Prevention and Management of Coronary Artery Disease in Patients with Diabetes Mellitus

Abdul Majid

Department of Physiology, Faculty of Medicine, University of Sumatera Utara-Adam Malik Hospital.
Jl. Bunga Lau no. 17, Medan, Sumatera Utara

Correspnodence mail to: *amajidleo@yahoo.com*

ABSRACT

Diabetes mellitus (DM) is a common medical problem and a major risk factor for the development of atherosclerotic coronary artery disease (CAD). Coronary artery disease is highly prevalent and is the major cause of morbidity and mortality in diabetic patients. Patients with CAD and prediabetic 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 recommended. Intense insulin therapy might be needed for glycemic control, and high-dose statin therapy might be needed for lipid control. For blood pressure control, ACE-Is and angiotensin receptor blockers are considered as first-line therapy. The outcomes 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 abciximab. Glycemic control is an important determinant of outcome after revascularization in diabetic patients. Improvements in PCI and coronary artery bypass graft surgery are leading to better results in diabetic patients, and clinical trials are presently comparing contemporary PCI with surgery.

Key words: *CAD, diabetes, risk factors, prevention, revascularization.*

INTRODUCTION

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; it is more pronounced in women than men. Patients with diabetes but no CAD have the same incidence of myocardial infarction (MI) as patients with CAD but no diabetes. Other risk factors such as hypertension, smoking, and hyperlipidemia 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. In this article, we will review the prevention and management of CAD in patients with diabetes.[1,2]

CAD PREVENTION IN DIABETIC PATIENTS

Screening for CAD in Diabetic Patients

Diabetes is commonly considered as a CAD risk equivalent .High-risk diabetic patients include those with typical or atypical symptoms, those 55 years of age or older, those with peripheral or carotid vascular disease, and those with 2 or more of the following risk factors: hyperlipidemia, hypertension, smoking, family history of premature CAD, microalbuminuria, and progressive retinopathy. Screening for CAD might be indicated in younger individuals, with a relatively short duration of DM and few risks 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 exercise stress testing and, as indicated, myocardial perfusion scintigraphy or stress echocardiography.[1,2,3,4]

Pharmacological Interventions to Prevent CAD in Diabetes

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.

Antiplatelet therapy. 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. The PROACTIVE study has shown that pioglitazone also seems to be beneficial but should be given carefully to patients with CAD to avoid ventricular dysfunction or heart failure.

Antihypertensive therapy. The current anti-hypertension treatment targets are <130/<80 mm Hg in diabetic patients (120/80 mm Hg after MI). 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), 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) substudy, 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). In the LIFE (Losartan Intervention For Endpoints) study 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 HPS and other trials, it is reasonable to target a LDL-C of 70 mg/dl for high-risk subjects such as diabetic patients.

CAD MANAGEMENT IN DIABETIC PATIENTS

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.[1,5-7]

Treatment Targets

Available treatment options, meant to preserve and optimize myocardial functions, achieve stabilisation of vulnerable plaques, prevent recurrent events by controlling prothrombotic activity, and to counteract progression of atherosclerotic lesions, are summerized in table 1. Evidence-based recommendations for secondary prevention are, in general terms, valid for patients 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 2, summarizing recommendations for secondary prevention on the basis of accumulated evidence, including data from recent guidelines and consensus documents. [1,2,6]

Table 1. Treatment options based on accumulated evidence[1]

Revascularization
Anti-ischaemic medication
Anti-platelet agents
Anti-thrombin agents
Secondary prevention by means of
    Lifestyle habits including food and physical activity
    Smooking cessation
    Blocking the renin-angiotensin system
    Blood pressure control
    Lipid-lowering medication
    Blood glucose control

Hyperglycemia and Acute Coronary Syndrome

Hyperglycemia, on admission in patients with acute coronary syndrome (ACS) is common, and it is a

Table 2. Recommended treament targets for patients with diabetes and CAD (modified from the European Guidelines for Cardiovascular Disease Prevention)[1]

Blood pressure (systolic/diastolic; mmHg)	< 130/80
In case of renal impairment,	
proteinuria > 1g / 24h	< 125/75
Glycemic control	≤ 6,5
HbA1c	
Glucose expressed as venous	
plasma mmol/L (mg/dL)	
Fasting	< 6,0
Post prandial (Peak)	< 7,5 (135) diabetes type 2
	7,5 – 9,0 (135 – 160) diabetes type 1
Lipid Profile expressed in mmol/L (mg/dl)	
Total cholesterol	< 4,5 (175)
LDL cholesterol	≤ 1,8 (70)
HDL cholesterol	
Men	> 1.0 (40)
Women	> 1,2 (> 46)
Triglycerides	< 1,7 (< 150)
TC/HDL	< 3
Smoking cessation	Obligatory
Regular physical activity (min/day)	> 30-45
Weight control	
BMI (kg/m^2)	< 25
In case of overweight, weight reduction (%)	10
Waist (optimum; ethnic spesific; cm)	
Men	< 94
Women	< 80
Dietary habits	
Salt intake (g / day)	< 6
Fat intake (% of dietary energy)	
Saturated	< 10
Trans-fat	< 2
Polyunsaturated n-6	4 – 8
Polyunsaturated n-3	2g / day of linolenic acid and 200 mg / day of very long chain fatty acids

powerful predictor of survival and increased risk of in-hospital complications in patients both with and without diabetes mellitus. [8]

AHA scientific statement recommend 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. *(Level of evidence A).*
2. In patients admitted to an ICU with ACS, glucose levels should be monitored closely *(Level of evidence B)*. It is reasonable to consider intensive glucose control in patients with significant hyperglycemia (plasma glucose > 180 mg/dl), regardless of prior diabetes history *(Level of evidence B)*.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 *(Level of evidence C)*.
3. Insulin, administered as an intravenous infusion, is currently the most effective method of controlling glucose among patients hospitalized in the ICU. *(Level of evidence B)*
4. In patients hospitalized in the non-ICU setting, efforts should be directed at maintaining plasma glucose levels <180 mg/dl, with subcutaneous insulin regimens. *(Level of evidence C)*.
5. ACS patients with hyperglycemia but without prior history of diabetes should have further evaluation. *(Level of evidence B)*.

Diabetes and Coronary Revascularization

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 heave a higher mortality and morbidity after CABG compared with non-diabetics, but this is also seen in patients undergoing PCIs.[1,9]

Surgery Versus Percutaneous Intervention

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 (BARI, CABRI, EAST, BARY

registry, ARTS, SoS, AWESOME studies). All studies mentioned still raise the question 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 management of CAD in diabetic patients poses a challenging problem. The risk factors need to be vigorously controlled with tight management of lipids and blood pressure. Strict control of hyperglycemia should be ensured.

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 on-going 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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