A Randomized Trial of Therapies for Type 2 Diabetes and Coronary Artery Disease


Conclusions: In patients with type 2 diabetes and stable coronary artery disease (CAD), a strategy of prompt revascularization with intensive medical therapy is no better than intensive medical therapy alone with respect to rates of death, myocardial infarction, or stroke.

Summary: The Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial assessed treatment strategies in patients with CAD and compared the effects of coronary revascularization in patients with type 2 diabetes and the uncertainty of how to deliver glycemic control in such patients, the authors evaluated two cardiac treatment strategies and two glycemic treatment strategies in patients receiving glycemic control and intensive therapy for stable CAD. There were two hypotheses. The first was that prompt revascularization would reduce long-term rates of death and cardiovascular events compared with medical therapy alone. The second was that insulin-sensitization with a targeted hemoglobin A1c level of <7.0% would reduce cardiovascular events and death compared with a strategy of insulin-provision.

There were 2,368 patients with type 2 diabetes and CAD assigned to undergo prompt revascularization with intensive medical therapy or intensive medical therapy alone and to receive either insulin-provision strategy or insulin-sensitization therapy. Primary end points were rates of death, a composite of death and myocardial infarction, or stroke. Randomization was stratified according to whether percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) was considered the most appropriate intervention for the patient's CAD.

At 5 years, survival rates did not differ between the revascularization groups (88.3%) and the medical therapy alone group (87.8%, P = .97). Furthermore, survival rates did not differ between the insulin-sensitization group (88.2%) and the insulin-provision group (87.9%, P = .89). Freedom from major cardiovascular events was not different in the revascularization group (77.2%) vs the medical therapy group (75.9%, P = .70). There was also no difference in freedom from major cardiovascular events in the insulin-sensitization group (77.7%) vs the insulin-provision group (75.4%, P = .13). In the patient stratum of PCI, there was no significant difference between the revascularization group and the medical therapy group in the rates of the primary end points. In the CABG stratum, the rate of major cardiovascular events was 80.5% in the medical therapy group vs 22.4% in the revascularization group (P = .01). Serious adverse events and adverse events were similar among groups, with the exception that severe hyperglycemia was more frequent in the insulin-provision group than in the insulin-sensitization group (9.2% vs 5.9%, P = .003).

Comment: The results of this study once again highlight the difficulty of achieving improvement in cardiovascular event rates in patients with type 2 diabetes. Previous studies have shown tight glycemic control does not improve cardiovascular event rates in patients with type 2 diabetes (N Engl J Med 2008;358:2560-72; N Engl J Med 2008;358:2545-59). This study indicates prompt revascularization in patients with type 2 diabetes also treated with intensive medical therapy does not improve rates of death from any cause or major cardiovascular event rates. In patients in whom CABG would be the preferred treatment of revascularization, CABG does appear able to reduce major cardiovascular event rates compared with medical therapy alone. However, if coronary angioplasty was felt to be the revascularization method of choice, it did not improve death in major cardiovascular event rates compared with medical therapy alone. It appears the era of the “occlusal stenotic reflex” for coronary artery angioplasty is drawing to a close. It needs to draw to a close for lesions in other vascular beds as well.

C-Reactive Protein-Bound Enzymatically Modified Low-Density Lipoprotein Does Not Transform Macrophages into Foam Cells


Conclusions: C-reactive protein (CRP) can prevent the formation of foam cells and may influence atherosclerosis.

Summary: Atherosclerosis is a complicated process that appears to begin when low-density lipoprotein (LDL) enters an arterial wall. Trapped LDL is sensitive to modifications such as enzymatic proteolysis and oxidation. When LDL is enzymatically modified (E-LDL), it can be engulfed by macrophages to form foam cells that subsequently contribute to the development of atherosclerosis. One strategy of decreasing atherosclerosis is therefore to capture and inactivate LDL, thereby preventing the formation of macrophage foam cells. CRP is a pentameric protein made of five identical 23,028 Dalton subunits.

Each subunit has a phospholipase binding site. Amino acids in the phospholipase binding site of CRP are Phe66 and Glu81. The phospholipase binding site of CRP participates in bonding of CRP to modified forms of LDL.

This study of CRP-LDL interactions specifically focused on the formation of macrophage foam cells by unbound and CRP-bound LDL. The authors found phospholipase inhibited interactions between CRP and E-LDL, implying involvement of the phospholipase binding site of CRP in binding to E-LDL. The amino acids Phe66 and Glu81 were not required for CRP-E-LDL interaction. Blocking the CRP phospholipase binding site with phosphoethanolamine increased the binding of CRP to E-LDL. CRP-bound E-LDL did not transform macrophages into foam cells, whereas free E-LDL did transform macrophages into foam cells. Blocking the binding of phosphoethanolamine inhibited the formation of foam cells by CRP. CRP in eliminating the ability of E-LDL to form foam cells was not impaired by phosphoethanolamine.

Comment: The data lead to two conclusions: First, phosphoethanolamine can potentiate the binding of CRP to enzymatically modified LDL. This can increase the efficiency of CRP to prevent the transformation of macrophages into LDL foam cells. The authors’ findings also suggest that CRP is present in sufficient amounts in an arterial wall and that each LDL molecule entering the arterial wall is bound to CRP, it may be able to prevent foam cell formation and thereby provide a targeting method to prevent atherosclerosis.

Comparison of Interventions According to Preoperative Indication: A Single Center Analysis of 2,240 Limb Revascularizations


Conclusion: Patients undergoing leg revascularization with tissue loss have significantly worse outcomes than those patients undergoing leg revascularization for ischemic rest pain.

Summary: The authors correctly point out that frequently in an analysis of revascularizations for critical limb ischemia (CLI), patients with tissue loss and ischemic rest pain are combined in the analysis. The authors hypothesize that combining such patients for assessment of both graft-related and patient-related outcomes may be inappropriate in that one group may fare worse than the other. Rather than stratify their results according to the level of peripheral arterial disease such as aortoiliac or infragenual, or the method of revascularization—open vs endovascular surgery—they sought to stratify results according to indication for procedure: classification of ischemic rest pain, and tissue loss. They evaluated the outcomes of 2,240 consecutive limb revascularizations in 1732 patients from January 1998 through December 2005. The patients were stratified and examined according to preoperative indication—claudication (990 limbs), ischemic rest pain (464 limbs), or tissue loss (777 limbs). Their end points included primary and secondary interventional or operative patency, limb salvage, amputation-free survival, maintenance of independence, maintenance of ambulation, and resolution of presenting symptoms. There was a mean follow-up of 1089 days (range, 0-3689 days).

Overall outcomes at 5 years declined according to indication for intervention—claudication, rest pain, or tissue loss—for all end points measured, including secondary reconstruction patency (98%, 80%, 66%, respectively; P < .001), limb salvage (99%, 81%, 68%, respectively; P < .001), survival (78%, 46%, 30%, respectively; P < .001), amputation-free survival (78%, 42%, 25%, respectively; P < .001), maintenance of independence (98%, 85%, 75%, respectively; P < .001), and resolution of presenting symptoms (79%, 61%, 42%, respectively; P < .001).

Comment: The authors chose an unusual method of analyzing their results, by lowering extremities to a venous graft, or tissue loss and systemic disease. Nevertheless, the article would have been strengthened by a more proper statistical analysis, stratifying patients according to method of revascularization (endovascular, autogenous vein, or prosthetic grafts) and level of revascularization (aortoiliac, femoropopliteal, or infrapopliteal). As written, the results are useful for analyzing the practice pattern at the authors’ institution, but without proper multivariable analysis, the results cannot be extrapolated to other institutions where practice patterns likely differ.