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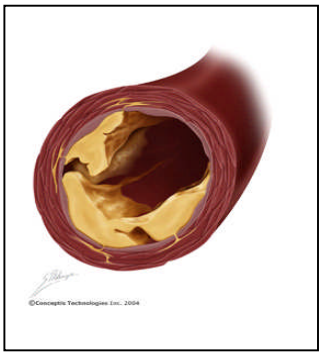
Giving COURAGE Its Due

"IF prevention is your goal, concentrate on the donut, not the hole". (Unknown.)

This quote has taken on even more significance after an evaluation of the recently released COURAGE trial. According to the results of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial, percutaneous coronary intervention (PCI)—coronary angioplasty plus stenting—and optimal medical therapy (OMT) is no better at preventing future events than OMT alone in patients with stable coronary artery disease (CAD).[1] These results just add fuel to the mounting fire over whether stents, including drug-eluting stents (DES), are being overused for the treatment of stable CAD and for the prevention of future cardiac events.



This *Heartbeat* will discuss the results and conclusions of COURAGE —and offer some perspective regarding implications and applicability as the data is studied and analyzed by various experts. For clinicians, these studies offer us a reminder that intervening at a single spot (*hole*) doesn't change the underlying pathophysiology in the walls of the coronary arteries (*donut*), and the next plaque that ruptures, precipitating an MI, won't be the one that was stented. Clinicians should also feel more comfortable initially treating the underlying pathophysiology with OMT (and not jumping right to PCI), realizing that this choice is safe and that the patient can cross over to PCI at any time if OMT is not effective. The most important conclusion of this study is just how good medical therapy has become. It emphasizes the value of comprehensive medical therapy which is needed even for patients post PCI.

Summoning COURAGE

Description

The goal of the trial was to evaluate the efficacy of percutaneous coronary intervention (PCI) compared with optimal medical therapy among patients with stable coronary artery disease.

Hypothesis

PCI with optimal medical therapy would reduce the risk of death and nonfatal MI in patients with stable coronary artery disease as compared with optimal medical therapy alone.

Drugs/Procedures Used

Patients were randomized to optimal medical therapy alone (n = 1,138) or PCI in addition to optimal medical therapy (n = 1,149). Optimal medical therapy included antiplatelet therapy with aspirin (81 to 325 mg/day), or clopidogrel (75 mg/day) if aspirin intolerant in the medical therapy group, and aspirin plus clopidogrel in the PCI group. All patients also received aggressive lipid-lowering therapy to a target LDL of 60 to 85 mg/dl. Anti-ischemic therapy included long-acting metoprolol, amlodipine, and isosorbide

mononitrate, alone or in combination, and either lisinopril or losartan as secondary prevention.

Principal Findings

The large majority of patients (95%) had objective evidence of myocardial ischemia. Multivessel disease was present in 69% of patients with only 31% having single vessel disease. One-third of patients had proximal disease of the left anterior descending artery. CCS class II or III angina was present in 58% of patients at study entry.

PCI was performed in 94% of the PCI cohort, with successful PCI in 93%. Optimal medication use during the study was high in both treatment groups, with use at 5 years of ACE-inhibitors in 64% of patients, statins in 93%, aspirin in 95%, and beta-blockers in 85%. LDL levels were reduced to a median of 71 mg/dl. Diet, exercise and smoking cessation were high in both groups.

The primary endpoint of death or MI did not differ for the PCI group compared with the medical therapy group (19.0% for PCI vs. 18.5% for medical therapy, hazard ratio [HR] 1.05, 95% CI 0.87 to 1.27, p = 0.62). There was also no difference between PCI and medical therapy in the secondary composite endpoint of death, MI or stroke (20.0% for PCI vs. 19.5% for medical therapy, HR 1.05, 95% CI 0.87-1.27, p = 0.62) or in the secondary endpoint of hospitalization for ACS (12.4% for PCI vs. 11.8% for medical therapy, HR 1.07, 95% CI 0.84 to 1.37, p = 0.56). Components of the composite endpoints did not differ between groups, including death (7.6% for PCI vs. 8.3% for medical therapy, HR 0.87, p = 0.38), nonfatal MI (13.2% vs. 12.3%, HR 1.13, p = 0.33), or stroke (2.1% for PCI vs. 1.8% for medical therapy, p = 0.19). Angina was significantly reduced in both groups during follow-up, with no difference in the reduction between PCI and medical therapy at 5 years (freedom from angina in 74% of the PCI group and 72% of the medical therapy group, p = 0.35) but slightly higher rates of freedom from angina in the early time frame with PCI (at 1 year: 66% for PCI vs. 58% for medical therapy, p < 0.001; at 3 years: 72% for PCI vs. 67% for medical therapy, p = 0.02).

Interpretation

Among patients with stable CAD, treatment with PCI was not associated with a difference in death or MI compared with treatment with medical therapy through 5 years of follow-up. Despite patients in the study having stable angina, disease severity was relatively intensive with the majority of patients having multivessel disease and objective evidence of ischemia at study entry. There were no differences in any of the clinical endpoints between the PCI and medical therapy groups, nor was there any treatment interaction with the prespecified subgroups. Freedom from angina occurred slightly more frequently with PCI early in the trial but did not differ between the PCI and medical therapy groups by 5 years, with both arms showing marked reductions in angina throughout the trial. Findings from the present study apply to stable angina patients and cannot be extrapolated to the acute coronary syndrome population, which have different pathophysiologic characteristics, although the majority of patients currently undergoing PCI are for stable angina. While the majority of the PCI group did not receive drug-eluting stents, since most of the enrollment was completed prior to the introduction of these stents, there is no reason to indicate that use of them would alter the findings of the trial since drug-eluting stents have never been shown to reduce death or MI compared with bare metal stents in any trial.

Limitations

The authors identify the low numbers of women and nonwhites in COURAGE as limitations of the study.

Commentary/Implications/ Applicability:

Too much effort (and marketing money) is spent on pushing PCI. It's obviously the easier treatment when compared to CABG and has the

mantra of curing the patient with obstructed arteries when compared to OMT. According to Dr Salim Yusuf (McMaster University, Hamilton, ON), a blunt critic of PCI, physicians and patients have been "brainwashed and deluded" into thinking that PCI will save them, while interventionalists fear that if they turn patients away, their referral base will dry up. "The reason for PCI is not scientific, it's not medical, it's sociological, and—we all know it, although we don't want to say it—it's economic. It's really time to confront this because medicine here has gone wrong." Easier said than done, Yusuf acknowledged. "We're going to have a hell of a time putting the genie back in the bottle."

Dr Valentin Fuster, Mount Sinai School of Medicine, one of my favorite cardiologists and a voice of reason, said that he thought the COURAGE findings were predictable because "15 years ago, trials comparing bypass surgery to medical therapy for patients with stable angina found no difference. This is the same story again." Dr Fuster stated he hoped the "not surprising" COURAGE findings would dampen the enthusiasm for stenting. "The community has been mislead by the results of acute trials that have shown a definite benefit for PCI. Those benefits have been transferred—wrongly—to the chronic patients and that is where the community was misled."

Christopher Cannon, MD, from the Brigham and Women's Hospital in Boston, Massachusetts, called the trial, confirmation of a "back-to-basics approach." He predicted that COURAGE "is going to shake things up in the cath labs" and pointed out that the trial addresses a very important segment of the population—the 30% to 40% of patients undergoing catheterization and PCI for stable disease. "This is actually what many people would have expected, thinking about the pathophysiology of stable CAD, but it runs a little bit counter to the current sucking sound of patients being drawn to the cath lab," Dr. Cannon told heartwire. "Anyone with ACS [acute coronary syndrome] ends up being cathed appropriately, but many other people have ended up in the cath lab as well."

"The real question is whether cardiologists will have the 'courage' to change the way they practice, which in 2007 flies in the face of the evidence," said James Stein, MD, from the University of Wisconsin, Madison. "We know PCI in the setting of an acute coronary syndrome saves lives, but 85% of PCI's in the US are done in stable patients and of those I'd bet that at least 25% are asymptomatic patients. This study clearly shows something we all knew—but many did not want to believe—that angioplasties don't save lives, except in acutely ill patients, and don't prevent heart attacks. Cardiologists say yes, we know that, we are relieving symptoms, but why are so many done on people who are asymptomatic? And why all the 'screening' stress tests?" In other words, if they are asymptomatic and on OMT, no testing is necessary.

Drs Cannon and Stein feel that most docs know that minor blockages, not seen on stress tests or opened by PCI, cause most heart attacks. "The problem is fear of malpractice: docs are afraid of getting sued if they don't do a stress test and if they don't do a cath in response to an abnormality," Dr. Stein explained (which frequently results in PCI). Dr. Cannon agreed, "Now we have something to fall back on."

Whether PCI rates take a dip based on the COURAGE trial remains to be seen. Dr. Stein noted, "Economic incentives favor procedures, rather than medical therapy with lifestyle and medications. PCIs are very lucrative for hospitals and doctors; talking to patients and taking care of their risk factors, unfortunately, is not.

This "mine-is-better-than-yours" mentality is the wrong way to go. All parties should work together to address the questions that will truly allow better healthcare. Care for patients with obstructive CAD should be evidence based, and PCI, using bare metal or drug-eluting stents, CABG and OMT should be thought of as complementary procedures. Each has benefits (and risks) for different categories (stages) of

patients based on CAD anatomy, LV function, and other comorbid conditions. In addition, patient values and preferences, including the costs and risks of being on clopidogrel for an extended period, should also be taken into consideration when deliberating about bare metal versus drug-eluting stents as part of PCI.

(1) One important point is to emphasize that these findings in no way address the very important role of PCI in acute coronary syndrome, not losing site of the reality that revascularization can help patients in that emergency situation.
(2) Catheter based interventions, CABG, and OMT have all improved in the last decade and allow us to offer a variety of very good options to our patients.
(3) Optimal medical therapy works very well—with very good results. The question becomes, "Are all of our patients on OMT?

COURAGE TOPS OAT

Added to this information is the recently released occluded artery trial (OAT). In this study 2166 stable patients with total occlusions of their infarct-related arteries were randomized either to routine PCI plus stenting and OMT (n=1082) or to OMT alone (n=1082), three to 28 days after their MI.[2] Patients with significant left main or three-vessel disease, angina at rest, hemodynamic or electrical instability, NYHA class 3 or 4 heart failure, or shock were excluded from the trial (intervention in these settings can be life-saving).

At follow-up, the estimated four-year cumulative primary event rate—a composite of death, reinfarction, or heart failure—did not differ between the PCI group and the medical group, a finding that held up in intention-to-treat analyses. Individually, rates of death and rates of heart failure were also no different between the two groups; however, the rate of nonfatal reinfarction trended to be higher among PCI-treated patients. Indeed, in secondary-end-point analyses based on site-determined event rates (that Hochman described as a more accurate reflection of international definitions of MI), the difference in nonfatal reinfarction rates between the two groups reached statistical significance (p=0.04). Fewer patients had angina among the PCI-treated patients at 4 months and 1 year, but over time the occurrence of angina declined in the overall study population, and differences between the two groups disappeared.

Conclusion: PCI is a reasonable strategy to treat persistent angina but not to prevent angina in stable patients. Intervening as a routine strategy more than 48 hours after MI or in other stable CAD patients to make them live longer or prevent MI or HF is not effective. If they develop angina that's not responsive to OMT or affects lifestyle, PCI is an effective therapy. Old habits die hard; hopefully clinicians will change their minds about using PCI in these stable patients. We experience a great desire to do angioplasty on an occluded vessel simply because it's blocked and it's easy to unblock it (minimal but some risk). OMT is just as beneficial and is significantly more cost effective in the described settings.

These results support routine use of aggressive secondary prevention (OMT) without revascularization as the preferred strategy in stable non-acute CAD patients.

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[1] Boden WE, et al. Optimal medical therapy with or without PCI for stable coronary disease. (COURAGE) *N Engl J Med* April 12 2007; 356:1503-1516.

[2] Hochman JS, et al. Coronary intervention for persistent occlusion after myocardial infarction. (OAT) *N Engl J Med* December 7 2006;355:2395-2407.