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Treating myocardial ischemia in diabetics: drugs, surgery, and stents

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Abstract

Diabetes mellitus (T2DM) is a chronic, progressively worsening disease associated with a variety of complications. Management of T2DM should take into account that coronary artery disease may be silent for many years in diabetic patients, and so both primary and secondary prevention must be a priority in the treatment of such disease. The management of chronic stable angina in patients with T2DM follows the same principles as those for patients without diabetes mellitus—controlling ischemic symptoms and reducing ischemic burden. To this end, treatment consists of medications combined with lifestyle modifications, the three main interventions being smoking cessation, regular moderate aerobic exercise, and correct nutrition. This article focuses on antianginal/anti-ischemic medications and myocardial revascularization procedures. Guidelines suggest use of β-blockers or calcium antagonists as first-line therapy for stable angina in T2DM. Nicorandil, ranolazine, and trimetazidine should be considered when first-line medications cannot be used or are insufficient. On the basis of findings from BARI-2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes), FREEDOM (Future REvascularization Evaluation in patients with Diabetes mellitus: Optimal Management of multivessel disease), and recent meta-analyses, coronary artery bypass grafting is considered the preferred coronary revascularization procedure in patients with T2DM and multivessel disease when reduction in clinical events is the main goal of treatment. ■ *Heart Metab*. 2017;73:13-17

Keywords: chronic angina; diabetes mellitus; therapeutic strategy

Introduction

Diabetes mellitus is a chronic, progressively worsening disease associated with a variety of complications. Over the last 2 decades, the decline in heart disease mortality in Western countries has not been paralleled by a similar trend in patients with diabetes mellitus. A reduction in cardiovascular risk factors and improvement in the treatment of heart diseases seem to be less effective in the diabetic population. Type 2 diabetes mellitus (T2DM) is an independent risk factor for atherosclerosis and future coronary artery disease. Diabetes mellitus is associated with a higher risk of coronary events and a two-to-fivefold increased risk of death.[1] Many patients with T2DM (from 17% to 59%, according to clinical studies) have silent myocardial ischemia on electrocardiography (ECG) stress testing, and a silent acute coronary syndrome occurs in 40% of cases. Management of T2DM should take into account that coronary artery disease is frequently silent for many years in diabetic patients. Thus, primary, as well as

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Abbreviations

BARI 2D: Bypass Angioplasty Revascularization Investigation 2 Diabetes [trial]; **CA:** calcium antagonist; **CABG:** coronary artery bypass grafting; **FREEDOM:** Future REvascularization Evaluation in patients with Diabetes mellitus: Optimal Management of multivessel disease; **OMT:** optimal medical therapy; **PCI:** percutaneous coronary intervention; **T2DM:** type 2 diabetes mellitus

secondary, prevention must be a priority in the treatment of such disease.[2]

The management of chronic stable angina in patients with T2DM follows the same principles as those for patients without diabetes mellitus, namely, controlling ischemic symptoms and reducing ischemic burden.[3,4] These objectives are reached by combining medications with lifestyle modifications based on three main interventions: smoking cessation, regular moderate aerobic exercise, and correct nutrition. Here, we focus on antianginal/anti-ischemic medications and myocardial revascularization.

Medications

To date, few specific trials have been published on the efficacy of antianginal agents in the diabetic population, and most information derives from subgroup analyses.

β-Blockers

Ischemic symptoms can be controlled by β-blockers. Large trials have shown that β-blockers are more effective in diabetic patients with myocardial infarction than in nondiabetic patients.[5] For instance, in the Göteborg Metoprolol trial, diabetic patients with myocardial infarction had a significantly greater relative risk reduction at 3 months than nondiabetic patients (58% vs 36% reduction; $P<0.05$). This trend was confirmed at 1-year follow-up.[6] β-Blockers are effective in reducing angina pectoris, increasing ischemic threshold during exercise, and improving work tolerance by reducing heart rate and double pressure product and myocardial oxygen (O_2) consumption at any work rate. β-Blockers are effective in hypertension, which is frequently associated with diabetic patients. They also prevent acute myocardial infarction and sudden death in diabetic patients with no previous myocardial infarction. These benefits overcome the negative effect of β-blockers on glycemic control and suggest the use of these medications in diabetic patients with stable angina. However, side effects, such as fatigue, depression, bradycardia, and sexual dysfunction may limit their use. Lipophilic agents, such as metoprolol, should be preferred in patients with renal dysfunction.

Calcium antagonists

The three major classes of calcium antagonists (CA) are the dihydropyridines (nifedipine, amlodipine, and felodipine), the phenylalkylamines (verapamil), and the modified benzothiazepines (diltiazem). They improve the balance of O_2 supply and demand and dilate blood vessels with a consequent reduction in blood pressure. These effects may explain the increasing use of CA in diabetics, especially those with concomitant hypertension, either as monotherapy or in combination with other agents.[7] Although some studies have shown a greater clinical efficacy of β-blockers, there are at present no significant differences in the rate of death or myocardial infarction as compared with CA.[8] However, their long-term administration has not been shown to improve survival in post–myocardial infarction patients. CAs are appropriate initial therapy in patients with contraindications to β-blockers or in combination when β-blockade monotherapy is unsuccessful.

Long-acting nitrates

Long-acting nitrates are widely used for preventing angina attacks in patients with stable angina with or without diabetes mellitus. They are potent vessel dilators, and this effect is predominant in the venous circulation, with subsequent reduction in preload, myocardial wall tension, and O_2 demand. This effect depends on the conversion of nitrates to nitric oxide, which activates guanylate cyclase to produce cyclic guanosine monophosphate (cGMP) and smooth muscle relaxation. Nitrate tolerance is less frequent when a daily interval is maintained. The antianginal effect appears to be greater when nitrates are combined with CA and/or β-blockers.[8]

Ranolazine

Ranolazine was recently approved as antianginal medication in stable angina.[9] Its efficacy depends on

two mechanisms, a metabolic effect of inhibition of fatty acid β-oxidation and a reduction in calcium overload in ischemic myocytes through inhibition of the late inward sodium current.[10] A recent trial showed that a dose of 1000 mg twice a day for 8 weeks significantly reduced the number of weekly angina attacks by 13% (*P*=0.008) and weekly sublingual nitroglycerin use by 23.5% (*P*=0.003) as compared with placebo.[11] Because of its effect in prolongation of the QT interval, ranolazine is contraindicated in patients with long-QT syndrome or in combination with other QT-prolonging drugs, such as amiodarone, sotalol, and other noncardiovascular active agents.

Ivabradine

Ivabradine decreases heart rate by a selective inhibitory effect on funny-current (I_f) channels of the sinoatrial node, without any effect on glucose metabolism or adrenergic activity. It has been approved in Europe for the treatment of patients with stable angina with or without diabetes who do not tolerate β-blockers or in those who are inadequately controlled with an optimal dose of a β-blocker.[12]

Nicorandil

Nicorandil dilates peripheral and coronary vessels through its action as an adenosine triphophate (ATP)-sensitive potassium-channel opener and nitric oxide donor. As a result, nicorandil reduces preload and afterload and vasodilates coronary arteries. Its antiischemic efficacy has been demonstrated in a trial studying 5126 patients with stable angina, with a significant improvement in outcome owing to a reduction in major coronary events in patients.[13] However, in that study, less than 10% of patients had diabetes mellitus.

Trimetazidine

Trimetazidine is a piperazine derivative with antianginal efficacy. Trimetazidine at doses of 20 mg three times a day or 35 mg twice a day improves the ischemic threshold during exercise and reduces the number of angina attacks and sublingual nitroglycerin use as compared with placebo. This beneficial effect is related to inhibition of β-oxidation requiring five times more O_2 than glucose oxidation, which is consequently accelerated. This results in a more efficient ATP production by ischemic myocytes and a subsequent greater contractility, translating into better left ventricular function.[14] Trimetazidine has no effect on glucose homeostasis, and its efficacy is predominant in diabetic patients with reduced left ventricular efficiency.

In summary, guidelines suggest use of β-blocker or CAs combined as first-line therapy for stable angina in T2DM. Nicorandil, ranolazine, trimetazidine, ivabradine, and long-acting nitrates should be con-

Medications	Mechanism	CV benefits	Side effects
β-Blockers	↓ O_2 demand ↓ Myocardial contractility	↑ Ischemic threshold ↓ Angina attacks ↑ Work tolerance	Bradycardia ↑ Blood glucose Depression Sexual dysfunction
Calcium antagonists	↓ O_2 demand ↑ O_2 supply	↑ Ischemic threshold ↓ Angina attacks ↑ Work tolerance	Bradycardia/tachycardia Leg edema
Nitrates	↓ O_2 demand ↑ O_2 supply	↑ Ischemic threshold ↓ Angina attacks ↑ Work tolerance	Headache Hypotension
Ranolazine	Late Na-channel inhibitors β-Oxidation inhibition	↓ Angina attacks	GI side effects QT prolongation
Trimetazidine	β-Oxidation inhibition	↑ Ischemic threshold ↓ Angina attacks ↑ Work tolerance	GI side effects
Ivabradine	I_f-channel inhibitors	↑ Ischemic threshold	Bradycardia
Nicorandil	ATP-channel opening NO donor	↑ Ischemic threshold ↓ Angina attacks	Hypotension

Table I *Medications to treat stable angina in patients with type 2 diabetes mellitus.*
Abbreviations: *ATP, adenosine triphosphate; CV, cardiovascular; GI, gastrointestinal; Na, sodium; NO, nitric oxide; O_2, oxygen*

sidered when first-line medications cannot be used or are insufficient. Mechanisms, cardiovascular benefits, and side effects of medications to treat stable angina in patients with T2DM are shown in *Table I*.

Coronary revascularization

In patients with T2DM and stable angina, the therapeutic strategy should focus on combining improvement in functional capacity and quality of life with reduction in cardiovascular events and life prolongation. These objectives are obtained with a combination of medications, lifestyle changes, and reduction in reversible cardiovascular risk factors. Revascularization approaches should be considered when optimal medical therapy (OMT) alone is insufficient to control symptoms and a patient is at-risk of cardiovascular events due to the severity and extent of coronary artery disease.[15,16] Recommendations for percutaneous coronary intervention (PCI; a nonsurgical intervention that may involve stent implantation) or coronary artery bypass grafting (CABG; a surgical intervention) should be based on both the severity and extent of inducible myocardial ischemia, the severity of symptoms and their control by pharmacological and nonpharmacological tools, and functional deterioration. On the basis of the BARI trial (Bypass Angioplasty Revascularization Investigation) results, patients with T2DM treated with percutaneous transluminal coronary angioplasty (PTCA) had a 5-year mortality of 35% vs 19% for those who underwent CABG (P=0.003).[17] At 10 years, the superiority of CABG was more evident. On the basis of the findings from BARI 2D (BARI 2 Diabetes), FREEDOM (Future REvascularization Evaluation in patients with Diabetes mellitus: Optimal Management of multivessel disease), and recent meta-analyses, CABG is considered the preferred coronary revascularization procedure in patients with T2DM and multivessel coronary artery disease when reduction in clinical events is the main goal of treatment.[18,19] In patients with angina not considered at high risk, survival is similar for surgery, PCI, and OMT. In patients with single-vessel disease in whom revascularization is necessary, PCI is preferable to CABG.

Conclusion

The management of chronic stable angina in patients with T2DM follows the same principles as those for patients without diabetes mellitus, namely, controlling ischemic symptoms and reducing ischemic burden. These objectives are reached through the combination of medications and lifestyle modifications, the three main interventions being smoking cessation, regular moderate aerobic exercise, and correct nutrition. According to guidelines, a combination of β-blockers and CAs should be considered as first-line therapy for stable angina in T2DM. Nicorandil, ranolazine, trimetazidine, ivabradine, and long-acting nitrates should be considered when first-line medications cannot be used or are insufficient. Revascularization approaches should be considered when OMT alone is insufficient to control symptoms and a patient is at-risk of cardiovascular events due to severity and extent of coronary artery disease. Recommendations for PCI or CABG should be based on both the severity and extent of inducible myocardial ischemia, the severity of symptoms and their control by pharmacological and nonpharmacological tools, and functional deterioration. ■

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