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Appropriate Treatment for CAD

This *Heartbeat* will review recent studies and guidelines on treating patients with coronary artery disease (CAD), attempting to resolve the controversy about the best way to optimize outcomes in a cost effective way.

Medical Therapy vs Revascularization?

The answer is complex and must be based on the current available data and the individual case; it will also require some information gathering and joint decision-making by patient and doctor.

Cardiovascular disease (CVD) and stroke mortality has decreased dramatically during the past 30 years. Most of this improvement has been attributed to lifestyle changes and medical therapy to reduce CV risk factors. About 7% of the survival benefit has been attributed to coronary revascularization with coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI). Randomized trials in the 1970s and 1980s demonstrated improved survival in selected subgroups of high-risk patients who were treated with CABG compared with those treated with the medical therapy of that era. These subgroups included patients with significant stenosis of the left main coronary artery, decreased left ventricular (LV) function and either three-vessel or two-vessel disease involving the proximal left anterior descending (LAD) coronary artery. Subsequently, this data was extrapolated to other lower-risk subgroups, in the belief that these subgroups would also have improved outcomes with revascularization.

Until 2002, clinical practice guidelines strongly recommended PCI or CABG for symptomatic or asymptomatic patients who have one- or two-vessel CAD and whose noninvasive test results indicate high-risk of death. Subsequent guidelines have been more cautious, but still have recommended PCI or CABG as probably effective for reducing events.

Despite increasing evidence supporting plaque instability as the proximate cause of CAD events, treatment strategies have continued to focus on anatomic stenosis. This preoccupation with coronary luminology causes physicians to perform stress tests and angiograms to identify flow-limiting lesions even in asymptomatic patients and to "fix" the obstruction by PCI or CABG.

Two recent studies focusing on PCI have challenged the assumption that revascularization improves patient outcomes in many patients with multivessel CAD. *An important caveat here is that all of the patients in these studies had coronary visualization to exclude left main and severe triple vessel disease.*

The **O**ccluded **A**rtery **T**rial **(OAT)** enrolled 2,166 patients who had infarct-related occlusion of a coronary artery early after myocardial infarction (MI) and met at least one additional high-risk criterion, such as LV dysfunction or proximal stenosis in a different artery.[1] Patients were randomized to elective PCI or optimal medical therapy. At 4 years, there were no significant differences between the treatment groups with respect to the combined endpoint of death, reinfarction, or severe heart failure (HF).

The **C**linical **O**utcomes **U**tilizing **R**evascularization **and** **A**ggressive Dru**G** **E**valuation **(COURAGE)** trial enrolled 2,287 patients with significant CAD and inducible ischemia.[2] The majority of trial participants had multivessel disease and ischemia in multiple coronary territories, and more than one third had stenoses in the proximal LAD.

Unlike the focus of medical therapy in previous trials, medical therapy in the COURAGE trial was focused on risk factor reduction combined with anti-ischemic therapy; it resulted in very high rates of adherence to national guidelines for blood pressure, lipid levels, exercise, diet, and smoking cessation. *When added to optimal medical therapy (OMT) as described, PCI did not provide any advantage with regard to the primary endpoint of death or MI.* Many experts agreed that these results in the largest reported randomized clinical trial in CAD suggest that revascularization can be safely deferred in many patients, provided that they receive OMT.[1]

Future revisions of existing clinical practice guidelines will incorporate the results of OAT and COURAGE, but *the reality is that it is very difficult to get patients to comply* with the Therapeutic Lifestyle Changes (TLC) component of OMT and to take all the medications at the optimal dosages administered in these two studies, even if they can afford them. *Unfortunately, payment to physicians for the extra time and effort to get patients to comply with OMT isn't commensurate to that for PCI, and that is undeniably part of the equation.*

In a follow-up study of COURAGE to ascertain whether PCI could provide an incremental benefit in quality of life over that provided by OMT among patients with stable angina pectoris and chronic CAD, both those treated with PCI and those treated with OMT alone had marked improvements in health status during follow-up. The PCI group had small, but significant, incremental benefits in quality of life (relief of angina and improved self-accessed health status)—especially early—that disappeared by 36 months compared to OMT alone.[3]

More COURAGE Needed

In an accompanying editorial Dr. Eric D. Peterson, a professor of medicine at the Duke Clinical Research Institute, concludes that "The COURAGE trial redefines the contemporary role of OMT and PCI in the management of patients with stable angina. Rather than one victor, COURAGE demonstrates that both treatment strategies can have a profoundly positive effect on patients' health status and suggests complementary roles—OMT as first-line therapy, with PCI reserved for patients who do not have a response or who have severe baseline symptoms." (21% crossed over and received PCI.) "Executing such a strategy, however, will require 'courage' to reconsider the algorithms of current care and the changes in policy that are necessary to give appropriate value to the effort that is required to manage medications optimally and to monitor patients' health status."

The third installment of the evaluation of the COURAGE trial evaluated the relative cost and cost effectiveness of PCI.[4] The authors report that PCI "adds $10,125 to a patient's medical bill without significantly extending life or improving health for someone with chest pain." The incremental cost-effectiveness ratio varied from just over $168,000 to just under $300,000 per life-year or quality-adjusted life-year gained with PCI. A large minority of the distributions found that medical therapy alone offered better outcome at lower cost. The costs per patient for a significant improvement in angina frequency, physical limitation, and quality of life were $154,580, $112,876, and $124,233 respectively.

In summary, the investigators concluded that "The COURAGE trial did not find the addition of PCI to OMT to be a cost-effective initial management strategy for symptomatic, chronic CAD."

The debate over the **COURAGE** trial results has led to some polarization of CVD professionals. It should be remembered that the COURAGE trial dealt with only a subset, stable angina, of all the patients who are treated with revascularization. For patients with AMIs and ACS, the emergent treatment PCI has never, ever been questioned. *The OAT trial, however, definitely challenges proceeding to PCI after 12 hours in these patients.* The OAT and COURAGE trials remind us again that medical therapy is very, very good and very effective.

Disconnect Between the Data and Clinical Practice

The latter half of 2007 saw a dramatic decrease in the use of drug-eluting stents (DES) for PCI in the United States. This decrease probably resulted mostly

from concerns over late thrombosis with these stents, though such events are actually rare. Some of the decrease likely stems from the higher use of DES (over bare metal stents), which reduce the need for repeat procedures, and better application of preventive medicine, including statins. Some thought that the OAT and COURAGE results were making patients and their physicians more likely to at least think of a trial of medical therapy before attempting PCI—not true! It's not happening yet.

Cardiologists are biased toward PCI by an "oculostenotic reflex" in which angiographic narrowing trumps the data or the demonstration of ischemic dysfunction.[5] We know that PCI in the setting of an acute coronary syndrome saves lives, but 85% of PCI's done in the US are still done on stable patients, and probably 25% of those are asymptomatic. PCI offers a quicker relief of angina but also carries an increased risk of revascularization and late–stent thrombosis in addition to the increased cost of the procedure itself and the need for prolonged treatment with clopidigrel.

Unfortunately patients also believe that PCI will extend their lives and/or prevent a future MI over and above medical therapy and still consider their procedure is an emergency. *Better patient education regarding evidence-based risks and benefits and the option of OMT is needed prior to elective PCI.*

Guidelines to the Rescue

In the 2007 focused update of the ACC/AHA STEMI guidelines, the writing committee reviewed the OAT data and other trials, concluding that elective PCI of an occluded infarct artery in stable patients (>24 hours after STEMI) has "no incremental benefit beyond OMT with aspirin, beta-blockers, ACE inhibitors, and statins in preserving LV function and preventing subsequent CV events."[6] The results of OAT and these guidelines should not be extrapolated to patients not included in the trial, including:

- Patients with rest or severe inducible ischemia
- Severe HF or shock
- Significant triple vessel or left main disease
- Patients with open arteries with severe stenosis

According to these updated guidelines, only in the case of a hemodynamically significant stenosis should PCI be considered > 24 hours after STEMI.

"Appropriate Use Criteria for Coronary Revascularization"

The brand-new release (published online, ahead of print, from JACC January 5 2009) of the current description of the appropriateness of coronary revascularization for CAD is meant to supplement existing guidelines.[7] The authors emphatically state that these guidelines should not replace clinical judgment regarding treatment for individual patients. The current criteria emphasize the importance of patient symptoms, demonstrable ischemia as well as an adequate trial of OMT in the decision whether to perform coronary revascularization procedures for patients with CAD. Interventions include CABG and PCI grouped together in most recommendations. Appropriate, inappropriate, and uncertain situations for coronary revascularization are outlined below.

Perspective: All CAD is not created equal with regard to survival outcomes. The current guidelines provide a review of 5-year survival rates associated with medical treatment of different degrees of CAD. Although the 5-year survival rate of 1-vessel disease with at least 75% stenosis is 93%, the respective rates of survival for 2-vessel and 3-vessel disease are 88% and 79%, respectively. However, 1-vessel disease with at least 95% occlusion of the LAD is associated with a 5-year survival rate of only 83%, and 3-vessel disease with similar LAD stenosis has a survival rate of 59%. Five-year survival rates generally decline with an increasing number of vessels affected by CAD, but 2-vessel disease that does not involve the LAD is associated with better survival rates vs significant 1-vessel disease of the LAD.

Clinical scenarios **Appropriate** for coronary revascularization:

- ST-segment elevation MI (STEMI) within 12 hours of symptom onset
- STEMI who present between 12-24 hours of symptom onset, who have persistent symptoms, severe HF, or hemodynamic or electrical instability (PCI is considered inappropriate in the absence of these features.)
- 2-vessel CAD without proximal LAD disease; low-risk findings on non-invasive risk stratification (Table 1); marked limitation of activity because of angina; receiving OMT

- 2-vessel CAD without involvement of the proximal LAD; high-risk findings non-invasive evaluation; slight limitation of activity because of angina; not receiving OMT
- 1 or 2-vessel CAD involving the proximal LAD; low-risk findings on stress testing; slight impairment of activity because of angina; receiving maximal OMT or just high-risk findings on non-invasive risk stratification
- In patients with a chronic total occlusions (CTO) who have high-risk features and have class III or IV angina on OMT
- Any patient with 2- or 3-vessel CAD and at least moderate-risk findings on non-invasive testing; receiving maximal OMT
- Left main stenosis and symptomatic triple vessel disease or asymptomatic triple vessel disease with high- or intermediate-risk features on noninvasive testing or in the presence of abnormal LV function (CABG is preferred and PCI is considered inappropriate.)

Clinical scenarios not appropriate for coronary revascularization:

- STEMI for 12 hours or more after symptom onset; patient asymptomatic
- STEMI with presumed successful treatment with fibrinolysis; patient asymptomatic with normal LV ejection fraction
- STEMI who have undergone primary PCI or fibrinolytic therapy and have no symptoms, electrical or hemodynamic instability, or provokable ischemia, revascularization of a nonculprit vessel
- 1 or 2-vessel CAD without involvement of the proximal LAD; low-risk findings on non-invasive testing; asymptomatic; not receiving OMT
- Chronic total occlusion of 1 major epicardial artery without other coronary stenosis; low-risk non-invasive testing; asymptomatic; not receiving OMT

Clinical scenarios in which the benefit vs risk for coronary revascularization is uncertain:

- 1-vessel CAD involving the proximal LAD; low or intermediate-risk findings on non-invasive testing; slight or no impairment of activity because of angina; not receiving OMT
- 2-vessel CAD involving the proximal LAD; low or intermediate-risk findings on stress testing; asymptomatic (uncertain regardless of OMT)
- In asymptomatic patients with CTOs, revascularization is either inappropriate (low-risk features on noninvasive risk stratification) or of uncertain value

Table 1. Non-invasive Risk Stratification

High-Risk (greater than 3% annual mortality rate)

1. Severe resting LV dysfunction (LVEF < 35%)
2. High-risk treadmill score (score ≤ - 11)
3. Severe exercise LV dysfunction (exercise LVEF < 35%)
4. Stress-induced large perfusion defect (particularly if anterior)
5. Stress-induced multiple perfusion defects of moderate size
6. Large, fixed perfusion defect with LV dilation or increased lung uptake (thallium-201)
7. Stress-induced moderate perfusion defect with LV dilation or increased lung uptake (thallium-201)
8. Echocardiographic wall motion abnormality (involving greater than two segments) developing at low dose of dobutamine (less than or equal to 10 mg/kg/min) or at a low heart rate (< 120 beats/min)
9. Stress echocardiographic evidence of extensive ischemia

Intermediate-Risk (1% to 3% annual mortality rate)

1. Mild/moderate resting left ventricular dysfunction (LVEF= 35% to 49%)
2. Intermediate-risk treadmill score (-11< score < 5)
3. Stress-induced moderate perfusion defect without LV dilation or increased lung intake (thallium-201)
4. Limited stress echocardiographic ischemia with a wall motion abnormality only at higher doses of dobutamine involving less than or equal to two segments

Low-Risk (less than 1% annual mortality rate)

1. Low-risk treadmill score (score ≥ 5)
2. Normal or small myocardial perfusion defect at rest or with stress
3. Normal stress echocardiographic wall motion or no change of limited resting wall motion abnormalities during stress

Combining the Art & Science of PCI

The **FAME** (**F**FR vs **A**ngiography for **M**ultivessel **E**valuation) study attempted to determine if revascularization of only the culprit lesions (those causing ischemia) would be the most effective strategy for PCI procedures.[8] Fractional flow reserve (FFR) is an invasive pressure measurement, using a guidewire placed distally to the stenosis to calculate the pressure gradient during hyperemic stress produced by adenosine-induced dilation of the microvasculature, to identify a hemodynamically significant culprit lesion. The study randomly assigned 1005 patients with multivessel CAD to FFR-based PCI (revascularization only of vessels with FFR ≤ 80%) or to conventional PCI (guided by angiography alone).

After 1 year, the rate of death, MI, or repeat revascularization was lower in the FFR-based group than in the conventional group (13.2% vs. 18.3%; P = 0.02). The mean number of coronary lesions per patient was similar in both groups (2.8 vs. 2.7), but 37% of lesions in FFR-based group were considered non-ischemic (FFR > 80%) resulting in significantly fewer DES in the FFR-based group than in the conventional group (1.9 vs. 2.7; P < 0.001). Cost was also lower ($5,332 vs. $6,007; P < 0.001).

The authors conclude that "routine measurement of FFR in addition to angiographic guidance, as compared with PCI guided by angiography alone, results in a significant reduction in major adverse events at 1 year, a finding that supports the evolving strategy of revascularization of ischemic lesions and medical treatment of non-ischemic lesions". If these results are sustained in long-term follow-up and a validation study, *FFR could indeed be a more accurate way of assessing the functional relevance of an angiographic stenosis that could improve safety and reduce costs and enhance the beneficial effects of PCI.*

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