President's Page

The Treatment of Stable Coronary Artery Disease in Diabetics: The Battle Between "Conservative" and "Invasive" Continues

Vlassis N. Pyrgakis

Department of Cardiology, "G. Gennimatas", Hospital, Athens, Greece

Diabetes mellitus (DM) and cardiovascular disease are nowadays considered to be two sides of the same coin. Patients with type 2 DM are at clearly higher risk (2-4 times) of cardiovascular events and death compared with non-diabetics.[1-4]

In patients with stable coronary artery disease (CAD) and type 2 DM there are two important questions that have gone begging for years now: 1) What is the best strategy for the treatment of ischaemia, which is known to be the main cause of death in diabetics with CAD? 2) What should be the treatment for insulin resistance, the basic mechanism underlying DM that is accompanied by cardiovascular complications?[5,6]

Recently, the results of the BARI 2D trial were announced.[7] This study was designed to seek answers to the following specific questions: a) to what extent do anti-diabetic insulin-sensitising drugs (metformin and thiazolidinediones) stop or slow the development of atherosclerotic CAD compared to insulin-providing medication (sulfonylureas, insulin); and b) to what degree can reperfusion in diabetics reduce mortality and cardiovascular events compared to medical treatment? The study randomised 2368 patients with type 2 DM and stable CAD along two axes:

- either prompt reperfusion or intensive medical therapy.
- control of DM with either insulin-sensitisation or insulin-provision therapy.

The choice of reperfusion method—percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG)—was made by the treating physician for each individual patient. The patients in the medication arm were treated according to current guidelines to a target glycated haemoglobin of <7%, low-density lipoprotein (LDL) cholesterol <100 mg/dL and blood pressure <130/80 mm Hg. Revascularisation was only performed in this group if there was worsening of angina, ischaemia, or acute coronary syndrome. The primary endpoint was death from any cause, with a secondary composite endpoint that included death, myocardial infarction and stroke. The mean follow-up duration was 5.3 years.

Results

- 42% of patients randomised to the medication arm needed to undergo reperfusion during the 5-year follow up.
- No statistically significant difference was found in 5-year survival or incidence of cardiovascular events between patients receiving insulin-sensitisation or insulin-provision therapy.
- No statistically significant difference was found in 5-year mortality between patients who were treated with medication (12.2%) and those who received prompt reperfusion (11.7%, p=0.97).
- The 5-year survival was similar for the PCI and CABG groups.
- Patients who underwent CABG had slightly lower 5-year mortality than patients treated with medication (13.6% versus 16.4%, respectively; p=0.33), but had a significantly lower incidence of the secondary endpoint (22.4% versus 30.5%; p=0.01). Most of the difference was due to the smaller number of infarctions (7.4% versus 14.6%).

- There was no difference in the secondary endpoint between patients who underwent PCI and those treated with medication.

The cardiological viewpoint

The BARI 2D trial failed to show any superiority for the strategy of prompt reperfusion with PCI or CABG compared with medical treatment, in terms of either mortality or major cardiovascular events, in patients with type 2 DM and stable CAD. The only patients who benefited from this strategy were those with extensive CAD who underwent CABG. Even in those cases, however, there was no difference in mortality, but only in cardiovascular events, mainly infarction. This may be the first time that a randomised study has shown that CABG can reduce the incidence of non-fatal infarction.

The results of BARI 2D reinforce the findings of the COURAGE trial,8 and show that many diabetic patients can be treated safely (at least initially) using optimum medication. However, in patients who show a large ischaemic burden, or a "high risk" anatomy for coronary lesions (e.g. left main or 3-vessel disease), it is preferable for them to undergo CABG (rather than PCI) in order to reduce the likelihood of future cardiovascular events.

The cardioprotective superiority of CABG over PCI could be explained by the fact that the placing of grafts in the mid-coronary vessels not only results in treatment of the culprit lesions, but also affords prophylaxis against new proximal disease, whereas stents treat only stenotic lesions that are suitable for PCI, without offering any protection against native coronary disease progression.[9]

References

1. The Bypass Angioplasty Revascularization Investigation (BARI) Investigators. Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease. N Engl J Med. 1996; 335: 217-215.
2. Geiss LS, Herman WH, Smith PJ. Mortality in non-insulin-dependent diabetes. In: Aubert RE, Ballard DJ, Barrett-Connor E, et al, editors. Diabetes in America, 2nd ed. Bethesda, MD: National Institute of Diabetes and Digestive and Kidney Diseases; 1995. p. 233-257. (NIH publication no. 95-1468.)
3. Mak KH, Moliterno DJ, Granger CB, et al. Influence of diabetes mellitus on clinical outcome in the thrombolytic era of acute myocardial infarction. J Am Coll Cardiol. 1997; 30: 171-179.
4. Malmberg K, Yusuf S, Gerstein HC, et al. Impact of diabetes on long-term prognosis in patients with unstable angina and non-Q-wave myocardial infarction: results of the OASIS (Organization to Assess Strategies for Ischemic Syndromes) Registry. Circulation. 2000; 102: 1014-1019.
5. Du X, Edelstein D, Obici S, Higham N, Zou MH, Brownlee M. Insulin resistance reduces arterial prostacyclin synthase and eNOS activities by increasing endothelial fatty acid oxidation. J Clin Invest. 2006; 116: 1071-1080.
6. Reaven GM. Banting Lecture 1988: role of insulin resistance in human disease. Diabetes 1988; 37: 1595-1607.
7. The BARI 2D Study Group. A randomized trial of therapies for type 2 diabetes and coronary artery disease. N Engl J Med; 2009; 360: 2503-2515.
8. Boden WE, O'Rourke RA, Teo KK, et al. COURAGE Trial Research Group. Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med; 2007 356: 1503-1516.
9. Taggart DP. PCI or CABG in coronary artery disease? Lancet. 2009; 373: 1150-1152.