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Editorial

Papering Over the Cracks: Meta-analysis to Define the Role of Percutaneous Coronary Intervention in Patients With Stable Angina

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See article by Thomas et al., pages 472-482 of this issue.

> "Our findings seem to indicate that summarizing all the information contained in a set of trials into a single odds ratio may greatly oversimplify an extremely complex issue. The popularity of meta-analysis may at least partly come from the fact that it makes life simpler and easier for reviewers as well as readers. However, over-simplification may lead to inappropriate conclusions.[1]"

In this issue of the *Canadian Journal of Cardiology*, a meta-analysis by Thomas et al. compares percutaneous coronary intervention (PCI) with medical therapy in patients with stable angina.[2] The authors include 10 randomized trials involving 6752 patients, and conclude that PCI was not associated with better angina relief, or reductions in all-cause or cardiovascular mortality, or myocardial infarction. They state that their findings "reinforce existing clinical practice guidelines that the initial approach to patients with stable angina should be medical therapy."

Other recent meta-analyses have addressed this topic,[3-6] and 2 of them came to similar conclusions as these authors.[3,6] However, Schömig et al. concluded that PCI reduced total and cardiovascular mortality compared with medical therapy,[4] and Wijeysundera et al. concluded that PCI provided better angina relief with no advantage for other end points.[5]

Why this divergence? Meta-analyses usually present a straightforward conclusion, leaving the messy details buried within the body of the report. In this instance, the results of a meta-analysis crucially depend upon the studies that are included. Do we wish to restrict our analysis to patients with stable angina, or should we include trials of patients with silent ischemia or survivors early after myocardial infarction? Perhaps we should dig deeper, to try to understand the factors that contribute to the results of the trials included, or not included, in these meta-analyses.

Improvements in PCI and Medical Treatment

The treatments being compared, PCI and medical therapy, have both improved greatly over the time period when these trials were conducted. For example, men with single or double vessel disease were enrolled into the **A**ngioplasty **C**ompared to **Me**dicine (ACME) study between 1987 and 1990.[7,8] Among the 100 angioplasties for single vessel disease, only 80 were successful, with success defined as a $>$ 20% decrease in stenosis severity without periprocedural infarction or the need for urgent bypass surgery.[7] Within 6 months, 16 patients required 18 additional procedures for restenosis and 5 others underwent coronary bypass surgery. Medical therapy consisted of aspirin in almost all patients, calcium channel blockers in approximately 3 quarters, and β-blockers in approximately half.

Early trials contribute disproportionately to the end points; for example, ACME contributed only 4.9% of the patients to the meta-analysis of Thomas et al., but 7.5% of the end point events. ACME was a perfectly acceptable trial for its era, but its results are not relevant to current practice. The fact that the results of ACME are within the range of the results of other trials is more than likely coincidental.

The second **R**andomized **I**ntervention **T**reatment of **A**ngina 2 (RITA-2) contributed 1018 of the 6757 patients in the meta-analysis; however, only 9% of the RITA-2 patients randomized to PCI received stents, and only 13% of all RITA-2 patients were receiving a lipid-lowering drug at baseline.[9] Although incremental advances have occurred in both technical and periprocedural aspects of PCI, and in medical therapy, the quantum leaps have been stents and statins respectively. Trials lacking stents and statins are archaic and do not apply to contemporary practice.

The Optimal Medical Therapy of COURAGE

Medical therapy was not the primary focus of the early trials comparing PCI with medical therapy. The aim of medical treatment in these trials was primarily angina prevention using nitrates, β-blockers, and calcium channel blockers. The **C**linical **O**utcomes **U**tilizing **R**evascularization and **Ag**gressive Drug **E**valuation (COURAGE) trial was different. COUR-

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AGE randomized 2287 patients with objective evidence of myocardial ischemia and coronary disease to either PCI plus optimal medical therapy or optimal medical therapy alone.[10] After a median follow-up of 4.6 years, the primary end point, death or nonfatal myocardial infarction, had occurred in 19.0% of patients in the PCI plus optimal medical therapy group and in 18.5% of patients in the optimal medical therapy alone group.

Medical therapy in COURAGE was multifaceted, intensive, persistent, and successful in meeting all targets but 1.[11] The proportion of smokers decreased from 23% to 19%, those who reported < 7% of calories from saturated fat increased from 46% to 80%, and those who walked for at least 150 minutes per week increased from 58% to 66% from baseline to 5 years. Medication use increased for antiplatelet drugs (87% to 96%), β-blockers (69% to 85%), renin-angiotensin-aldosterone inhibitors (46% to 72%), and statins (64% to 93%). Systolic blood pressure decreased from a median of 139 to 123 mm Hg and low-density lipoprotein (LDL)-cholesterol from 101 to 72 mg/dL (2.6 to 1.9 mmol/L).[11] COURAGE patients did not lose weight, but were successful in every other aspect of their medical treatment.

Can we estimate the extent to which these medical interventions reduced the event rate in COURAGE? The **T**reating to **N**ew **T**argets (TNT) trial randomized 10,001 patients with stable coronary disease to atorvastatin 10 or 80 mg per day and followed them for a median of 4.9 years.[12] The difference in LDL-cholesterol levels between the treatment groups, 101 vs 77 mg/dL (2.6 vs 2.0 mmol/L), is slightly less than the improvement seen in COURAGE, from 101 to 72 mg/dL (2.6 to 1.9 mmol/L), and was associated with a 22% reduction in the primary composite end point. Among the 5407 TNT patients who had previously undergone PCI, this LDL-cholesterol difference was associated with a 21% difference in the primary end point, 10.6% vs 8.6%, but also a large reduction in the need for repeat revascularization during follow-up, from 22.9% to 17.3% (hazard ratio 0.73; 95% confidence interval, 0.65-0.82; $P < 0.0001$).[13]

In a meta-analysis of 147 randomized blood pressure-lowering trials involving 464,000 patients, a 10 mm Hg decrease in systolic blood pressure was associated with a 22% reduction in coronary events and a 41% reduction in stroke.[14] The median reduction of 16 mm Hg obtained in COURAGE would be expected to reduce cardiovascular events by approximately 50% according to this meta-analysis.[14] The effects of the other components of the medical program in COURAGE are harder to calculate, and some of them such as fenofibrate and niacin probably produced no benefit based upon the results of recent randomized trials. Nevertheless, it seems reasonable to estimate that medical therapy may have reduced the risk of events by as much as 75% in COURAGE.[15]

Critics have asserted that the COURAGE program of medical therapy cannot be replicated in the real world.[16] The COURAGE investigators dispute this,[17] and indeed it seems obvious that serious effort should be expended to provide this level of medical care to patients with coronary disease, whether or not they undergo revascularization.

Because all patients in COURAGE received optimal medical treatment, this trial cannot tell us whether or not stable angina patients with less intensive levels of medical care might derive benefit from PCI. It is possible that PCI produces some of the same benefits as optimal medical therapy, even though the combination of both is not superior to optimal medical therapy alone. A physician who does not recommend PCI based upon the results of COURAGE, and does not implement COURAGE-like medical treatment is both misinterpreting the trial and under-treating the patient.

The Role of Myocardial Ischemia

Old randomized trials comparing coronary bypass surgery with medical treatment established the concept that high-risk patients benefited from revascularization whereas low-risk patients did not.[18] The main factors underlying higher risk were multivessel disease or left main stenosis, impaired ventricular function, and the presence and extent of myocardial ischemia. In the absence of symptoms, some cardiologists consider the presence of a severe narrowing by itself to be reason enough to perform PCI. Most would definitely recommend PCI if the narrowing was associated with a large reversible perfusion defect.

Considerable evidence can be mustered to support this position. The **A**symptomatic **C**ardiac **I**schemia **P**ilot (ACIP) trial randomized 558 patients with coronary anatomy suitable for revascularization, myocardial ischemia by stress testing, and at least 1 episode of silent myocardial ischemia on ambulatory electrocardiographic monitoring, to angina-guided therapy, angina- plus ischemia-guided therapy, or revascularization.[19] At 2 years, the total mortality was 6.6% in the angina-guided strategy, 4.4% in the ischemia-guided strategy, and 1.1% in the revascularization strategy groups ($P < 0.02$). The rate of death, myocardial infarction, or recurrent cardiac hospitalization was 41.8% in the angina-guided strategy, 38.5% in the ischemia-guided strategy, and 23.1% in the revascularization strategy ($P < 0.001$).

In a COURAGE substudy, 314 patients underwent serial rest/stress nuclear perfusion imaging before and at 6 and 18 months after randomization.[20] PCI reduced myocardial ischemia more than optimal medical therapy alone, and a significant ischemia reduction was associated with a reduction in the risk of death or myocardial infarction, although this benefit was no longer statistically significant after risk adjustment. Asymptomatic patients with silent myocardial ischemia comprised just 12% (n = 283) of the COURAGE population; however, in a post hoc analysis, a trend toward fewer deaths occurred in the PCI patients in this subgroup (7 vs 16, $P = 0.12$).[21] On the other hand, all COURAGE patients were required to have some evidence of myocardial ischemia as an entry criterion for the trial, and PCI provided no benefit beyond optimal medical therapy alone across the entire trial.

What Is Happening in Cardiology Practice?

Among patients with stable coronary disease undergoing angiography in the state of New York between 2003 and 2008, 89% subsequently received PCI, 2% underwent coronary bypass surgery and 11% received only medical therapy.[22] A total of 933 PCI and medically treated patients could be propensity matched for 20 outcome variables. In this analysis, PCI patients had a lower rate of death and myocardial infarction at 4 years (16.5% vs 21.2%; $P = 0.003$). The medical treatment in this study was unknown, but in a recent study from the National Cardiovascular Data Registry, optimal medical therapy, defined as any dose of an antiplatelet agent, a β-blocker, and a

statin, was being given to about half of stable patients before PCI and about 2 thirds at discharge after PCI.[23]

In the Northern New England Cardiovascular Disease PCI Registry, publication of the results of COURAGE in March 2007 was followed by a significant and sustained 26% peak decrease in the use of PCI to treat patients with stable angina.[24] Substantial geographic variation in rates of PCI has been widely documented, and the degree to which these findings can be extrapolated to other regions is unknown. Recent Canadian data on the intensity of medical treatment in patients undergoing PCI or changes in the rates of PCI are lacking.

Defying the gravitational pull of clinical trial evidence, many patients with minimal symptoms continue to flow uphill from noninvasive testing to coronary angiography, where severe stenoses are treated with PCI. Focus groups of cardiologists have documented a chasm between knowledge and behaviour; while aware of the results of clinical trials, they recommend and perform PCI because they believe that it helps in some ill-defined way.[25]

Advantages and Limitations of Meta-analysis

The quotation at the beginning of this editorial comes from a study where the accuracy of meta-analyses could be assessed because a subsequent large randomized trial provided a definitive answer.[1] The results of 12 such trials were not predicted accurately 35% of the time by the preceding meta-analyses. The authors concluded that if the clinical trials had not been done, the meta-analyses would have led to the adoption of ineffective treatment in 32% of cases and to the rejection of a useful treatment in 33% of cases. While better than a coin toss, this level of accuracy is dismayingly low.

On the other hand, meta-analyses of very large datasets have been very informative to cardiology practice. The aforementioned meta-analysis of blood pressure treatment, involving 147 trials and 464,000 patients, provides important information as to the comparability of different drugs, the comparative benefits of different intensities of treatment, and what optimal treatment targets should be.[14] Similarly, the Cholesterol Treatment Trialists' Collaboration, in a meta-analysis of 26 randomized trials involving 170,000 patients, calibrates the extent of event reduction to be expected per mmol/L of LDL-cholesterol lowering, reassures us with respect to the safety of statins, and provides crucial data on subgroups, such as individuals with diabetes.[26,27]

In the end, meta-analysis is just a statistical tool. The value of a meta-analysis is mainly defined by the quantity and quality of the available data. It all depends on how much wallpaper you have, and the size of the cracks.

Disclosures

Dr Waters was a member of the Data and Safety Monitoring Board of the COURAGE trial. He has received fees for participating in clinical trial committees and for consulting from Aastrom, Anthera, Biosante, Cerenis, Genentech, Merck Schering Plough, Pfizer, Roche, and Servier, and he has received honoraria for lectures from Bristol-Myers Squibb and Pfizer.

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