Revascularization Trumps Medicine for Patients With Type 2 Diabetes Mellitus and Chronic Angina (or Does It?)

Steven P. Marso, MD

Chronic angina is the most common clinical manifestation of ischemic heart disease, affecting as many as 54 million people globally1 and over 10 million people in the United States.2 The prevalence of angina varies by region, and tends to affect more women than men. Although difficult to quantify, the lifetime cost of managing chronic angina approaches 1 million dollars.3

The explicit goals of therapy for managing chronic angina are to prevent major cardiovascular complications, namely nonfatal myocardial infarction/vascular death, and improve quality of life.4 Both the Canadian Cardiovascular Society (CCS) classification and the Seattle Angina Questionnaire (SAQ) are frequently used in both clinical trials and practice to quantify angina severity. Although common and simple to administer, CCS is relatively insensitive in discriminating angina severity, which limits its usefulness in evaluating therapeutic efficacy and quantifying patients’ functional status. The SAQ is a patient-assessed questionnaire used to quantify 5 domains: physical limitation, change in angina symptoms, angina frequency, treatment satisfaction, and quality of life.5

In this issue of Circulation, Dagenais et al from the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) study group report on the effectiveness of an initial strategy of optimal medical therapy with coronary revascularization versus optimal medical therapy alone in treating angina among patients with type 2 diabetes mellitus and ischemic heart disease.6 This planned substudy was designed to evaluate angina and quality of life in the 2368 such patients from BARI 2D (http://www.clinicaltrials.gov/ct2/show/NCT00006305).7 As previously reported, the main study findings demonstrated no significant differences in serious adverse cardiovascular events, including death, nonfatal myocardial infarction, or stroke at 5 years between revascularization or medical therapy alone.

In the present analysis, initial coronary revascularization was superior to medical therapy in maintaining freedom from angina, preventing new-onset angina, and arresting worsening angina in patients with type 2 diabetes during 3 years of follow-up. Differences between the revascularization and medical therapy groups were striking during the first year after randomization, but diminished over time. During year 1, the medical therapy group was 60% more likely to progress in CCS angina class and 100% more likely to develop new-onset angina in patients without angina at baseline. The revascularization group also had a significantly lower need for subsequent revascularization that persisted over time.

Both the magnitude and durability of benefit was noticeably greater in patients undergoing coronary artery bypass grafting (CABG) than percutaneous coronary intervention (PCI), a relationship also apparent in other studies. The Stent or Surgery (SoS) trial assessed health status using the SAQ in patients randomized to multivessel stenting or CABG.8 Both strategies improved health status at 6 and 12 months. Although angina was less frequent at 6 months in the CABG group, the difference remained statistically significant but not likely clinically meaningful at 1 year. Comparable to other quality-of-life studies, the health status of both the stent and CABG patients continued to improve over time, such that at 1 year there was no difference in measures of quality of life. The results of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial9 mirror those of BARI 2D in many ways. Over 2000 patients, including 78% with symptoms of angina at enrollment, were randomized in COURAGE to medical therapy with or without PCI. There were no differences in death or myocardial infarction rates during median follow-up of 4.6 years. However, there were improvements in angina as assessed by the SAQ in both the PCI and medical therapy groups. At 6 months, freedom from angina was greater in PCI-treated than in medical therapy patients. As in BARI 2D, 2 patterns occurred over time. First, there was a steady improvement in quality of life in both groups. Second, the magnitude of benefit initially seen in the PCI group diminished over time.

Recognizing that CCS is an insensitive tool to quantify angina, the majority of BARI 2D patients had minimal or no documented symptoms at enrollment. Among the total group, 42% had CCS class I (no angina during ordinary activity, only with strenuous or prolonged exercise) or II (slight angina with ordinary activity such as walking 2 blocks), 18% had no documented angina, and 21% had anginal equivalent symptoms. Although these findings seem uncharacteristically low, they are consistent with other angina studies. However, the severity of angina in less exclusive clinical registries is greater, and, in fact, 10% demonstrate symptoms of refractory ischemia.4 In essence, the use of an insensitive tool to discriminate angina in a population with a paucity of symp-
toms would be expected to bias the results toward the null hypothesis. Yet, in BARI 2D, coronary revascularization was associated with a significant improvement.

Even though the overall findings from Dagenais and colleagues showed PCI to be superior to medical therapy, the debate on the relative merits of initial revascularization in low-risk stable angina patients with type 2 diabetes will certainly continue, perhaps for good reason, as there are important unsettled issues.

First, how does one establish a clinically meaningful difference in angina severity? Although this has been a focus for health-status investigators, defining clinically meaningful is challenging, and requires the use of arbitrary cut points in health-status assessment tools. After caring for patients with complex ischemic heart disease for over a decade, I have come to the conclusion that a clinically meaningful difference varies materially between patients. Angina frequency, severity, or impact on activity is likely valued differently for individual patients. Occasional patients appear to do very well, and thrive despite frequent episodes of stable angina. Others are hindered by even infrequent episodes, which seem to limit activity and quality of life. Whereas some angina assessment tools are sensitive and responsive to therapy, the particular health-status domains, such as those measured by the SAQ, and corresponding changes within each domain between baseline health status and follow-up that defines a clinically meaningful difference have yet to be established.

The second issue is understanding the factors driving the late catch up in the control population over time. A number of studies, including SoS, COURAGE, and BARI 2D, have demonstrated this pattern (ie, diminished effect size between therapies) in angina patients over long-term follow-up. This appears to be driven by improvement in the control population rather than decremental benefit of active treatment. There are several potential biologically plausible explanations at play here. Angina symptoms often wane over time for patients with diabetes mellitus. It is uncertain whether this is partially due to the development of necrosis in regions of prior ischemia, ischemic preconditioning, self-imposed activity restriction to limit symptom severity, or expected lag time before medications attenuate or resolve angina. Lastly, there is significant crossover from medical therapy to revascularization in patients with the most symptoms. This was particularly evident in BARI 2D, where 38% of patients in the medical therapy arm crossed over to revascularization by 12 months.

Should physicians base individual treatment decisions on the cost effectiveness of therapies? Though necessary in the broader discussion of healthcare policy, it seems appropriate- ness should be largely predicated on the safety and efficacy of therapies rather than cost effectiveness. Nevertheless, the cost effectiveness of revascularization versus medical therapy in BARI 2D has been reported. Specifically, there were significantly greater study costs for revascularization compared with medical therapy ($80 900 versus 60 600). In the PCI cohort, the difference was less ($73 400 versus 67 800; P=0.02). Given that trial costs are an imperfect measure because they primarily reflect initial costs, it is reasonable to estimate lifetime cost to account for future benefit. In BARI 2D, the projected lifetime costs were similar, and, in fact, medical therapy costs were slightly higher ($238 100 versus $237 900). Therefore, the lifetime costs would be expected to be similar between the 2 strategies in patients with diabetes mellitus.

On what criteria (efficacy, durability, patient preferences, cost) should physicians ultimately base this important decision? According to American College of Cardiology/Society for Cardiovascular Angiography and Interventions/American Heart Association appropriate use criteria (AUC) for coronary revascularization, PCI is classified as inappropriate for patients with CCS class I or II on minimal or no anti-ischemic medical therapy. Although the AUC authors acknowledge that the criteria are intended to provide guidance for patients and clinicians and are not intended to supplant clinical experience and judgment, they also point out that for CCS class I and II patients (inappropriate indication), it is unlikely that an initial PCI strategy is better than medical therapy even in a rare patient. A trial of initial medical therapy is deemed less important in establishing AUC in patients with CCS class III and IV angina. Recognizing that stable ischemic heart disease represents a continuum of disease severity, patients form BARI 2D certainly tended to be on the most stable side of the spectrum. As noted, PCI was associated with superior improvements in angina symptoms without an increased risk, and the projected lifetime expenses were cost neutral. These results from BARI 2D seem particularly relevant to help inform future AUC for revascularization in stable angina patients with type 2 diabetes mellitus. If shared decision making is valued, it would be inappropriate for physicians not to include coronary revascularization in the discussion of treatment options for relief of chronic angina in patients with type 2 diabetes mellitus.

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References


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