Ischemia Is the Critical Determinant of Revascularization Benefit: An Interventionalist's Perspective of the COURAGE Trial

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Although advances in percutaneous catheter-based interventions (PCI) for coronary artery disease have been associated with reductions in angiographic as well as clinical restenosis, no consistent reduction in the occurrence of death or nonfatal myocardial infarction (MI) has been observed either between devices (balloon vs bare-metal stent vs drug-eluting stent [DES]) or between device and medically treated patients with chronic stable coronary disease. Objective evidence of myocardial ischemia—irrespective of the methodology used to demonstrate its presence—is qualitatively and quantitatively related to the occurrence of death and/or nonfatal MI. The magnitude of ischemia is directly proportional to the magnitude of revascularization benefit (reduction in death or MI). Revascularization by PCI is more effective in reducing ischemia than medical therapy alone. The evolution of both PCI technology (DES) and adjunctive pharmacology has improved the relative magnitude and durability of PCI benefit compared with medical therapy alone.
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Key words: Ischemia • Revascularization • Coronary artery disease • Drug-eluting stents

Percutaneous coronary intervention (PCI) has played an integral role in the therapeutic management strategies for patients who present with either acute or nonacute coronary artery disease (CAD) syndromes. Although technologic iteration from balloon to bare-metal stents (BMS) and subsequently to drug-eluting stents (DES) has been accompanied by a progressive decline in both angiographic as well as clinical restenosis,[1-3] no discernible differences in the occurrence of death or nonfatal myocardial infarction (MI) have been

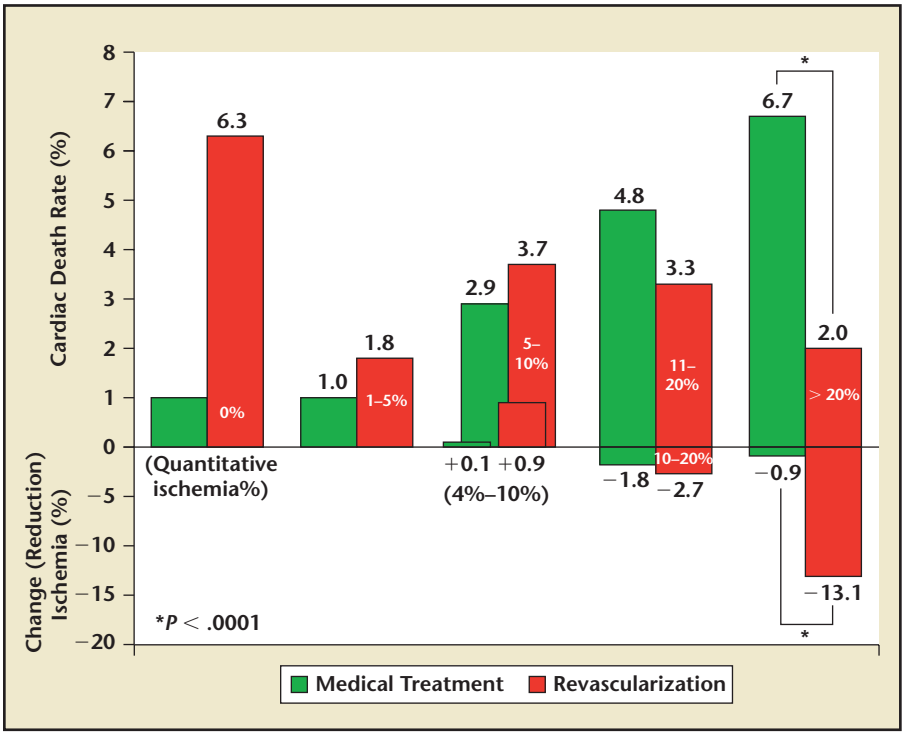
observed either among devices (balloon vs BMS vs DES) or between device and medically treated patients with chronic stable CAD.[4,5]

In general, the nature and magnitude of clinical benefit attributable to either PCI or medical therapy have been directly proportional to the acuity of the clinical syndrome being treated.[6] Multiple randomized controlled clinical trials have compared revascularization with PCI (in combination with medical therapy) versus medical therapy alone for the management of chronic CAD.[7-9] The dynamic evolution of both catheter-based and pharmacologic therapies as well as subtle differences in patient cohorts have made either across-trial or pooled trial analyses difficult and, at times, divergent with respect to the apparent impact of revascularization on subsequent survival.[4,7-9] However, one common observation has been that objective evidence of myocardial ischemia is both qualitatively and quantitatively related to the occurrence of death and/or nonfatal MI. Furthermore, the degree of myocardial ischemia is directly proportional to the magnitude of relative clinical benefit (reduction in death or MI) provided by PCI (vs medical therapy). Finally, the evolution in both PCI technology and adjunctive periprocedural pharmacology has improved the relative magnitude and durability of PCI benefit compared with medical therapy alone.

The Link Between Ischemia and Outcomes

Quantitative myocardial perfusion single-photon emission computed tomography (SPECT) scanning (MPS)–documented ischemia has been directly correlated with the occurrence (rate/year) of cardiac-related death or nonfatal MI.[10] Those patients with the largest ischemic burden have the highest incidence of death or MI in follow-up. Importantly, patients with the largest ischemic burden also demonstrate the greatest relative reduction in objective ischemia following successful revascularization (compared with medical therapy alone).[11] Finally, the greater reduction in myocardial ischemia afforded by revascularization appears to translate into improved survival (Figure 1).[12] In an analysis of 10,627 consecutive patients followed for about 2 years, MPS quantitative ischemia was directly proportional to mortality on medical therapy.[12] Furthermore, the relative survival advantage provided by revascularization (vs medical therapy) was a direct function of ischemic burden (Figure 2). The relationship of ischemia to adverse clinical outcomes is evident regardless of the methodology used to demonstrate ischemia. For example, in the Asymptomatic Cardiac Ischemia Pilot (ACIP) study, ischemia documented on ambulatory electrocardiographic (AECG) monitoring was a powerful correlate of death, nonfatal MI, or subsequent hospitalization for an ischemic event in asymptomatic patients.[13] Importantly, AECG and SPECT perfusion imaging demonstrated a lack of concordance.[14] Thus, AECG provided additional, prognostic information not evident by MPS imaging alone. Revascularization of asymptomatic patients with objective evidence of ischemia in the ACIP trial was associated with improvement in survival

Figure 1. *Cardiac death rate stratified by myocardial perfusion SPECT scanning quantification of ischemia (% myocardium) and treatment modality in 10,627 consecutive patients followed for 1.9 years ± 0.6 years (top). Death rate is proportional to the size of the ischemic defect. Patients with larger ischemic burden have a lower relative death rate following revascularization (vs medical treatment). Change (reduction) in ischemic defect stratified by size (quantitative ischemia %) of baseline ischemic defect and treatment modality (bottom). Patients with the largest baseline ischemic defects had a greater reduction in effect size following revascularization (vs medical treatment). SPECT, single-photon emission computed tomography. Adapted with kind permission from Springer Science+Business Media.* Journal of Nuclear Cardiology. *Serial changes on quantitative myocardial perfusion SPECT in patients undergoing revascularization or conservative therapy. Volume 8. 2001:428-437. Berman DS et al.[11] Figure 1; and Hachamovitch R et al. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography.* Circulation. *2003;107(23):2900-2907.[12]*



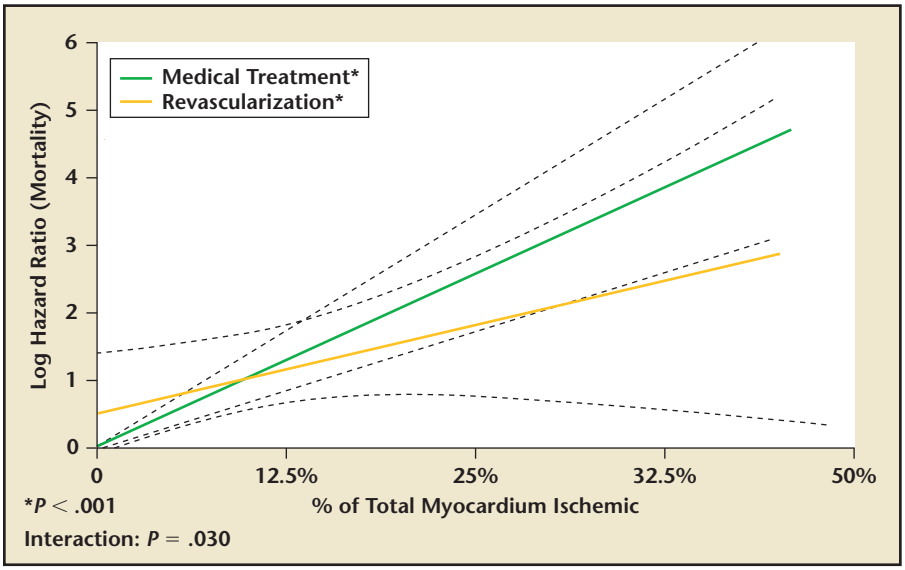


Figure 2. *Mortality hazard by treatment modality and quantitative SPECT ischemia in 10,627 consecutive patients followed for 1.9 years ± 0.6 years. Mortality in medically treated patients is directly proportional to the quantity (%) of ischemic myocardium, as is the relative magnitude of survival benefit afforded by revascularization (vs medical therapy). SPECT, single-photon emission computed tomography. Data from Hachamovitch R et al.*[12]

free from MI compared with angina or ischemia-guided medical therapy at 2-year follow-up.[15] Stress echocardiographic evidence of ischemia, with or without accompanying anginal symptoms, was associated with significant hazard for cardiovascular death or MI in the Heart and Soul Study.[16] Those patients with both angina and echocardiographic evidence of ischemia had the greatest risk of adverse events even after adjustment for multiple other predictive variables. Recent data have also demonstrated a relationship between in-laboratory coronary lesion hemodynamic functional assessment by fractional flow reserve (FFR) and important clinical outcomes, even in patients with normal regional perfusion by MPS and noncritical angiographic stenoses.[17] FFR-guided PCI was demonstrated to be more safe and effective than angiography alone in a large, randomized trial.[18] Finally, recent data have compared and correlated the anatomic extent of CAD by computed tomography angiography (CTA) with the functional degree of ischemia by MPS.[19] Annual risk-adjusted mortality was similar in propensity-matched cohorts stratified by either CTA or MPS risk categories.

The COURAGE Nuclear Substudy

The prespecified nuclear substudy of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial enrolled 314 patients who underwent serial rest/stress MPS both prerandomization and at 6 to 18 months following random assignment to either PCI plus optimal medical therapy (OMT) or OMT alone.[20] The timing of late (6-18 months) MPS was chosen to be beyond the window for occurrence for in-stent restenosis and delayed enough to allow the effects of OMT to be observed. The total perfusion defect (TPD) was quantified both during stress and at rest, and the percent ischemic myocardium was calculated as the stress TPD–rest TPD. Patients were classified as having minimal (< 5%), mild (5.0%-9.9%), or moderate to severe (≥ 10%) ischemia. A significant reduction in ischemia was defined as 5% or greater because this value exceeds the threshold for test repeatability and was used as the study primary endpoint.[21]

PCI in combination with OMT was more effective in reducing ischemia than OMT alone (Figure 3), despite the fact that 15% of patients randomly assigned to OMT required subsequent PCI for refractory and/or progressive anginal symptoms. The trial primary endpoint (ischemia reduction ≥ 5%) was more frequent in the PCI plus OMT cohort than following OMT alone (33.3% vs 19.8%; $P = .004$). Importantly, ischemia reduction of 5% or more was associated with improved event-free survival for all enrolled patients, particularly for those with at least moderate (≥ 10%) ischemia at baseline (Figure 4). Finally, the quantitative degree of ischemia on MPS at 6 to 18 months was directly related to the occurrence of death or MI in follow-up (Figure 4). The COURAGE nuclear substudy concluded that "PCI added to OMT was more effective in reducing ischemia and improving angina than OMT alone, particularly in patients with moderate to severe pretreatment ischemia." This conclusion should be tempered by the applicable caveats regarding the performance of PCI in COURAGE, including: 1) PCI was suboptimal with respect to both per-patient and per-lesion success rates; 2) PCI was incomplete in that only 47% of patients with multivessel disease had complete coronary revascularization; and 3) PCI was inadequate with respect to utilization of leading-edge technology of proven efficacy (only 3% of stents were DES and 14% of cases had balloon angioplasty). To fully understand the artificial

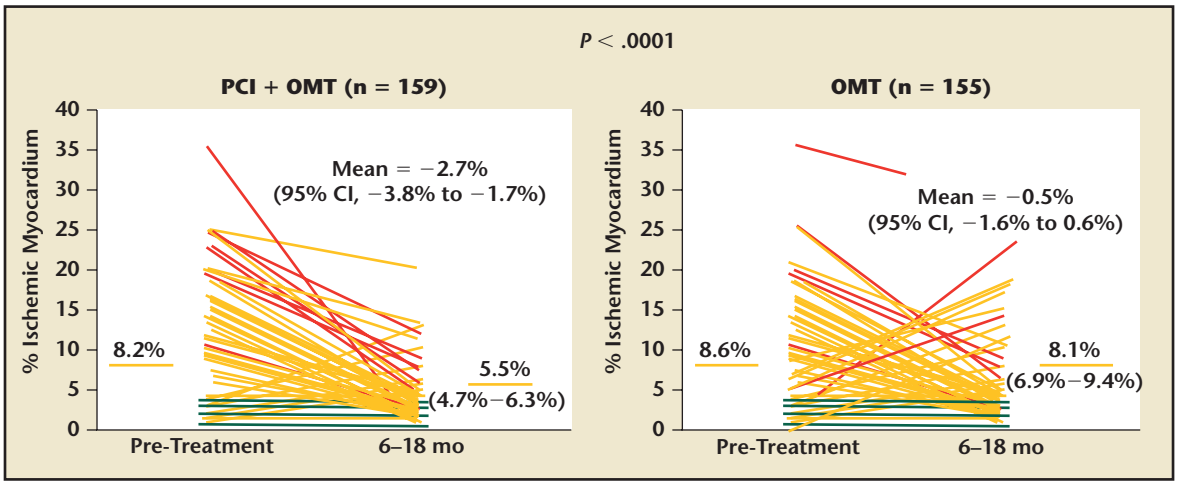


Figure 3. *Baseline (pretreatment) and follow-up (6-18 months) SPECT myocardial perfusion scan results by randomly assigned treatment strategy in the COURAGE trial nuclear substudy. The strategy of PCI plus OMT was more effective in reducing myocardial ischemia than OMT alone. SPECT, single-photon emission computed tomography; COURAGE, Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation; PCI, percutaneous coronary intervention; OMT, optimal medical therapy; CI, confidence interval. Data from Shaw LJ et al.*[20]

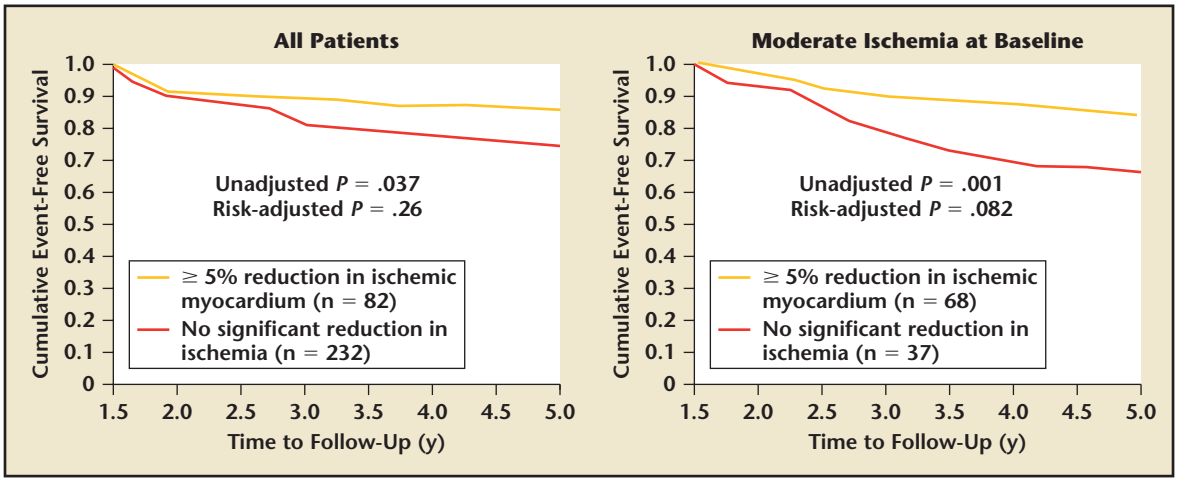


Figure 4. *Cumulative event-free survival for all patients (left) and for those patients with moderate to severe (≥ 10%) ischemia at baseline stratified by attainment of the study primary endpoint (≥ 5% ischemia reduction). Those patients who achieved the study primary endpoint enjoyed significant improvement in event-free survival. Data from Shaw LJ et al.*[20]

limitations of PCI as performed in COURAGE and, thus, the potential for more marked and durable benefit following revascularization, each of these points should be addressed.

First, of 1149 patients randomly assigned to PCI, 76 did not undergo the procedure. These patients either refused, were felt to be unsuitable for PCI on rereview of the qualifying baseline angiogram, or had unsuccessful attempts at crossing any target lesion (n = 27) with a guidewire and then, inexplicably, were lost to long-term follow-up.[5] The true per patient success rate is not 89% (as reported) but instead, 83% for intention-to-treat or 87% based on treatment received (attempt to cross with guidewire).[22] Similarly, the per-lesion success rate is not 93% (as reported) but, instead, is at best 91% by treatment-received analysis.[23] Secondly, although 69% of the 1149 patients assigned to PCI had multivessel disease, only 36% of patients received 2 or more stents. Thus, at least 371 of the 787 patients (47%) with multivessel disease had incomplete revascularization. Recent data suggest that an incomplete revascularization by PCI with DES is associated with increased hazard for death or nonfatal MI, even in the absence of chronic total coronary occlusion (Figure 5).[24] Third, the efficacy of DES (vs BMS)

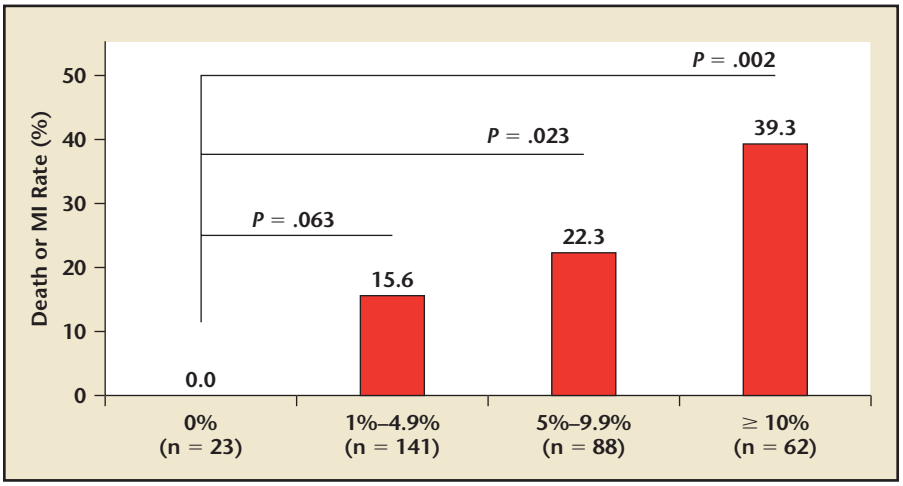


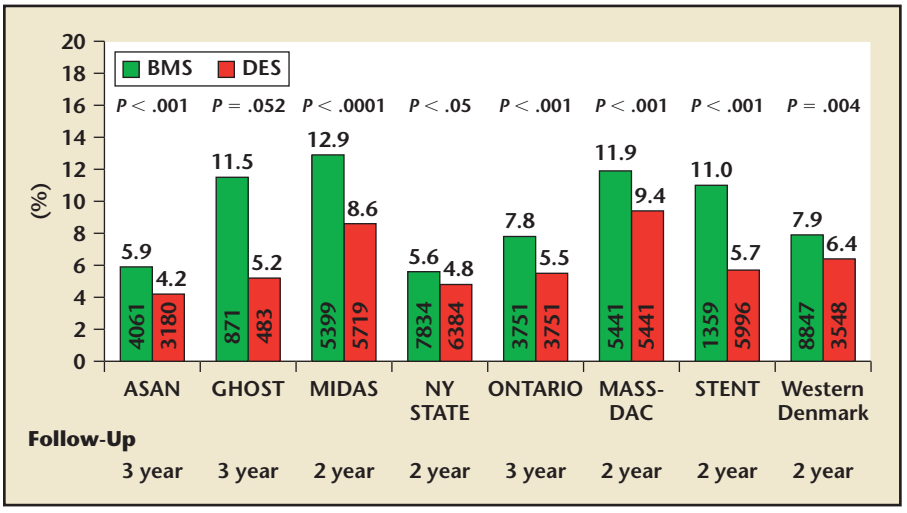
Figure 5. *The incidence of death or nonfatal MI stratified by the degree of residual myocardial ischemia present on the 6-month to 18-month myocardial perfusion scan. The composite occurrence of death or MI is directly proportional to the degree of residual myocardial ischemia. MI, myocardial infarction. Data from Hannan EL et al.*[24]

based on multiple randomized controlled clinical trials has been predominantly based on an observed 70% to 80% reduction in binary angiographic and 50% to 70% reduction in clinical (target lesion or vessel) restenosis.[25] This remarkably durable benefit is achieved with no "penalty" with respect to the incidence of death or nonfatal MI in late follow-up. The durable coronary patency benefit of DES (compared with BMS) was reflected by a reduction in target vessel distribution ischemia assessed by MPS at 6 months following PCI in the Basel Stent Cost-Effectiveness (BASKET) trial nuclear substudy.[26] Furthermore, multiple large and well-constructed clinical registries suggest a directionally consistent and significant reduction in mortality (~20%) at 1- to 2-year follow-up in patients treated with DES compared with BMS (Figure 6). The substantial relative benefit of DES has been observed in both older patients (Medicare beneficiaries)[27-29] and, particularly, in those treated for off-label indications. Indeed, a recent pooled analysis of 5 separate registries evaluating DES versus BMS treatment of off-label indications demonstrated a significant reduction in mortality as well as target vessel revascularization in favor of DES.[30] This observation has been complemented by similar findings in the Scottish Revascularization Registry.[31] Finally, a recent meta-analysis of 22 randomized controlled clinical trials and 34 observational studies involving 193,371 stented patients demonstrated the safety of DES (vs BMS) and a highly significant reduction in target vessel revascularization[32] (Figure 7). Taking all these issues into account, a reasonable final conclusion of the COURAGE nuclear substudy would be that more effective and complete revascularization using contemporary proven technology (DES) would have increased the relative magnitude and durability of ischemia reduction associated with PCI (plus OMT) compared with OMT alone.

Silent, Asymptomatic Ischemia

The fact that many patients with severe coronary stenoses and objective evidence of myocardial ischemia have no symptoms of angina is well recognized. In the COURAGE trial, 12% of patients enrolled had silent ischemia as defined by the presence of new, abnormal ST-T changes at rest, exercise-induced ischemic electrocardiographic changes, or stress-induced (either exercise or pharmacologic) MPS defects.[33] The clinical demographics and nuclear stress test findings were similar between patients with silent or symptomatic ischemia, including the proportion

Figure 6. *All-cause mortality at 2- to 3-year follow-up of patients treated with BMS or DES from multiple clinical registry experiences. DES treatment is associated with significant improvement in survival. The numbers of patients in each treatment are shown. BMS, bare-metal stent; DES, drug-eluting stent; ASAN, Asan Medical Center, Seoul, South Korea; GHOST, Guthrie Health System PCI registry; MIDAS, Multicenter International Diabetes–Acute Coronary Syndromes registry; NY STATE, New York State registry; MASS-DAC, Massachusetts Data Analysis Center registry; STENT, Strategic Transcatheter Evaluation of New Therapies.*



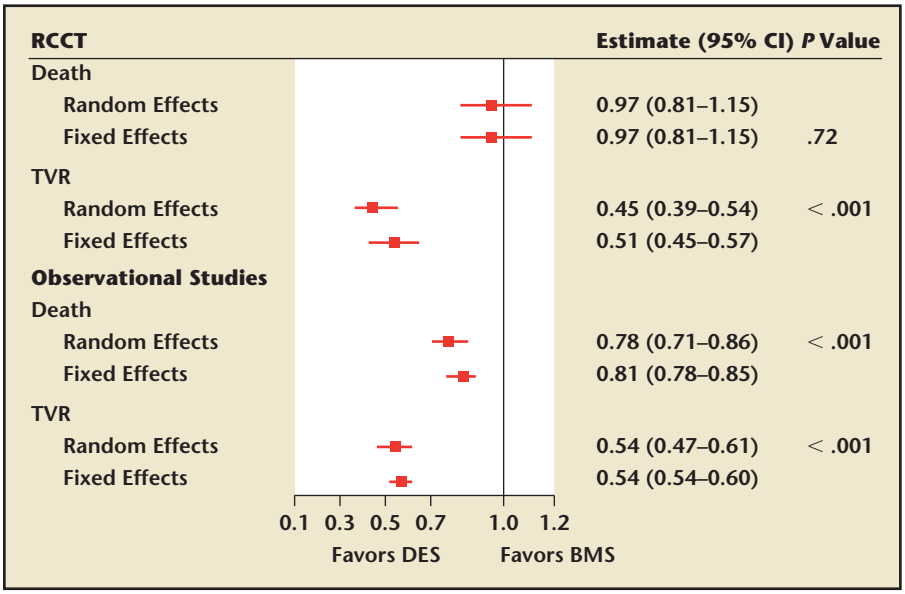


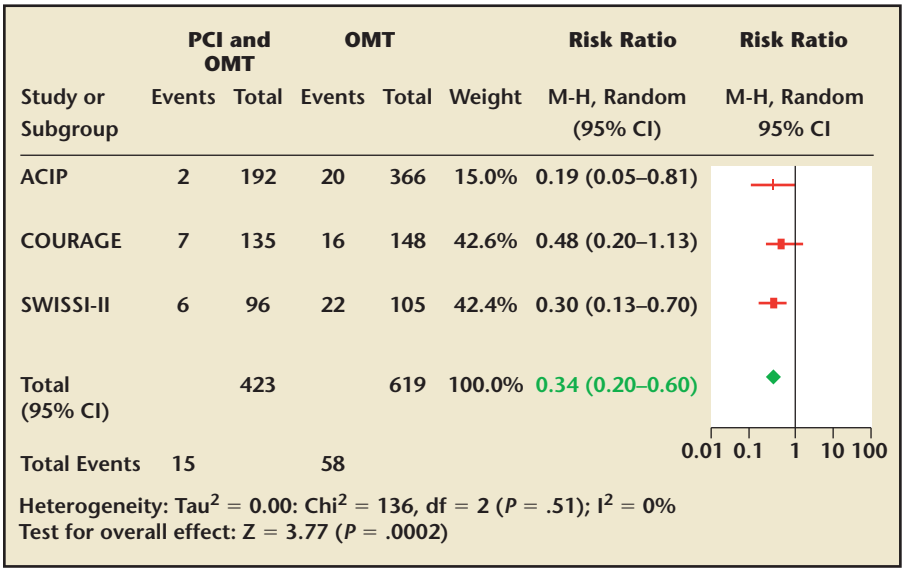
Figure 7. *Comparative safety and efficacy of DES and BMS from 22 RCCT involving 9470 patients as well as 34 observational studies involving 182,901 patients. Death (all-cause) and TVR were assessed from studies with cumulative follow-up of at least 1 year. Results of both random and fixed meta-analyses are shown. DES, drug-eluting stents; BMS, bare-metal stents; RCCT, randomized controlled clinical trials; TVR, target vessel revascularization; CI, confidence interval. Reprinted with permission from Kirtane AJ et al. Safety and efficacy of drug-eluting and bare metal stents: comprehensive meta-analysis of randomized trials and observational studies.* Circulation. *2009;119(25):3198-3206.*[32]

of patients (30%) with moderate to severe (> 10%) MPS ischemic defects. After adjustment for relative covariates, those patients randomized to PCI plus OMT had a strong trend toward reduction in mortality during follow-up compared with those assigned to OMT alone (5% vs 11%, respectively; $P = .06$). When the patients with silent myocardial ischemia from the COURAGE trial are pooled with those enrolled into the ACIP or Swiss Interventional Study on Silent Ischemia Type II (SWISSI-II) trials of revascularization versus medical therapy (n = 1042), the relative salutary effects of revascularization (vs medical therapy alone) are evident. In this pooled silent ischemia cohort, those patients randomly assigned to PCI (in combination with medical therapy) had significant reductions in both mortality (Figure 8) as well as the composite endpoint of death or nonfatal MI when compared with patients receiving medical therapy alone (Figure 9). Of note, the changes in endpoint occurrence are directionally consistent in favor of PCI across each trial.

Summary

Ischemia—irrespective of the methodology used to demonstrate its presence (MPS, AECG, stress-echo, FFR)—is qualitatively and quantitatively correlated with the occurrence of adverse clinical outcomes (death or nonfatal MI) in follow-up. In addition, ischemia is quantitatively proportional to the magnitude of revascularization benefit. Revascularization (PCI) is more effective in reducing ischemia than medical therapy alone. Finally, complete revascularization with contemporary technology (DES) in patients appropriately selected for PCI will improve the magnitude and durability of objective/subjective ischemia reduction that was observed following PCI (vs OMT) alone in the COURAGE trial. The weight of clinical data suggest that objective evidence of ischemia reduction will be translated into improvement in significant clinical outcomes such as cardiovascular death and/or nonfatal MI. ■

Figure 8. *Mortality in follow-up by randomly assigned treatment strategy (PCI plus OMT vs OMT alone) from the ACIP, COURAGE, and SWISSI-II trials in patients with silent myocardial ischemia. PCI, percutaneous coronary intervention; OMT, optimal medical therapy; ACIP, Asymptomatic Cardiac Ischemia Pilot; COURAGE, Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation; SWISSI-II, Swiss Interventional Study on Silent Ischemia Type II; CI, confidence interval. Adapted with permission from Boden WE et al.*[33]



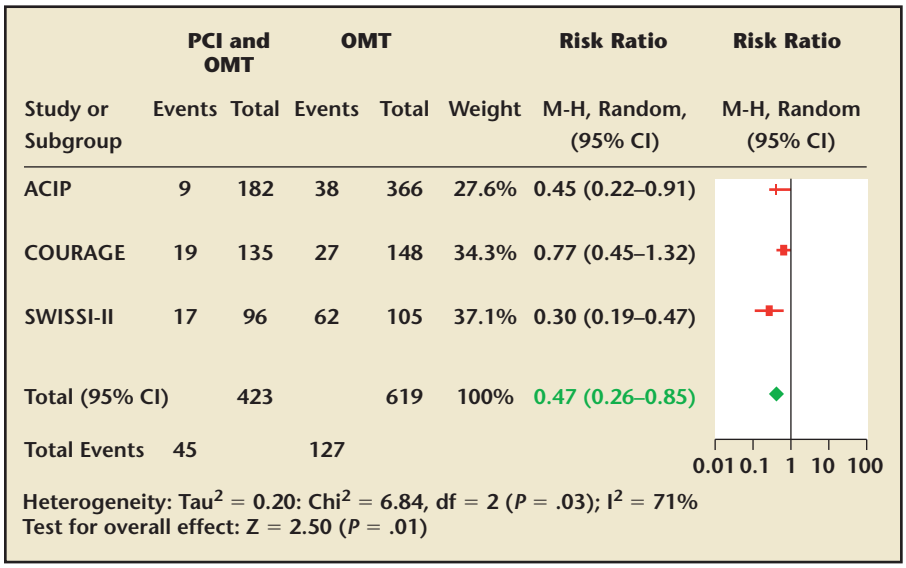


Figure 9. *The composite occurrence of death or nonfatal MI by randomly assigned treatment strategy (PCI plus OMT vs OMT alone) from the same trials and patient cohorts as noted in Figure 8. MI, myocardial infarction; PCI, percutaneous coronary intervention; OMT, optimal medical therapy; CI, confidence interval; ACIP, Asymptomatic Cardiac Ischemia Pilot; COURAGE, Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation; SWISSI-II, Swiss Interventional Study on Silent Ischemia Type II. Adapted with permission from Boden WE et al.*[33]

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References

1. Al Suwaidi J, Holmes DR Jr, Salam AM, et al. Impact of coronary artery stents on mortality and nonfatal myocardial infarction: meta-analysis of randomized trials comparing a strategy of routine stenting with that of balloon angioplasty. *Am Heart J*. 2004;147:815-822.
2. Babapulle MN, Joseph L, Bélisle P, et al. A hierarchical Bayesian meta-analysis of randomised clinical trials of drug-eluting stents. *Lancet*. 2004;364:583-591.
3. Serruys PW, Kutryk MJ, Ong AT. Coronary-artery stents. *N Engl J Med*. 2006;354:483-495.
4. Katritsis DG, Ioannidis JP. Percutaneous coronary intervention versus conservative therapy in nonacute coronary artery disease: a meta-analysis. *Circulation*. 2005;111:2906-2912.
5. Boden WE, O'Rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med*. 2007;356:1503-1516.
6. Bavry AA, Kumbhani DJ, Rassi AN, et al. Benefit of early invasive therapy in acute coronary syndromes: a meta-analysis of contemporary randomized clinical trials. *J Am Coll Cardiol*. 2006;48:1319-1325.
7. Schömig A, Mehilli J, de Waha A, et al. A meta-analysis of 17 randomized trials of a percutaneous coronary intervention–based strategy in patients with stable coronary artery disease. *J Am Coll Cardiol*. 2008;52:894-904.
8. Jeremias A, Kaul S, Rosengart TK, et al. The impact of revascularization on mortality in patients with nonacute coronary artery disease. *Am J Med*. 2009;122:152-161.
9. Trikalinos TA, Alsheikh-Ali AA, Tatsioni A, et al. Percutaneous coronary interventions for non-acute coronary artery disease: a quantitative 20-year synopsis and a network meta-analysis. *Lancet*. 2009;373:911-918.
10. Hachamovitch R, Berman DS, Shaw LJ, et al. Incremental prognostic value of myocardial perfusion single photon emission computed tomography for the prediction of cardiac death: differential stratification for risk of cardiac death and myocardial infarction. *Circulation*. 1998;97:535-543.
11. Berman DS, Kang X, Schisterman EF, et al. Serial changes on quantitative myocardial perfusion SPECT in patients undergoing revascularization or conservative therapy. *J Nucl Cardiol*. 2001;8:428-437.
12. Hachamovitch R, Hayes SW, Friedman JD, et al. Comparison of the short-term survival benefit associated with revascularization compared

Main Points

- In general, the nature and magnitude of clinical benefit attributable to either percutaneous coronary intervention (PCI) or medical therapy have been directly proportional to the acuity of the clinical syndrome being treated.
- Recent data have also demonstrated a relationship between in-laboratory coronary lesion hemodynamic functional assessment by fractional flow reserve and important clinical outcomes, even in patients with normal regional perfusion by myocardial perfusion single-photon emission computed tomography scanning and noncritical angiographic stenoses.
- In the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial, PCI in combination with optimal medical therapy (OMT) was more effective in reducing ischemia than OMT alone, despite the fact that 15% of patients randomly assigned to OMT required subsequent PCI for refractory and/or progressive anginal symptoms.
- The fact that many patients with severe coronary stenoses and objective evidence of myocardial ischemia have no symptoms of angina is well recognized.
- The weight of clinical data suggest that objective evidence of ischemia reduction will be translated into improvement in significant clinical outcomes such as cardiovascular death and/or nonfatal myocardial infarction.

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13. Pepine CJ, Sharaf B, Andrews TC, et al. Relation between clinical, angiographic and ischemic findings at baseline and ischemia-related adverse outcomes at 1 year in the Asymptomatic Cardiac Ischemia Pilot study. ACIP Study Group. *J Am Coll Cardiol*. 1997;29:1483-1489.
14. Mahmarian JJ, Steingart RM, Forman S, et al. Relation between ambulatory electrocardiographic monitoring and myocardial perfusion imaging to detect coronary artery disease and myocardial ischemia: an ACIP ancillary study. The Asymptomatic Cardiac Ischemia Pilot (ACIP) Investigators. *J Am Coll Cardiol*. 1997; 29:764-769.
15. Davies RF, Goldberg AD, Forman S, et al. Asymptomatic Cardiac Ischemia Pilot (ACIP) study two-year follow-up: outcomes of patients randomized to initial strategies of medical therapy versus revascularization. *Circulation*. 1997; 95:2037-2043.
16. Gehi AK, Ali S, Na B, et al. Inducible ischemia and the risk of recurrent cardiovascular events in outpatients with stable coronary heart disease: the heart and soul study. *Arch Intern Med*. 2008;168:1423-1428.
17. Chamuleau SA, Meuwissen M, Koch KT, et al. Usefulness of fractional flow reserve for risk stratification of patients with multivessel coronary artery disease and an intermediate stenosis. *Am J Cardiol*. 2002;89:377-380.
18. Tonino PA, de Bruyne B, Pijls NH, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med*. 2009;360:213-224.
19. Shaw LJ, Berman DS, Hendel RC, et al. Prognosis by coronary computed tomographic angiography: matched comparison with myocardial perfusion single-photon emission computed tomography. *J Cardiovasc Comput Tomogr*. 2008;2:93-101.
20. Shaw LJ, Berman DS, Maron DJ, et al. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial nuclear substudy. *Circulation*. 2008;117:1283-1291.
21. Slomka PJ, Nishina H, Berman DS, et al. Automated quantification of myocardial perfusion SPECT using simplified normal limits. *J Nucl Cardiol*. 2005;12:66-77.
22. Kereiakes DJ, Teirstein PS, Sarembock IJ, et al. The truth and consequences of the COURAGE trial. *J Am Coll Cardiol*. 2007;50:1598-1603.
23. Kereiakes DJ. Medical and catheter-based therapies for managing stable coronary disease: lessons from the COURAGE trial. *Curr Treat Options Cardiovasc Med*. 2009;11:45-53.
24. Hannan EL, Wu C, Walford G, et al. Incomplete revascularization in the era of drug-eluting stents: impact on adverse outcomes. *JACC Cardiovasc Interv*. 2009;2:17-25.
25. Stettler C, Wandel S, Allemann S, et al. Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis. *Lancet*. 2007;370:937-948.
26. Zellweger MJ, Kaiser C, Brunner-La Rocca HP, et al. Value and limitations of target-vessel ischemia in predicting late clinical events after drug-eluting stent implantation. *J Nucl Med*. 2008;49:550-556.
27. Groeneveld PW, Matta MA, Greenhut AP, Yang F. Drug-eluting compared with bare-metal coronary stents among elderly patients. *J Am Coll Cardiol*. 2008;51:2017-2024.
28. Malenka DJ, Kaplan AV, Lucas FL, et al. Outcomes following coronary stenting in the era of bare-metal vs the era of drug-eluting stents. *JAMA*. 2008;299:2868-2876.
29. Douglas PS, Brennan JM, Anstrom KJ, et al. Clinical effectiveness of coronary stents in elderly persons: results from 262,700 Medicare patients in the American College of Cardiology-National Cardiovascular Data Registry. *J Am Coll Cardiol*. 2009;53:1629-1641.
30. Galla JM, Kumbhani DJ, Becker MC, Ellis SG. Off-label use of drug-eluting stents is associated with a reduction in all-cause mortality compared with bare-metal stents: results from a combined analysis [abstract]. *Circulation*. 2008;118:S1040.
31. Austin D, Oldroyd KG, McConnachie A, et al. Drug-eluting stents versus bare-metal stents for off-label indications: a propensity score–matched outcome study. *Circ Cardiovasc Intv*. 2008;1:45-52.
32. Kirtane AJ, Gupta A, Iyengar S, et al. Safety and efficacy of drug-eluting and bare metal stents: comprehensive meta-analysis of randomized trials and observational studies. *Circulation*. 2009;119:3198-3206.
33. Boden WE, Teo KK, Hartigan PM, et al. Comparison of optimal medical therapy with or without PCI on cardiovascular endpoints in patients with silent myocardial ischemia [abstract]. *J Am Coll Cardiol*. 2009;53:A352.