Editorial on management of diabetes mellitus with coronary artery disease

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The review article by Athyros *et al*. [1] is an excellent review article. I concur with the issues discussed by the authors. This editorial discusses my current approach to the management of patients with diabetes mellitus and coronary artery disease (CAD).

Patients with diabetes mellitus and CAD should be treated with optimal medical management. All modifiable risk factors should be treated. Patients should be strongly encouraged to stop smoking and be referred to a smoking cessation program.

Hypertension should be treated with the blood pressure reduced to < 140/90 mmHg [2]. The initial drug of choice should be an angiotensin-converting enzyme (ACE) inhibitor [2].

The Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction (PROVE IT-TIMI) 22 trial enrolled 4,162 patients with an acute coronary syndrome (acute myocardial infarction with or without ST-segment elevation or high-risk unstable angina pectoris) [3]. The lowest cardiovascular events rates occurred with a systolic blood pressure between 130 mmHg to 140 mmHg and a diastolic blood pressure between 80 mmHg to 90 mmHg with a nadir of 136/85 mmHg. An observational subgroup analysis was performed in 6,400 of the 22, 576 persons enrolled in the International Verapamil SR-Trandolapril Study (INVEST) who had diabetes and CAD [4]. Persons were categorized as having tight control of blood pressure if they could maintain their systolic blood pressure below 130 mmHg and their diastolic blood pressure below 85 mm Hg, usual control if they could maintain their systolic blood pressure between 130 mmHg to 139 mmHg, and uncontrolled if their systolic blood pressure was 140 mmHg or higher.

During 16,893 patient-years of follow-up, a cardiovascular event rate of 12.6% occurred in patients with usual control of blood pressure vs. 19.8% in patients with uncontrolled hypertension, $p < 0.001$. The incidence of cardiovascular events was 12.6% in patients with usual control of blood pressure vs. 12.7% in patients with tight control of blood pressure. The all-cause mortality rate was 11.0% with tight control of blood pressure vs. 10.2% with usual control of blood pressure ($p = 0.06$). When extended follow-up was included, the all-cause mortality rate was 22.8% with tight control of blood pressure vs. 21.8% with usual control of blood pressure, $p = 0.04$.

Dyslipidemia should be treated. The serum low-density lipoprotein cholesterol should be reduced to < 70 mg/dl [5-7].

Diabetes mellitus should be treated with the hemoglobin A_{1c} reduced to < 7.0%. Hypoglycemia must be avoided in patients with CAD. In 10, 251

high-risk diabetics in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study, patients randomized to intensive treatment reached a hemoglobin A_{1c} of 6.4%, and patients randomized to conventional treatment reached a hemoglobin level of 7.5% [8]. At 3.5-year follow-up, intensive therapy increased mortality 22% from 4.0% to 5.0% (p = 0.04) and did not significantly reduce major cardiovascular events.

Obese diabetics with CAD must lose weight by dietary therapy and by aerobic physical activity. They should exercise for at least 30 min daily for 7 days per week with a minimum of 5 days of physical exercise per week [9].

Diabetics with CAD should be treated with aspirin, ACE inhibitors, β-blockers, and statins to reduce cardiovascular events and mortality and coronary revascularization [6, 9-13]. Angina pectoris should be treated with β-blockers and nitrates [14]. If angina persists, I would add a calcium channel blocker, and if needed, ranolazine.

In the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial, of 2, 248 patients with stable CAD randomized to optimal medical therapy plus percutaneous coronary intervention (PCI) vs. optimal medical therapy alone, 766 patients (34%) had diabetes mellitus, and 1,362 patients (61%) had the metabolic syndrome [15].

At 4.6-year median follow-up, the risk of death or myocardial in infarction in patients with diabetes mellitus and in patients with the metabolic syndrome was similar in patients with and without early PCI. On the basis of these data, I would not recommend early PCI to patients with diabetes mellitus or the metabolic syndrome who have stable CAD.

In the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial, 2,368 patients with diabetes mellitus and CAD were randomized to undergo either prompt coronary revascularization with intensive medical therapy or intensive medical therapy alone and to undergo either insulin-sensitization or insulin-provision therapy [16]. Randomization was stratified according to the choice of PCI or coronary artery bypass grafting (CABG). At 5-year follow-up, survival was 88.3% for the coronary revascularization group and 87.8% for the medical therapy alone group (p not significant) and 88.2% for the insulin-sensitization group and 87.9% for the insulin-provision group (p not significant). The incidence of freedom from major cardiovascular events was also not significantly different between the coronary revascularization and medical therapy alone groups and between the insulin-sensitization and insulin provision groups. In the PCI stratum, the primary endpoints of death and of death or major cardiovascular events were similar in the PCI and medical therapy alone groups. However, in the CABG stratum, the incidence of death or myocardial infarction or stroke was 22.4% in the CABG group vs. 30.5% in the medical therapy alone group (p = 0.01) [16].

In the BARI 2 D trial, 1,191 patients were randomized to optimal medical therapy alone and 1,173 patients to coronary revascularization with 796 patients preselected for PCI and 377 patients to CABG [17]. Compared with the medical therapy group alone, at 3-year follow-up, the coronary revascularization group had a lower incidence of worsening angina pectoris (8% vs. 13%, $p < 0.001$), a lower incidence of new angina pectoris (37% vs. 51%, p = 0.001), a lower incidence of subsequent coronary revascularization (18% vs. 33%, $p < 0.001$), and a higher incidence of angina-free status (66% vs. 58%, p = 0.003). The CABG patients were at higher risk than the PCI patients and had the greatest benefits from coronary revascularization. The symptomatic benefits were observed particularly for high-risk patients.

These data favor optimal medical therapy alone in patients with diabetes mellitus and stable CAD. However, if disabling angina pectoris despite optimal medical therapy occurs, I would recommend coronary revascularization. In high-risk patients, I would recommend CABG over PCI at this time. At 10.4-year follow-up of diabetics with CAD in the BARI trial, the CABG group had a survival rate of 57.8% vs. 45.5% for the PCI group (p = 0.025) and a subsequent coronary revascularization incidence of 20.3% for the CABG group vs. 76.8% for the PCI group ($p < 0.001$) [18].

On the basis of the available data, I would treat patients with diabetes mellitus and ST-segment elevation myocardial infarction [19] or unstable angina/non-ST-segment elevation myocardial infarction [20] with coronary revascularization with the choice of PCI or CABG depending on the coronary angiographic findings. The blood sugar in these patients should have a target goal between 140-180 mg/dl. Diabetics who have received stents should be treated with dual antiplatelet therapy for at least 1 year after PCI and preferably longer.

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