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Encouragement to optimize medical therapy for coronary heart disease

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Therapeutic goals in treating ischemic heart disease include improving outcomes and reducing symptoms. Medical therapy for coronary artery disease (CAD) has been substantially improved in the last three decades with the addition of HMG-co reductase inhibitors (statins), niacin, fibrates, angiotensin converting enzyme inhibitors and receptor blockers, beta blockers, and novel anti-platelet agents to supplement aspirin. The incremental value of each of these therapies has been demonstrated by the gold standard of clinical science, the randomized controlled trial. Percutaneous coronary intervention (PCI), first performed by Dr. Andreas Gruentzig in September 1977 [1] also has the capacity in selected populations to relieve symptoms and enhance survival. Since its introduction, percutaneous coronary revascularization has undergone many revisions and improvements and is currently performed ~1 million times annually in the United States alone [2]. The importance of identifying the patient populations that benefit from these medical and revascularization interventions is underscored by the recently published COURAGE trial [3].

Substantial clinical benefit of PCI has been demonstrated in trials examining patients with ST elevation myocardial infarction (STEMI) and high risk patients with non-ST elevation myocardial infarction (NSTEMI) [4]. Prior to the publication of the COURAGE Trial in April 2007, the evaluation of medical therapy and PCI in patients with stable CAD has been limited: Fewer than 3000 patients in small randomized controlled trials and observations thus far indicate faster and more durable anginal relief in patients receiving PCI when compared to optimal medical therapy (OMT). A recent meta-analysis of 11 randomized trials comparing PCI to OMT in patients with stable CAD demonstrated no superiority of one strategy over the other for the endpoints of total mortality, cardiac death, non-fatal myocardial infarction or rates of coronary artery bypass surgery (CABG) or PCI [5]. What was sorely needed to settle the debate of the incremental prognostic and symptomatic benefit in stable CAD afforded by PCI was a large, multi-center randomized clinical trial in which all patients receive aggressive, guideline driven medical therapy with upstream randomization of the use of PCI. These considerations provide the impetus for the design and execution of the Clinical Outcomes Utilizing Revascularization and Aggressive Guideline driven drug Evaluation (COURAGE) trial.

COURAGE was funded by the Veteran Affairs Administration and several pharmaceutical companies (several coronary catheter companies refused the opportunity to support this trial). COURAGE randomized 2287 patients with stable obstructive CAD and myocardial ischemia to either OMT or OMT with PCI. Importantly, all patients in this trial were treated with aggressive, guideline driven medical and lifestyle therapy, and randomization assignment in the trial occurred only after careful education of patient and referring physicians and acceptance of an interventionalist to perform PCI if this randomization arm was selected. Quality of life and angina metrics as well as hard event outcomes were carefully tracked. Patients with severe left ventricular dysfunction (LVEF < 30%), those with left main CAD (> 50%) or those with a recent revascularization were excluded. At a mean follow up of 4.6 years, no significant differences between the PCI group and the medical therapy group in the composite of death, MI and stroke were observed. Similarly, hospitalization for acute coronary

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syndrome (ACS) or MI was similar. The only significant difference between the 2 groups was a modest improvement of anginal relief at during the first 3 years in the PCI group, which was insignificant at 5 years. Economic analyses, currently unpublished, were presented by Dr. William Weintraub at the American College of Cardiology's 2007 Annual Scientific Session. The preliminary data indicate unfavorable cost effectiveness for patients randomized to PCI with an average quality-adjusted life-year (QALY) gained by PCI compared to optimal medical therapy of > $200,000. The QALY threshold of cost effectiveness is widely considered to be under $50,000.

The COURAGE investigators envisioned a decade ago in the trial design the therapeutic value of aggressive, guideline driven targets for treatment beyond the popular recommendations of that era to achieve excellent results in terms of hypertension control, lipid reduction (average LDL reached was 71 mg/dL) and lifestyle factors in all patients treated in both arms of this trial. Except for a higher usage of calcium channel blockers and nitrates in the medical-therapy arm, no differences between treatment arms were found in the eventual medical regimens of patients enrolled in COURAGE. Importantly, no pre-specified subgroups revealed benefit from either the PCI or medical-therapy strategies. By the play of chance, more patients with proximal LAD disease were assigned to the OMT arm. The significant annual and cumulative event rates of the COURAGE trial indicate these patients with stable CAD were at expected levels of significant subsequent cardiac risk.

Several factors were unique about this study. This was a North American trial with fifty U.S. and Canadian centers involved in this study making it the largest randomized investigation of stable CAD patients to date. Secondly, an impressive total of 2168 (95%) of patients had objective evidence of ischemia, the majority of which had multiple reversible defects determined by routine radionuclide perfusion imaging (SPECT). Thirdly, in the PCI group, 94% of patients received a contemporary PCI strategy consisting of at least one stent. Drug-eluting stents were only available towards the latter stages of this trial which meant only 3% of patients assigned to PCI received a coated stent. Lastly, OMT provided superior relief from angina than previously thought possible, and symptom relief was reliably obtained in both arms of the trial. Relief from angina at 1 year was 66% in the PCI group and 58% in the medial-therapy group (a difference of 8%) while at 3 years the difference declined with rates of 72% and 67%, respectively. Perhaps most importantly, the trial gives us the courage to recognize in stable patients with CAD an initial strategy of optimal, aggressive, guideline driven medical therapy did not put patients in harm's way, and leaves the door open for later revascularization for the one-third of patients who may require it for anginal relief.

The COURAGE study presents an opportunity for cardiologists and the general healthcare community to pause and re-examine current practice trends. In this modern age of spiraling healthcare costs one wonders whether a more evidenced-based approach to the management of stable CAD might curtail some of the costs. Additionally, these results provide good news for patients and their physicians worldwide who are now able to choose medical therapy with full confidence that it is not inferior to a strategy of PCI in terms of death, MI, stroke or ACS. It would be interesting if the COURAGE investigators revealed the data on the differences in morbidity that patients in the PCI arm may have suffered due to complications from their invasive procedures. Many pre-specified analyses of the COURAGE data will be forthcoming to evaluate cost-effectiveness, the role of SPECT perfusion imaging and PCI to identify high risk groups that may selectively benefit from the addition of upstream PCI not reported in the initial paper.

How generalizable are these results? One of the criticisms of the study was that 35,539 patients underwent screening assessments and only 3071 met eligibility criteria (< 9%) prior to randomization. This may partly be explained by difficulties encountered in randomizing patients with significant proximal coronary disease due to local physician bias and misconception. If one is biased to believe, on the basis of PCI studies in acute MI that the intervention applies to patients with stable CAD as well, an ethical dilemma is posed for the physician or patient considering randomization in COURAGE. While recruitment was problematic due to referral biases, the final study group reportedly reflected the initial screened cohort.

Are the results of COURAGE surprising? Despite a prevalent bias based on MI studies that the majority of patients with stable coronary disease can be better treated successfully with focal treatment (balloon and stent angioplasty), consideration of pathophysiology and other clinical trials argue against this supposition. The reality is that coronary disease is a diffuse, widespread and systemic disease of atherosclerosis affecting much of the cardiovascular tree, and patients presenting with ACS

usually have more than one active, inflamed plaque in need of treatment [6]. Data from four angiographic trials, summarized by the widely quoted meta-analysis of Ernst Falk [7], are remarkably consistent in demonstrating the vast majority of MIs occur in areas of the coronary artery that are not hemodynamically significant.

In the COURAGE trial, SPECT myocardial perfusion scintigraphy (MPS) may hold a key to understanding who benefits most from PCI, and when patients actually succeed or fail to respond to aggressive, guideline treated therapy prior to the onset of clinical events. Studies comparing the prediction of subsequent hard coronary events in men and women demonstrate the perfusion and functional variables of radionuclide myocardial perfusion imaging consistently out-perform clinical, ECG, and arteriographic data [8–10]. A nuclear substudy of COURAGE has been undertaken from the beginning of the trial, and pre-specified analysis of the serial SPECT MPS data in the COURAGE trial are planned to assess the hypothesis that ischemic perfusion defect size and functional data (LV volume indices and EF) can identify those patients with stable CAD who benefit most from PCI. Identification and correlation of scintigraphic and clinical responses to treatment is also planned, to assess the question as to whether further broadening or intensification of treatment following SPECT MPS was associated with changed outcome. We should remember that even patient groups fortunate to have been randomized to active arms of medical therapy trials still suffered substantial rates of coronary events. Beyond the framework of existing guidelines which in practice become artificial surrogates of success in treatment, much work remains to be done to optimize care and minimize morbidity and mortality in patients with stable ischemic heart disease [11].

Thus, optimizing therapy and risk for patients with stable CAD in 2007 should ideally be accomplished by treating systemically to target diffuse plaque instability and rendering it unlikely to rupture and precipitate acute infarction or death. Improving coronary specific endothelial function and enhancing regional myocardial blood flow can be accomplished by the combination of lifestyle and medical therapeutic interventions as has been demonstrated for over a decade by multiple studies employing PET and SPECT radionuclide MPS. Angina will improve substantially on medical therapy, and no increase in death or MI is associated with an initial strategy of aggressive, guideline driven medical therapy. If additional anginal relief is required and the patient cannot afford to wait for the full anti-anginal benefit of medical therapy, PCI remains a safe and viable option.

The COURAGE trial has encouraged us all to give our patients with CAD aggressive, guideline driven lifestyle and medical therapy. The challenge of the COURAGE study now is to educate physicians and patients to place these results in the appropriate context of the stable CAD patient population to which the study applies, and to give patients time and opportunity to sample the fruits of this contemporary approach to high quality, cost effective care.

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