy, the leading cause of death being cardiovascular disease^{2, 3}. The 16-year follow-up of the Framingham study⁴ demonstrated an equal risk of cardiovascular morbidity and mortality among diabetic men and women. Diabetes mellitus is the most potent risk factor for coronary artery disease (CAD). Patients with diabetes are two to four times more likely to have cardiovascular disease. This increased risk is seen in both type I and type II diabetes. Patients with diabetes but no CAD have the same incidence of myocardial infarction (MI) as patients with CAD but no diabetes⁵. Other risk factors such as hypertension, smoking, and hyperlipi-

demia carry a worse prognosis in patients with diabetes than in those who do not have diabetes. Moreover, there is an increased prevalence of these risk factors in patients with diabetes.

Prevention Of Coronary Artery Disease In Patients With Diabetes Mellitus Screening for Coronary Artery Disease in Diabetic Patients

Diabetes mellitus (DM) increases the risk of cardiovascular events in patients with cardiovascular disease as well as in patients without any previous history of ischemic heart disease (IHD). Diabetes is known as the CAD risk equivalent. High-risk diabetic patients include those who have typical or atypical symptoms, 55 or more years of age, having peripheral vascular disease, and with 2 or more of the following risk factors: hyperlipidemia, hypertension, smoking, family history of premature CAD, microalbuminuria, and progressive retinopathy. Screening for CAD may be indicated in younger individuals, with a relatively short duration of DM and few risks factors or diabetic complications, because most guidelines recommend more aggressive management of risk factors in the presence of CAD. Detection of CAD involves the usual diagnostic methods, which

include electrocardiography, exercise stress testing and, as indicated, myocardial perfusion scintigraphy or stress echocardiography⁵⁻⁸.

Lifestyle modifications

Obesity is a common problem in diabetes and is estimated to account for approximately 60% of type 2 diabetes⁹. The central distribution of fat¹⁰⁻¹² and history of weight gain^{12,13} in addition to body mass are independent risks of developing diabetes. A recent statement from the American Heart Association acknowledges the importance of targeting obesity to prevent cardiovascular disease¹⁴. The precise cause of increased cardiovascular morbidity and mortality in obesity is not known. Observational studies suggest that it may be related to insulin resistance and hyperinsulinemia. Patients should be counseled to avoid high-risk behaviors such as smoking and excessive alcohol consumption.

Finally the implementation of lifestyle modification, including dietary measures and aerobic exercise aiming at long-term weight loss, are even more critical in patients with diabetic CAD than in those with DM alone, because of the higher risk of CV events in these patients.

Interventions to Prevent CAD in Diabetes

Use of Antiplatelet

Primary prevention therapy with aspirin is recommended in diabetic patients >40 years of age, with additional risk factors, and/or with diabetes >10 years' duration. Contemporary guidelines recommend prophylactic therapy with aspirin for diabetic patients with CAD. In patients who do not tolerate or have a contra-indication to aspirin, clopidogrel can be used as an alternative antiplatelet agent.

Optimization of glycemic control

The goal of anti-diabetic drug therapy is to ensure optimal glycemic control (HbA1c <7% for all patients and, for the individual patient, an HbA1c as close to normal [<6%] as possible) with minimization of diabetes-related complications. There is no specific threshold for glycemia in relation to CV risk. Thus, optimal glycemic control must be a clear objective in diabetic patients, not only for prevention of microvascular but also of macrovascular events.

Antihypertensive therapy

The current anti-hypertension treatment targets are <130/<80 mm Hg in diabetic patients. In the UKPDS BP-lowering substudy, intensive therapy was associated with reduced risks of stroke and MI. Greater risk reduction was achieved with lower BP levels, and there was no threshold for risk reduction. The evidence for drug efficacy in reducing CV events in high-risk patients with DM is largely derived from subgroup analyses of recent trials. In the

ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial)¹⁵, the benefits of the Amlodipine-based regimen (with or without Perindopril) versus the Atenolol-based regimen on rates of nonfatal MI and fatal CAD were similar for hypertensive patients with or without DM. In the diabetic patients randomized in the MICRO-HOPE (Microalbuminuria, Cardiovascular, and Renal Outcomes-Heart Outcomes Prevention Evaluation) substudy¹⁶, Ramipril reduced the primary composite end point of MI, stroke, or CV death. Diabetic patients derived similar risk reductions with Perindopril in the EUROPA (EUROpean trial on reduction of cardiac events with Perindopril in stable coronary Artery disease).¹⁷ In the LIFE (Losartan Intervention For Endpoints) study¹⁸ reduction in hypertension study, the primary composite end point of CV death, stroke, or MI occurred less often in patients assigned to Losartan than in those assigned to Atenolol. Thus, compared with a beta-blocker-based regimen, Losartan therapy conferred consistent CV risk reduction in hypertensive diabetic patients.

Current clinical guidelines recommend primary prevention measures with ACE-I therapy in diabetic patients with 1 other CAD risk factor and secondary prevention with these drugs in diabetic patients with CAD. Recognizing that diabetic patients will usually need 3 or 4 antihypertensive drugs to lower BP to the recommended level, ACE-Is and ARBs (along with long-acting calcium channel blockers) are recommended as first-line therapy.

Lipid-lowering therapy

Lipid lowering therapy is recommended for diabetic patients >40 years of age or subjects <40 years of age with additional risk factors. The current lipid target ranges are LDL-C <100 mg/dl or a reduction in LDL-C by 30% to 40%, triglycerides <150 mg/dl, and HDL-C >40 mg/dl. In women, an HDL-C goal of 10 mg/dl higher (50 mg/dl) might be considered. The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines recommend lower LDL-C targets for patients suffering from both DM and CAD than for those suffering from DM alone.³ On the basis of the HPS¹⁹ and other trials, it is reasonable to target a LDL-C of 70 mg/dl for high-risk subjects such as diabetic patients.

Management Of Coronary Artery Disease In Patient With Diabetes Mellitus

Managing CAD patients with DM requires special attention. The majority of data on the management of CAD in DM are based on retrospective subgroup analysis of major clinical trials, which on an average included 20%–30% diabetic patients. Patients with DM have a number of adverse clinical, angiographic and metabolic features contributing to poor prognosis. Diabetic patients with CAD are more often female, obese and hypertensive. They usually have severe

angina, history of previous MI or CABG and marked left ventricular failure. They have abnormal endothelial function with reduced coronary flow reserve. There is platelet activation with increased thromboxane A₂ secretion. The levels of fibrinogen and factor VII are higher than normal, while antithrombin III and plasma fibrinolytic activity are lower. Angiographically, they have diffuse, extensive involvement of smaller reference vessels, multivessel involvement, higher incidence of left main coronary artery disease, poorer collaterals, lower ejection fraction and more thrombus formation^{6,20,21}.

Treatment Targets

Available treatment options, meant to preserve and optimize myocardial functions, achieve stabilization of vulnerable plaques, prevent recurrent events by controlling prothrombotic activity, and to counteract progression of atherosclerotic lesions. Evidence-based recommendations for secondary prevention are, in general terms, valid for patients with diabetes as well as without diabetes. The management strategy should, if anything, be even more ambitious in the former category of patients. Important treatment targets are outlined in table, summarizing recommendations for secondary prevention on the basis of accumulated evidence, including data from recent guidelines and consensus documents^{1,2,6}.

Table: Goal for the patients with diabetes mellitus and coronary artery disease (modified from European Guidelines for Cardiovascular Disease Prevention)

Blood pressure (mm Hg)		<130/80
	If renal impairment (Proteinuria > 1 gm/day)	<125/75
Glycemic control		
	HbA _{1c} (%)	≤6.5
	Fasting blood glucose (mmol/l)	<6.0
	Post prandial glucose (mmol/l)	<7.5
Lipid profile (mmol/l)		
	Total cholesterol	<4.5
	LDL cholesterol	<1.8
	HDL cholesterol	
	Men	>1.0
	Women	>1.2
	Triglyceride	<1.7
Smoking cessation		Obligatory
Regular physical activity (min/day)		>30-45
Weight control		
	BMI	<25
	In case of overweight	10% reduction.
Dietary habit		
	Salt (gm/day)	<6
	Fat intake (% of dietary energy)	<10

Acute Coronary Syndrome and Hyperglycemia

Hyperglycemia, on admission in patients with acute coronary syndrome (ACS) is common, and it is a powerful predictor of survival and increased risk of in-hospital complications in patients both with and without diabetes mellitus.⁸ AHA scientific statement recommends management of hyperglycemia during ACS hospitalization as follows:

1. Glucose level should be a part of the initial laboratory evaluation in all patients suspected or confirmed ACS.
2. In patients admitted to a CCU with ACS, glucose levels should be monitored closely. It is reasonable to consider intensive glucose control in patients with significant hyperglycemia (plasma glucose > 180 mg/dl), regardless of prior diabetes history. Until further data are available, approximation of normoglycemia appears to be reasonable goal (suggested range for plasma glucose 90-140 mg/dl), as long as hypoglycemia is avoided.
3. Insulin, administered as an intravenous infusion, is currently the most effective method of controlling glucose among patients hospitalized in the CCU.
4. In patients hospitalized in the non-CCU setting, efforts should be directed at maintaining plasma glucose levels <180 mg/dl, with subcutaneous insulin regimens).
5. ACS patients with hyperglycemia but without prior history of diabetes should have further evaluation.

Coronary Revascularization in Diabetics

Revascularization procedures may be indicated in diabetic patients with stable or unstable coronary syndromes, covering the whole spectrum of ischemic heart disease from asymptomatic patient to ST-elevation MI, ACS, and prevention of sudden cardiac death. Patients with diabetes have a higher mortality and morbidity after CABG compared with non-diabetics, but this is also seen in patients undergoing PCIs^{1,9}.

Percutaneous Intervention versus Bypass Surgery

The effectiveness of PCI and bypass surgery as a mode of revascularization has been compared in several randomized, controlled trials. Later when stents became available, studies were conducted, comparing this new percutaneous technology with CABG in multivessel CAD. The combined impression from these studies is that survival does not differ, but that diabetic patients have a significantly higher incidence of repeat revascularization and that restenosis is still a major problem especially in this patient category. This is still a debate issue whether revascularization by means of PCI or CABG is to be preferred in patients with diabetes and multivessel disease. Stents and later DES, have been hailed to improve the outcome of PCIs in the diabetic patients^{1,2,9-11}.

Conclusion

The prevalence of diabetes is increasing worldwide. The number of people with cardiovascular morbidity will also increase. In addition, the risk of sudden death in diabetic patients without known heart disease is as high as the rate seen in nondiabetic subjects with a history of myocardial infarction. Thus, it is imperative that the efforts at treating this disease emphasize preventive approaches. Early screening and identification of risk factors, including testing for microalbuminuria, should be instituted. Earlier and more rigorous control of blood pressure may well be the most important therapeutic strategy. The goals of therapy have to be individualized, taking into account the patient's coexisting medical problems and ability to adhere to prescribed regimens. Overall, it appears that diabetic subjects would benefit from a more aggressive preventive program that sets more stringent standards. It is likely that achieving these goals is a challenging task. Nevertheless, these measures are bound to reduce the incidence of cardiovascular morbidity and mortality in a very high-risk group of people. In recent years, technical advances have resulted in greater capability for revascularization with PCI coupled with improved safety. In the current era of DES, DM remains an independent risk factor for restenosis. The results of ongoing randomized trials are awaited to inform us on the comparative efficacy of contemporary PCI and CABG in patients with diabetes. Finally, better risk factor control might decrease any difference between revascularization strategies.

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