Most Important Outcomes Research Papers on Treatment of Stable Coronary Artery Disease

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The following are highlights from the new series, *Circulation: Cardiovascular Quality and Outcomes* Topic Review. This series will summarize the most important manuscripts, as selected by the Editor, that have been published in the *Circulation* portfolio. The objective of this series is to provide our readership with a timely, comprehensive selection of important papers that are relevant to the quality and outcomes, and general cardiology audience. The studies included in this article represent the most significant research related to treatment of stable coronary artery disease (CAD). (*Circ Cardiovasc Qual Outcomes*. 2013; 6:e17-e25.)

Thought of broadly, the management of patients with stable coronary artery disease (CAD) involves significant complexity including the diagnosis of CAD, assessment of associated risk, treatment, and monitoring of symptoms during follow up. To provide sufficient focus in this month’s topic review in *Circulation: Cardiovascular Quality and Outcomes*, we have concentrated on the subset of studies examining treatment for this common condition.

On the one hand, significant consensus exists on the role of risk factor modification among patients with stable CAD. It is well accepted that patients with CAD should live a healthy lifestyle that includes regular moderate-intensity physical activity, maintenance of a healthy weight, and avoidance or cessation of smoking, all of which are class IB recommendations. It is also widely believed that barring contraindication, traditional cardiac risk factors such as hypertension, hyperlipidemia, and diabetes should be aggressively managed through a combination of lifestyle modification and evidence-based pharmacotherapy.

Yet despite these areas of consensus, significantly more controversy exists about the role of revascularization among patients with stable CAD, even in the presence of symptoms. Studies such as COURAGE and BARI-2D failed to demonstrate a reduction in major adverse cardiac events between patients revascularized with PCI or CABG as compared with patients receiving optimal medical therapy with aspirin, ACE inhibitors, statins, and other agents. However, trials such as ISCHEMIA and FAME-2 raise questions as to whether there is a subgroup of patients without left main CAD that is more likely to benefit from an invasive strategy, such as those with moderate to severe inducible ischemia on stress testing or patients with hemodynamically significant lesions by fractional-flow reserve (FFR).

We focus predominantly on these areas of controversy in the following topic review for *Circulation: Cardiovascular Quality and Outcomes*. We have therefore included papers on the clinical benefit of revascularization relative to optimal medical therapy, the cost-effectiveness of different approaches to revascularization, and trends in use of revascularization procedures. We have also included a small number of papers evaluating topics related to secondary prevention and risk factor modification.

**Risk of Elective Major Noncardiac Surgery After Coronary Stent Insertion: A Population-Based Study**

**Summary**—The optimal timing of elective noncardiac surgery after percutaneous coronary intervention (PCI) is a controversial area given the need to discontinue antiplatelet therapy. Using databases from Ontario, Canada, the authors evaluated cardiovascular outcomes of 8116 patients who underwent major elective noncardiac surgery between 2003 and 2009 and who had received coronary stents within 10 years of surgery. Approximately 34% (n=2725) had undergone stent insertion within 2 years of surgery, of whom 905 (33%) received drug-eluting stents (DES). The authors also assembled a separate cohort of 341,350 surgical patients who had not undergone previous coronary revascularization as a comparator group. The primary outcome of post-surgical 30-day major adverse cardiac events (mortality, readmission for acute coronary syndrome, or repeat coronary revascularization) occurred in 2.1% (n=170) of the study cohort. When the interval between stent insertion and surgery was <45 days, event rates were high for patients who had received both bare-metal stents (BMS) (6.7%) and DES (20.0%). The event rate for BMS approached that of intermediate-risk nonrevascularized individuals when the interval was 45 to 180 days (2.6%) but increased beyond 180 days. The event rate for DES approached that of intermediate-risk nonrevascularized individuals only after 180 days (1.2%).

**Conclusions**—While current AHA/ACC guidelines recommend waiting at least 1 month after BMS implantation and 1 year after DES implantation for elective noncardiac surgery, the authors of this study concluded that the optimal wait time was at least 46–180 days after BMS placement and 6 months after DES placement. These findings suggest that elective non-cardiac surgery may be relatively safe at shorter time intervals after stent implantation than is currently recommended, especially in the case of DES. However, numerous questions remain that may relate to perioperative complications such as the optimal strategy for antiplatelet withdrawal and reinitiation as well as the optimal management of thrombotic and bleeding complications, when they occur. Ongoing randomized trials that examine the safety of antiplatelet therapy withdrawal prior to 1 year among patients undergoing PCI may help further guide the perioperative use of antiplatelet therapies.
Public Reporting on Risk-Adjusted Mortality After Percutaneous Coronary Interventions in New York State: Forecasting Ability and Impact on Market Share and Physicians’ Decisions to Discontinue Practice

**Summary**—Although public reporting of risk-adjusted mortality rates (RAMRs) for percutaneous coronary intervention (PCI) has been adopted in several states, little is known about the influence of this reporting on PCI outcomes and cardiologist practice. Using New York state data from 1998 to 2007, the authors examined average inhospital and 30-day RAMRs for hospitals, changes in market share for hospitals and cardiologists over time as a function of RAMRs, and the proportion of physicians leaving practice in the year after each report. The authors identified 8 reports over the study period involving 351 cardiologists at 48 hospitals. The difference in RAMRs between the best and worst-performing hospitals ranged from 0.35% to 1.03% depending on year. There were no more than 3 hospitals which performed better than expected or 4 hospitals which performed worse than expected in any given year of study. The authors found that high performers had significantly lower RAMRs in the year following public reporting compared with hospitals performing as expected or worse than expected (0.47% versus 0.61% and 0.72%, respectively; p=0.02). Public reporting had no impact on market share of hospitals or cardiologists (p=0.24). In addition, there was no association between a physician’s performance quartile and the decision to leave practice in the following year after adjusting for volume of nonemergency PCI cases and years in practice (p=0.71).

**Conclusions**—This study found that New York State’s public reporting of PCI outcomes did identify and accurately predict future rates of mortality for hospitals at the extremes of performance, but was unable to differentiate between the majority of hospitals. Public reporting did not appear to stimulate changes in hospital/cardiologist market share or decisions by physicians to leave practice. Despite these limitations, public reporting of PCI performance may still be able to improve cardiovascular outcomes as public reporting of outcomes following coronary artery bypass graft surgery did in New York State over a decade ago. As experience has shown with public reporting of hospital 30-day mortality and readmission rates by the Centers for Medicare & Medicaid Services, this strategy may need to be paired with financial incentives in order to truly motivate changes in practice and the healthcare marketplace.

**Revascularization for Stable Coronary Artery Disease**

Percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) have been the primary revascularization options for patients with stable coronary artery disease (CAD) with the goals of improving survival, reducing ischemic events, and relieving symptoms. Trials comparing PCI with CABG have generally found that CABG provides more complete revascularization, with lower risk of subsequent repeat revascularization and myocardial infarction. Some studies have also suggested a survival benefit for CABG relative to PCI in certain subgroups including diabetics with multivessel CAD. On the other hand, these studies also suggest that CABG is associated with greater procedural mortality and risk of stroke.

More recent research has also compared the utility of revascularization with optimal medical therapy. The landmark COURAGE trial failed to show the superiority of PCI over optimal medical therapy with regard to death, major adverse cardiovascular events, or its subcomponents. Additional studies have investigated whether specific subgroups of patients with stable CAD may particularly benefit from revascularization. For example, the recent FAME and FAME-2 trials suggest that functional stenosis, as measured by fractional flow reserve, may identify a group of patients more likely to benefit from PCI. The ongoing ISCHEMIA trial aims to determine whether patients with moderate to severe reversible ischemia and no left main disease benefit from revascularization.

The following section contains summaries related to the outcomes of patients receiving complete versus incomplete revascularization, the cost effectiveness of medical therapy versus revascularization (PCI or CABG), the effect of revascularization (PCI or CABG) on angina symptoms, trends in use of elective PCI after publication of the COURAGE trial, and other related topics.

**Effect of Complete Revascularization on 10-Year Survival of Patients with Stable Multivessel Coronary Artery Disease: MASS II Trial**

**Summary**—The importance of complete revascularization among patients with stable multi-vessel coronary artery disease (CAD) is uncertain based on data from registries and trials. The authors performed a post-hoc analysis to determine the effect of complete revascularization on 10-year survival of patients with stable multi-vessel CAD and preserved left ventricular ejection fraction (EF) who were randomly assigned to percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) in the Second Medicine, Angioplasty, or Surgery Study (MASS II) Trial. MASS II was a randomized trial designed to compare medical treatment, angioplasty/stent treatment, and CABG in patients with multi-vessel proximal stenoses >70% with concomitant ischemia. The authors analyzed the subset of patients who underwent CABG or PCI. Primary endpoints were overall survival and cardiovascular survival among patients who underwent complete (CR) or incomplete revascularization (IR). Of 390 patients who underwent revascularization (198 CABG, 192 PCI), CR was achieved in 224 (57.4%), 63.8% of whom were in the CABG group. A greater percentage of patients in the IR group had prior myocardial infarction and 3-vessel disease. The authors found that in 10-year follow up, overall survival was no different between CR and IR groups, but cardiovascular survival was higher in the CR group (90.6% vs. 84.4%; P=0.04). This difference was mainly driven by outcomes among patients receiving PCI.

**Conclusions**—The suggestion of greater cardiovascular survival with CR must be interpreted with great caution, as the primary aim of MASS II was to study the effect of different revascularization modalities (CABG/PCI) compared with medical therapy, not to study outcomes related to the degree of revascularization. Indeed, a greater percentage of patients in the IR group had prior myocardial infarction and 3-vessel CAD, both of which would be expected to predict worse outcomes. Furthermore, it is uncertain how to interpret the finding that differences in mortality between CR and IR was driven mainly by results from the subset of patients receiving PCI.

**Cost-Effectiveness Analysis for Surgical, Angioplasty, or Medical Therapeutics for Coronary Artery Disease: 5-year Follow-Up of the MASS II Trial**

**Summary**—The authors studied comparative cost-effectiveness of major therapeutic strategies for patients with multi-vessel coronary artery disease (CAD) using data from the Second Medicine, Angioplasty, or Surgery Study (MASS II). The authors examined the cost effectiveness of 3 initial strategies for treatment: medical therapy (MT, n=203), percutaneous coronary intervention (PCI, n=205), and coronary artery bypass graft surgery (CABG, n=203). The primary end point was a composite of death, myocardial infarction, or revascularization for angina. For this study of cost-effectiveness, the authors first calculated the cumulative medical costs of each strategy for 5-years after randomization. The authors then adjusted these cumulative costs for average event-free survival time and the combination of angina-free and event-free survival. For event-free survival, MT presented 3.79 quality-adjusted life-years (QALYs),
PCI presented 3.59 QALYs, and CABG demonstrated 4.4 QALYs. Event-free costs were $9071.00 for MT, $19,967.00 for PCI, and $18,263.00 for CABG. There was a significant difference in event-free costs favoring MT versus PCI (P<0.01), MT versus CABG (P<0.01), and CABG versus PCI (P=0.01). For the combined end point of angina-free and event-free survival, MT presented 2.07 QALYs, PCI presented 2.77 QALYs, and CABG demonstrated 2.81 QALYs. Event-free plus angina-free costs were $16,553.00, $25,831.00, and $24,614.00, respectively. There was a significant event-free plus angina-free cost difference favoring MT versus PCI (P=0.04) and MT versus CABG (P<0.001).

Conclusions—Most contemporary cost-effectiveness analyses of MT and revascularization have compared MT with PCI. 32,33 This study importantly finds that MT may be more cost-effective than CABG and that CABG may be more cost effective than PCI. These results are particularly important in light of the fact that PCI and CABG have not demonstrated reduced mortality or myocardial infarction in the general population with stable multi-vessel CAD and preserved left ventricular ejection fraction. Results do require caution in interpretation, as the study was a relatively small single center trial from Brazil; treatment patterns and associated costs may differ in other international settings.

Effectiveness of Preprocedural Statin Therapy on Clinical Outcomes for Patients With Stable Coronary Artery Disease After Percutaneous Coronary Interventions

Summary—It is unknown whether the effects of preprocedural statin therapy last beyond the periprocedural period for patients undergoing percutaneous coronary intervention (PCI). Ko and colleagues 22,23 conducted a propensity-matched analysis of 6196 stable patients undergoing PCI and examined whether preprocedural statin therapy, defined as use of statins within 90 days prior to PCI, was associated with adverse cardiovascular outcomes. The primary combined end point of death or recurrent acute coronary syndrome occurred in 5.6% of patients with and 7.4% of patients without preprocedural statin therapy at 90 days after PCI (P=0.005) and in 16.7% and 19.3% of patients at 2 years after PCI, respectively (P=0.007). In multivariable Cox-models also adjusting for postprocedural statin therapy, preprocedural statin use was associated with reduced risk for the composite endpoint at 90 days (P=0.03) but not at 1-year (P=0.26) or 2-year (P=0.18) follow-up.

Conclusions—The authors proposed that preprocedural use of statins might have long term benefits and called for routine pre-procedural use of statins. There are several concerns regarding such a recommendation, however. First, the adjusted associations were not statistically significant after 1 year. Second, and more importantly, we need randomized controlled trials powered for hard endpoints to test the results of this interesting observational study before adopting widespread increases in preprocedural statin therapy, especially as statin use has been associated with potential harms including increased fasting blood glucose.

Effects of Optimal Medical Treatment with or Without Coronary Revascularization on Angina and Subsequent Revascularizations in Patients With Type 2 Diabetes Mellitus and Stable Ischemic Heart Disease

Summary—The Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) was a trial of 2364 diabetic patients with stable ischemic heart disease randomized to prompt revascularization and optimal medical therapy (n=1173, 796 patients in the percutaneous coronary intervention (PCI) stratum and 377 in the coronary artery bypass grafting (CABG) stratum) versus medical therapy alone with the option of subsequent revascularization (n=1191, 806 patients in the PCI stratum and 385 in the CABG stratum). This trial did not show a reduction in either of the two co-primary endpoints of all-cause death or a composite of cardiovascular death, myocardial infarction, and stroke with prompt revascularization. In this manuscript, the authors report on the end points of new angina, worsening angina, and subsequent coronary revascularization in the group of patients assigned to prompt revascularization compared to the group receiving medical therapy alone. They found that these 3 markers of ischemia were all less frequent in patients assigned to prompt revascularization: occurrence of new angina 37% versus 51% (P=0.001); occurrence of worsening angina 8% versus 13% (P<0.001); and subsequent coronary revascularization 18% versus 33% (P<0.001). The magnitude of benefit for all of these three endpoints was more pronounced for patients in the CABG stratum compared with the PCI stratum.

Conclusions—This report from BARI-2D suggests that among diabetic patients with stable coronary artery disease, an early revascularization strategy is associated with symptomatic benefits. It is important to note, however, that BARI-2D was not primarily designed to assess the effects of prompt revascularization on anginal symptoms. While the patient preferences remain central to decisions for revascularization and the choice of the procedure, results of studies such as BARI-2D 36 and FREEDOM indicate that CABG confers more benefits among most diabetics with multivessel coronary artery disease.

Differential Clinical Responses to Everolimus-Eluting and Paclitaxel-Eluting Coronary Stents in Patients With and Without Diabetes Mellitus

Summary—Diabetic patients undergoing percutaneous coronary intervention (PCI) with drug eluting stents (DES), as compared with bare metal stents (BMS), are known to have greater absolute reduction in target lesion revascularization (TLR) and target vessel revascularisation (TVR). However, whether the use of specific types of DES is associated with better outcomes among diabetic patients is unknown. Four previous randomized trials demonstrated that everolimus-eluting stents (EES) were superior to paclitaxel-eluting stents (PES) for all comers with stable coronary artery disease. In this study, the authors pooled data from these 4 studies to specifically evaluate whether EES or PES stents are associated with better outcomes among patients with and without diabetes. Of the 6780 pooled patients included, 869 (27.6%) had diabetes. As expected, diabetic patients were more likely to experience adverse outcomes compared to non-diabetic patients over the study period. Patients without diabetes mellitus treated with EES compared with PES had significantly reduced 2-year rates of mortality (1.9% versus 3.1%; P=0.01), myocardial infarction (2.5% versus 5.8%; P<0.0001), stent thrombosis (0.3% versus 2.4%; P<0.0001), and ischemia-driven target lesion revascularization (3.6% versus 6.9%; P<0.0001). However, among patients with diabetes mellitus, there were no significant differences between the 2 stent types for these outcomes.

Conclusions—Through use of pooled data for non-acute patients undergoing PCI for simple and moderate coronary lesions, this study furthers suggests the superiority of EES compared to PES in non-diabetic patients via significant reductions in 2-year mortality, myocardial infarction, stent thrombosis, and TLR. These results mirror the overall results shown by the individual trials pooled in this analysis, thereby demonstrating that EES should be the stent of choice to improve outcomes among non-diabetic patients. However, the benefit of EES over PES was not present among diabetic patients. In contrast, a more recent meta-analysis involving a larger number of trials in a broader cohort of diabetic patients (including patients with acute coronary syndromes) suggests EES may be more efficacious.
and associated with a better safety profile compared to other DES types. Thus while it is generally accepted that DES are superior to BMS in treatment of stable coronary lesions among diabetics, the choice of optimal DES remains uncertain.

The Cost-Effectiveness of Percutaneous Coronary Intervention (PCI) as a Function of Angina Severity in Patients With Stable Angina

Summary—The COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial compared percutaneous coronary intervention (PCI) plus optimal medical therapy (OMT) to OMT alone in reducing the risk of cardiovascular events in 2287 patients with stable coronary disease. This trial showed no difference in death, myocardial infarction or other common cardiovascular endpoints between groups at a median follow-up time of 4.6 years but did show a reduction in angina severity with PCI, which can be an important therapeutic goal in and of itself. However the cost effectiveness of PCI for relief of angina and the relation of cost-effectiveness to baseline angina severity is unknown. In this paper, using the COURAGE study population, the authors used the Seattle Angina Questionnaire (SAQ) to assess the severity of angina prior to PCI and determine the incremental cost effectiveness ratio (ICER) of PCI +OMT versus OMT alone. A higher SAQ score indicates better health status; clinically significant symptomatic improvement in physical limitation, angina severity, and quality of life was defined as an increase of ≥28, ≥20, and ≥16 in each domain of the SAQ score respectively. The study demonstrates that clinically significant symptomatic improvement with PCI was achieved in patients with the lowest and middle tertiles of SAQ scores. However, across all patients, the ICER of PCI was high with values ranging between US$80,000 and US$330,000 per patient to gain significant clinical improvement in the lowest and middle tertile SAQ scores and US$520 000 to >US$ million for those in the highest tertile SAQ score (minimal angina or disability).

Conclusions—This important analysis questions the cost-effectiveness of the widely employed practice of PCI for symptom improvement. The landmark COURAGE trial showed no improvement in major adverse cardiac events with PCI over optimal medical therapy alone in the treatment of stable coronary disease but did show a reduction in angina severity, which can be an important endpoint from a patient perspective. The present analysis confirms the improvement in angina, disability, and health related quality of life as measured by the SAQ with the greatest benefit seen in those who had the most disabling symptoms prior to PCI. However this benefit comes at a high price - a marked increase in the ICER that exceeds the typically accepted cost thresholds for intervention, which are generally between US$50,000 and US$100,000. Whether such cost is warranted for symptomatic improvement may be important to consider when patients are referred for PCI.

Percutaneous Coronary Intervention Versus Optimal Medical Therapy in Stable Coronary Artery Disease: A Systematic Review and Meta-Analysis of Randomized Clinical Trials

Summary—The authors sought to evaluate the benefit of percutaneous coronary intervention (PCI) in addition to optimal medical therapy compared to optimal medical therapy alone for management of stable ischemic heart disease. They performed a systematic review and meta-analysis, searching PubMed, EMBASE, and CENTRAL databases, until January 2012, for randomized clinical trials comparing revascularization with PCI to optimal medical therapy (OMT) in patients with stable coronary artery disease. The primary outcome was all-cause mortality, and secondary outcomes included cardiovascular death, nonfatal myocardial infarction, subsequent revascularization, and freedom from angina. Primary analyses were based on longest available follow-up, while secondary analyses were stratified by trial duration, with short-term (≤1 year), intermediate (1–5 years), and long-term (>5 years) follow-up periods. They identified 12 randomized clinical trials enrolling 7182 participants meeting inclusion criteria. For the primary analyses, when compared with OMT, PCI was not associated with a significant improvement in mortality (risk ratio [RR], 0.85; 95% CI, 0.71–1.01). PCI was also not associated with improvement in cardiac death (RR, 0.71; 95% CI, 0.47–1.06), nonfatal myocardial infarction (RR, 0.93; 95% CI, 0.70–1.24), or repeat revascularization (RR, 0.93; 95% CI, 0.76–1.14), with consistent results over all follow-up time points. However, for freedom from angina, there was a significant improved outcome with PCI as compared with the OMT group (RR, 1.20; 95% CI, 1.06–1.37) at all time points after intervention.

Conclusions—Outcomes associated with the non-invasive management of stable ischemic heart disease appears similar to invasive management with PCI in the current era of stents and potent antiplatelet therapy. While the ISCHEMIA trial examines the role of medical therapy in patients with moderate to severe ischemia, the recent COURAGE and BARI-2D studies have demonstrated no additional mortality benefit with PCI in patients with mild to moderate ischemic heart disease. The above analysis reinforces the role of medical therapy as a viable alternative to PCI. However, certain limitations such as the heterogeneity of trials included in the analysis as well as the lack of comparator groups receiving more recent drug eluting stents may limit the generalizability of study results to routine medical practice.

Percutaneous Coronary Intervention Versus Optimal Medical Therapy for Prevention of Spontaneous Myocardial Infarction in Subjects With Stable Ischemic Heart Disease

Summary—The authors sought to examine the prognostic significance of both periprocedural myocardial infarction associated with percutaneous coronary intervention (PCI) and spontaneous myocardial infarction following intervention. They searched PubMed, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) for randomized clinical trials published before October 2012 that compared PCI to optimal medical therapy (OMT) for stable ischemic heart disease and reported the following MI outcomes: spontaneous nonprocedural MI, procedure-related MI, and all MI, including procedure-related MI. The authors identified 12 randomized clinical trials with 37 548 patient-years of follow-up and used a mixed effect Poisson regression model to compare outcomes. PCI compared to OMT alone was associated with a significantly lower incident rate ratio (IRR) of spontaneous nonprocedural MI (IRR=0.76; 95% confidence interval [CI], 0.58–0.99) at the risk of a higher rate of procedural MI (IRR=4.11; 95% CI, 2.53–6.88) without any difference in the risk of all MI (IRR=0.96; 95% CI, 0.74–1.21). No significant difference was noted with PCI compared to OMT for all-cause mortality (IRR=0.88; 95% CI, 0.75–1.03) or cardiovascular mortality (IRR=0.70; 95% CI, 0.44–1.09).

Conclusions—Recent evidence has demonstrated no discernible difference in mortality with use of OMT compared to PCI. The present review suggests a possible reason for this lack of difference, as any benefit in reduction of spontaneous MI with PCI may be counterbalanced by the increased risk of periprocedural MI. While the prognostic importance of periprocedural MI has been the subject of some debate, the results of this study suggest that these events may be of material significance. These results are also consistent with a more controversial hypothesis that PCI in patients with stable coronary disease does not improve mortality as neither procedural MI nor spontaneous MI in this specific population is associated with significant enough harm to influence overall mortality.
Recent Changes in Practice of Elective Percutaneous Coronary Intervention for Stable Angina

Summary—The COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial showed that percutaneous coronary intervention (PCI) for patients with stable coronary artery disease failed to reduce the risk of major adverse cardiovascular events when added to optimal medical therapy. The authors of the current study sought to analyze the impact of the COURAGE trial results on clinical practice using the Northern New England Cardiovascular Disease PCI Registry that enrolled 26,388 consecutive patients who underwent PCI between January 2006 and June 2009. Over the study period, there was a significant decrease in total PCI volume from 2064 cases in first quarter of 2006 (before COURAGE) to 1708 cases in third quarter of 2007 (after COURAGE) (P<0.01). These trends were sustained through June 2009. In addition, the proportion of patients receiving PCI for stable angina decreased from a high of 20.9% before COURAGE to 16.1% (P<0.01) in the second quarter of 2007 after COURAGE. As with overall PCI volume, the decrease in percentage of PCI cases for stable angina was maintained through the end of the study period.

Conclusions—The findings from this study provide empirical data supporting the adoption of findings from the COURAGE trial regarding the equivocal benefit of PCI above and beyond optimal medical management in patients with stable angina. During a time of growing demand for comparative effectiveness studies, these study findings provide encouragement that new evidence can be translated into practice. However, this study cannot clearly demonstrate a causal impact of COURAGE on PCI practices. In addition, these findings may not be broadly generalizable, as the database is geographically limited. Finally, it is unclear what impact these changes in PCI volumes have had on patient outcomes.

Comparative Outcomes for Patients Who Do and Do not Undergo Percutaneous Coronary Intervention for Stable Coronary Artery Disease in New York

Summary—In real world practice, it is unknown how frequently patients with stable coronary artery disease (CAD) undergoing cardiac catheterization receive percutaneous coronary intervention (PCI) in addition to routine medical treatment (RMT). The authors describe PCI rates among patients with stable CAD undergoing cardiac catheterization in the state of New York between 2003 and 2008. The authors also compare outcomes of patients who did and did not undergo PCI using a propensity match analysis over a median follow-up time of 2.9 years. Overall, 89% of patients undergoing cardiac catheterization also received PCI. At 4 years, patients undergoing PCI plus RMT had significantly lower event rates compared with RMT alone for a composite of mortality or myocardial infarction (MI) (16.5% versus 21.2%; P=0.003), mortality (10.2% versus 14.5%; P=0.02), MI (8.0% versus 11.3%; P=0.007), and subsequent revascularization (24.1% versus 29.1%; P=0.005). Adjusted hazard ratios for RMT alone versus PCI with RMT were 1.49 (95% confidence interval, 1.16–1.93) for mortality/MI and 1.46 (95% confidence interval, 1.08–1.97) for mortality.

Conclusions—This real world experience shows that a surprisingly high proportion (89%) of patients with stable CAD undergoing cardiac catheterization also received PCI. Yet despite this high number of interventions, the propensity-matched analysis demonstrated improved outcomes among the PCI group, which sharply contrasts with results from landmark clinical trials such as COURAGE2 and BARI-2D.1 This discrepancy could be due to several reasons including potential differences between RMT used in New York state and the “optimal medical therapy” used in COURAGE and other trials.

In addition, it is likely that some degree of residual confounding remains despite propensity analysis. For example, it is likely that some patients with severe 3VD or extremely complex lesions did not receive PCI.49

Appropriateness of Percutaneous Coronary Interventions in Washington State

Summary—A growing number of states across the US are adopting the 2009 Appropriateness Criteria for percutaneous coronary intervention (PCI).50 With these criteria as a guide, the authors sought to determine the prevalence of appropriate, uncertain, and inappropriate PCI use at the patient level along with any facility-level variations in Washington State prior to the implementation of these standards. The study used the Clinical Outcomes Assessment Program (COAP) to identify all 13,291 PCIs from 31 facilities in Washington in 2010, of which 9,924 (75%) could be classified by the Appropriate Use Criteria. Fifteen percent of PCI procedures performed in the acute setting were considered unclassifiable, and 50% of PCI procedures performed in the non-acute setting were considered unclassifiable. Of acute procedures, 98% were appropriate, <1% were uncertain, and 1% were inappropriate. Of non-acute procedures, 44% were appropriate, 39% were uncertain, and 17% were inappropriate. Angina severity was generally low among non-acute patients, as 77% had ≤ class II angina. Sixty-eight percent of non-acute patients did not have a documented non-invasive risk assessment. Across facilities, there was little variation in PCI appropriateness for acute indications (IQR 0.3%, 1.1%); variation was more marked for non-acute indications (IQR 9%, 24%).

Conclusions—This study found that PCIs performed in Washington in 2010 for acute indications were largely appropriate but that PCIs performed for non-acute indications were much more often unclassifiable or inappropriate. Appropriateness of PCI for non-acute patients varied markedly across hospitals. These findings are consistent with previous studies utilizing the National Cardiovascular Data Registry (NCDR), which identified 1% of acute PCIs and 12% of non-acute PCIs as inappropriate.51 However, both of these studies are limited by the inability to properly categorize the appropriateness of a large percentage of elective PCIs. Without this information, it is hard to feel confident about the point estimates for PCI appropriateness among the stable CAD population.52

Secondary Prevention

The role of secondary prevention of coronary artery disease (CAD) by optimal medical therapy and comprehensive risk factor modification is well established; these measures prevent disease progression and in doing so improve mortality, reduce risk of subsequent cardiac events, and improve quality of life.53 Medical therapies for secondary prevention are extensively summarized in clinical guidelines. Briefly, aspirin reduces the risk of subsequent vascular events by approximately 25% in high risk individuals.44 Similarly, β-blockers reduce the risk of recurrent myocardial infarction, sudden cardiac death, and mortality.55 In addition to dietary modification, lipid lowering therapy with a statin improves long-term survival with an estimated 10% relative reduction in death per 38.6 mg/dl reduction in serum LDL level.56 Similarly ACE-inhibitors and angiotensin receptor blockers (ARBs) reduce the relative risk of death in patients with stable CAD irrespective of left ventricular systolic function.57 Beta-blockers, ACE/ARBs, and other antihypertensives may be useful for lowering blood pressures (BP) to a target BP < 140/90 (or < 130/80 in those with diabetes or chronic kidney disease).46 Joint guidelines from the American Heart Association/American College of Cardiology give class 1A or 1B recommendations for all of the above therapies.

Evidence is not limited to medical therapies – additional studies have demonstrated the salutary impact of lifestyle changes on risk...
factors and subsequent outcomes. Smoking cessation is estimated to reduce mortality by at least 33% after an acute myocardial infarction (AMI) or coronary artery bypass grafting.88 Meta-analyses of exercise-based cardiac rehabilitation programs have shown a medium to long term reduction in cardiac and all-cause mortality.7,51,60 More broadly, 30 to 60 minutes of moderate-intensity physical activity has been associated with lower lipid levels and systolic blood pressure.53

While no data has shown that weight reduction improves outcomes, even modest weight loss (~10%) in obese patients is associated with an improvement in risk factor profile.44 Finally, depression is common after AMI.52 Given the debilitating effects of this condition and because symptom improvement may be achieved with treatment, current guidelines recommend routine screening for depression when assessing patients for secondary prevention.3

The following section contains summaries related to outpatient statin therapy use, cardiovascular risk of high- versus moderate-intensity aerobic exercise,50 routine screening of depression,44 and risk stratification among patients with established CAD.10

**Antiplatelet Drug Response Status Does Not Predict Recurrent Ischemic Events in Stable Cardiovascular Patients: Results of the Antiplatelet Drug Resistances and Ischemic Events study**

**Summary**—Although previous studies among patients with acute coronary syndromes or those undergoing percutaneous coronary interventions suggested that antiplatelet drug response could be a marker of subsequent recurrent major adverse cardiovascular events (MACE), such associations were uncertain for patients with stable ischemic atherothrombotic disease.10 The authors tested the utility of platelet function testing for risk stratification among stable patients in the Antiplatelet Drug Resistances and Ischemic Events (ADRIE) study (n=771). After a median follow-up of 3 years, the primary endpoint of recurrent MACE occurred in 120 patients (15.6%). Hypertension, smoking, older age, and elevated LDL were predictive of recurrent MACE (C-index: 0.63, P<0.001). However, none of the antiplatelet drug response tests, including the serum thromboxane B2 for the aspirin response, the vasodilator phosphoprotein assay for the clopidogrel response, and the aggregation-based assays yielded significantly different results between patients with and without recurrent MACE. Platelet function testing results were likewise unable to add incremental predictive value to other commonly assessed clinical variables and laboratory results for detection of recurrent MACE. The results were consistent under a variety of sensitivity analyses.

**Conclusions**—This contribution, in conjunction with other recent investigations, underscore the lack of utility of platelet function testing as a marker for ensuing MACE in patients with stable cardiovascular disease. Even when a marker of increased risk of MACE, these assays have not been shown to improve outcomes when used to guide treatment strategies in the context of randomized controlled trials.69 It is critical that improved outcomes be demonstrated prior to widespread adoption of novel expensive biomarker assays.10

**Statin Use in Outpatients With Obstructive Coronary Artery Disease.**

**Summary**—Despite the guideline recommendation that all patients with coronary artery disease (CAD) receive a statin medication, even when low-density lipoprotein cholesterol (LDL-C) level is <100 mg/dL, it is unknown what fraction of outpatients with CAD receive statin therapy. The authors therefore used the American College of Cardiology’s Practice Innovation and Clinical Excellence (PINNACLE) registry to evaluate treatment with statins among 38,775 outpatients with obstructive CAD and no contraindications to statin therapy. The primary outcome was the fraction of patients treated with a statin, a non-statin lipid-lowering medication, or no lipid-lowering therapy. The authors found that 78% (30,610) of patients were treated with a statin—60% (23,719) received a statin only and 17% (6,441) received a statin plus another non-statin lipid-lowering agent. About 5% (2,042) of patients were treated only with a non-statin, and 17% (6,573) were not treated with any lipid-lowering therapy. The authors also used multivariate hierarchical regression models to determine independent predictors of statin use. Male sex (adjusted risk ratio (RR) 1.10), coexisting hypertension (adjusted RR 1.07), prior coronary artery bypass graft surgery (adjusted RR 1.09), and prior percutaneous coronary intervention (adjusted RR 1.11) were associated with higher likelihood of statin use, whereas lack of medical insurance (adjusted RR 0.94) was associated with lower likelihood of statin use. Additionally, among 3,365 untreated patients who had LDL-C levels available, 53% (1,794) had LDL-C levels <100 mg/dL, while 47% (1,571) had LDL-C levels ≥100 mg/dL.

**Conclusions**—This large multicenter registry study demonstrates that 22% of eligible patients with stable CAD are not receiving statin therapy. The national rate of statin use in the CAD population is likely to be even lower than in this study, as PINNACLE sites are highly motivated to participate in data sharing and performance improvement. Women, patients without prior procedures, and patients who lack medical insurance are less likely to receive statin therapy, suggesting that, despite strong clinical evidence and clear guidelines, significant gaps exist in outpatient care for CAD. Furthermore, among patients with stable CAD not receiving any lipid-lowering therapy who had LDL-C levels available, about half had LDL-C <100 mg/dL and half had LDL-C ≥100 mg/dL. The former finding suggests that some physicians may not prescribe statins to eligible patients with stable CAD.
patients with stable CAD solely because they have LDL-C levels < 100 mg/dl, despite evidence that statins have efficacy even in this subgroup.66 The latter finding suggests that, surprisingly, there may be some stable CAD patients who are simply not considered for lipid-lowering therapy.9

Cardiovascular Risk of High- Versus Moderate-Intensity Aerobic Exercise in Coronary Heart Disease Patients

Summary—Aerobic exercise reduces the risk of cardiovascular events in patients with prior cardiovascular disease, but concerns have been raised that vigorous exercise may result in severe cardiac events among susceptible patients. The authors studied an unselected group of 4,846 patients with stable coronary artery disease (CAD) who underwent cardiac rehabilitation at 3 centers in Norway between 2004 and 2011. The mean age was 57.8 years, and 70% of patients were male. Patients were evaluated with medical exams and full-lead electrocardiograms and then underwent multiple 1-hour sessions of either high-intensity exercise, defined as interval training at an intensity of 85% to 95% of peak heart rate, or moderate-intensity exercise, defined as continuous exercise at 60% to 70% of peak heart rate. Exercise typically consisted of treadmill use, and the average number of sessions per patient was 37. The primary outcome was defined as cardiac arrest or acute myocardial infarction during exercise or within the first hour of finishing exercise. Overall, there were 129,456 hours of moderate-intensity exercise and 46,364 hours of high-intensity exercise. One fatal cardiac arrest occurred during moderate-intensity exercise, 2 nonfatal cardiac arrests occurred during high-intensity exercise, and there were no acute myocardial infarctions.

Conclusions—The most important finding of this study is that the rate of severe cardiac events is low during exercise among an unselected group of patients with stable CAD—1 event per 129,456 hours of moderate-intensity exercise and 1 event per 23,182 hours of high-intensity exercise. This provides reassuring evidence about the safety of even high-intensity exercise among patients undergoing cardiac rehabilitation. However, it is unknown whether high intensity exercise in unsupervised settings would result in similarly low event rates, as rehabilitation specialists are trained to monitor patients for potential symptoms and signs of instability and adjust work-load as needed. In addition, as the calculated power for detecting a difference in event rates between the two exercise groups was only 23%, the negative results may not reflect true underlying differences in risk associated with increasing exercise intensity.65

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References


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