The Immediate Impact of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) Trial on the Management of Stable Angina

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ABSTRACT

Background: The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial confirmed that percutaneous coronary intervention is no better than optimal medical therapy for the prevention of major adverse cardiac events in patients with stable angina. The impact of these findings on clinical practice remains unknown.

Hypothesis: Clinicians may more frequently opt for medical rather than procedural therapy of stable angina in response to the COURAGE trial.

Methods: Clinical information was collected from patients with stable angina referred to our hospital for cardiac catheterization between January 1, 2007 and June 18, 2007 ($n = 332$). Catheterization referral volume and the use of medications and coronary revascularization were compared before and after the release of the COURAGE trial.

Results: There was a significant increase in anti-ischemia medication use prior to catheterization referral following the COURAGE trial (mean = 1.31 [SD 0.83] medications pre-COURAGE, mean = 1.54 [SD 0.84] medications post-COURAGE, $P = 0.012$). Among 217 patients with coronary disease on catheterization, treatment with medication rather than percutaneous or surgical revascularization increased after COURAGE (11.1% pre-COURAGE vs 23.0% post-COURAGE, $P = 0.03$). There was also a significant decrease in referral volume following the COURAGE trial (3.12 referrals/day pre-COURAGE vs 2.51 referrals/day post-COURAGE, $P = 0.034$).

Conclusions: The COURAGE trial immediately impacted the management of stable angina. Catheterization referral volume decreased, medication use increased, and the use of medical therapy rather than revascularization increased among patients with coronary disease.

Introduction

The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial was officially released on March 26, 2007 and generated considerable controversy regarding the appropriate clinical impact of the major findings.^{1–4} The study investigators concluded that an initial management strategy of percutaneous coronary intervention (PCI) with optimal medical therapy did not reduce the risk of major adverse cardiovascular events compared to medical therapy alone for patients with stable angina. A 10% drop in coronary stent sales from March 2007 to April 2007 suggested that the COURAGE trial made an immediate impact on clinical practice,⁵ but concerns about

late stent thrombosis likely affected stent sales during the same time period.

Previous work demonstrates a significant delay between the release of clinical trial evidence and the broader implementation of that evidence into medical practice.^{6,7} For example, the majority of patients with stable coronary artery disease failed to receive aspirin therapy and lipid screening more than 10 years after the release of clinical evidence showing clear mortality benefits.^{7,8} The objective of the current study was to formally test the immediate impact of the COURAGE trial on the management of stable angina at an academic medical center.

Methods

Charts were retrospectively reviewed on all patients referred to the University of Wisconsin Hospitals and Clinics for coronary angiography from January 1, 2007 through June 18, 2007 to determine the indication for referral.

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Indications were defined in a standard fashion⁹ and included stable angina, unstable angina, non-ST-elevation myocardial infarction, ST-elevation myocardial infarction, and preoperative evaluation. Clinical characteristics and medication use were collected on all patients who met the definition of stable angina and were referred for coronary angiography from March 27, 2007 through June 18, 2007 (post-COURAGE) and compared to patients referred from January 1, 2007 through March 26, 2007 (pre-COURAGE). β -Blocker (BB), nitroglycerin (NTG), and calcium-channel blocker (CCB) use prior to coronary angiography referral were compared among patients referred pre-COURAGE and post-COURAGE. Among those patients with significant coronary artery disease (CAD) on coronary angiography, defined as >70% stenosis of at least 1 major epicardial vessel, the frequencies of treatment with medical therapy, PCI, or coronary artery bypass graft surgery (CABG) were also compared. The institutional review board at the University of Wisconsin approved the study protocol and waived the requirement for informed consent. Continuous variables were expressed as mean $\pm$ standard deviation (SD) and were tested using unpaired Student *t* tests. Categorical variables were tested using χ^2 tests. All statistical testing was 2-sided and a *P* value <0.05 was considered significant for all tests.

Results

Between January 1, 2007 and June 18, 2007, 873 patients were referred to our laboratory for coronary angiography including 332 patients (38.0%) with stable angina. Patient characteristics are shown in Table 1. Medication data were available for 330/332 patients (99.4%) and are shown in Table 2. Pre-COURAGE, 70.7% of patients were treated with BB, 39.7% were treated with NTG, and 20.1% were treated with CCB prior to coronary angiography. Post-COURAGE, there was a 13% increase in BB use (*P* = 0.065), a 39.8% increase in NTG use (*P* = 0.006), and an 8.6% reduction in CCB use (*P* = 0.819). The mean number of anti-ischemia medications used prior to coronary angiography increased from 1.31 ($\pm$ 0.825) to 1.54 ($\pm$ 0.840) post-COURAGE (17.6% increase, *P* = 0.012).

Pre-COURAGE, 184 patients were referred for coronary angiography for stable angina during the 59 days the catheterization laboratory was available for elective cases (mean 3.12 patients per day, $\pm$ 1.47). Post-COURAGE, 148 patients were referred for coronary angiography for stable angina during the 59 days the catheterization laboratory was available for elective cases (mean 2.51 patients per day, $\pm$ 1.61; difference in total referral volume = -19.6%, *P* = 0.034). Pre-COURAGE, 117/184 patients were found to have significant CAD on coronary angiography (63.6%). Of these, 13 patients received medical therapy (11.1%), 90 were referred for PCI (76.9%), and 14 were referred for CABG surgery (12.0%). Post-COURAGE, 100/148 patients were found to have significant CAD on coronary angiography

(67.6%, difference + 6%, *P* = 0.609 compared to pre-COURAGE). Of these, 23 patients received medical therapy

Table 1. Patient and Referral Characteristics

	Pre-COURAGE (January 1, 2007– March 26, 2007)	Post-COURAGE (March 27, 2007– June 18, 2007)	<i>P</i> Value
n	184	148	
Calendar days	85	84	
Days of elective cases	59	59	
Significant coronary artery disease (%)	63.6	66.9	0.609
Age (years)	61.5 $\pm$ 11.10	63.7 $\pm$ 10.9	0.076
Female sex (%)	33.7	37.2	0.588
Prior myocardial infarction (%)	25.0	23.6	0.876
History of heart failure (%)	6.5	5.4	0.847
Creatinine (mg/dL)	1.03 $\pm$ 0.28	1.15 $\pm$ 0.68	0.041
Dialysis (%)	0	0.68	0.913
Cerebrovascular disease (%)	5.4	5.4	0.816
Peripheral vascular disease (%)	7.1	12.2	0.162
Diabetes mellitus (%)	33.9	32.4	0.900
Hypertension (%)	74.5	83.1	0.077
Tobacco use (%)	57.1	63.9	0.281
Hyperlipidemia (%)	85.4	87.8	0.685
Family history of premature coronary artery disease (%)	46.2	50.7	0.483
Previous percutaneous coronary intervention (%)	33.7	39.9	0.295
Previous coronary artery bypass graft surgery (%)	17.4	18.9	0.829
Positive stress test (%)	63.6	60.5	0.596

Abbreviation: COURAGE, Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation.

Table 2. Results

	Pre-COURAGE (January 1, 2007– March 26, 2007)	Post-COURAGE (March 27, 2007– June 18, 2007)	P Value
n	184	148	
Referrals/day	3.12±1.47	2.51±1.61	0.034
β-Blocker use (%)	70.7	80.1	0.065
Nitroglycerin use (%)	39.7	55.5	0.006
Calcium-channel blocker use (%)	20.1	18.5	0.819
Number of anti-ischemia medications prior to coronary angiography	1.31±0.83	1.54±0.840	0.012
Significant coronary artery disease (%)	117 (63.6)	100 (66.9)	0.609
Medical therapy (%)	13 (11.1)	23 (23)	0.030
Percutaneous coronary intervention (%)	90 (76.9)	65 (65)	0.074
Coronary artery bypass surgery (%)	14 (12)	12 (12)	0.840
Abbreviation: COURAGE, Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation.			

(23%, +11.9% compared to pre-COURAGE, $P = 0.030$), 65 were referred for PCI (65%, –11.9% compared to pre-COURAGE, $P = 0.074$), and 12 were referred for CABG surgery (12%, no change compared with pre-COURAGE, $P = 0.840$).

Discussion

The COURAGE trial immediately impacted the management of stable angina in several ways. Patients referred for coronary angiography post-COURAGE were treated with more aggressive medical therapy prior to referral than patients referred pre-COURAGE, suggesting that the results reminded providers of the proven benefits of medical therapy. There was a significant reduction in coronary

angiography referral volume immediately post-COURAGE; suggesting that the trial results increased referral selectivity. This increase in referral selectivity did not translate to an increase in the frequency of significant CAD found on angiography, suggesting that intensification of medical therapy prior to referral for angiography was as likely to relieve anginal symptoms among those patients with significant CAD as those without. Finally, patients with stable angina and significant CAD on coronary angiography were more than twice as likely to receive medical therapy rather than PCI or CABG as an initial management strategy post-COURAGE. Interestingly, these changes occurred within the first few months of the COURAGE trial release. The immediacy of clinical practice change in response to the COURAGE trial is unusual and may have resulted from the near simultaneous presentation of results at a major biomedical meeting and publication in a well-respected peer-reviewed journal, the associated media coverage, and the accompanying clinical controversy. The single center retrospective design and the relatively modest referral volumes limit the general applicability of these findings. Conclusions regarding rates of referral for coronary angiography are also limited by the lack of information regarding the number of patients presenting with stable angina to our referring clinics over the study period.

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