Current Indications for Stenting: Symptoms or Survival CME

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ABSTRACT: The major goals of treating ischemic heart disease are to reduce angina, improve quality of life, and ultimately reduce mortality. While medical therapy can effectively address these aims, there is still much research and debate about the role of percutaneous coronary intervention in the treatment spectrum—specifically, whether or not stenting prolongs life or simply treats symptoms without impacting survival. The data supporting revascularization for survival benefit came from patients who underwent bypass graft surgery prior to the introduction of effective medical management. Although both physicians and patients continue to believe in the life-saving ability of coronary stenting, little data exist to support this belief outside of when used during an acute myocardial infarction. Strategy trials designed to test the benefit of coronary stenting have limitations that have curbed physicians' willingness to accept the results, but they provide the best evidence for how to optimally manage these patients. In this article, we explore the data supporting the use of coronary stenting for various indications and the questions that remain to be answered.

INTRODUCTION

The major goals of treating patients with coronary artery disease (CAD) are to reduce patients' risk of major adverse cardiovascular events, prolong life, and improve symptoms, functional status, and quality of life. From a pharmacological standpoint, there is a clear division among treatments in terms of which goal they address. Medications such as aspirin,[1] thienopyridines (in patients with high DAPT scores),[2] and statins[3] are indicated for cardiovascular risk reduction but do not improve quality of life (except indirectly by reducing nonfatal ischemic events); in fact, they are associated with side effects that may worsen quality of life (e.g., nuisance bleeding,[4] myalgias). Anti-ischemic medications such as calcium channel blockers, nitrates, and ranolazine all reduce angina and improve quality of life but have not been shown to reduce morbidity or mortality.[5,6] Even beta-blockers, which are a mainstay of medical treatment for patients with CAD, show little evidence that they reduce cardiovascular events or mortality[7] in the absence of left ventricular dysfunction or during the early period after a myocardial infarction (MI).[8] While CAD medications each have a specific function, the role of coronary revascularization, specifically coronary stenting, in the treatment plan for CAD is more complicated (Figure 1).

STENTING IN THE SETTING OF MYOCARDIAL INFARCTION

In the setting of an acute ST-elevation MI (STEMI), primary percutaneous coronary intervention (PCI) is strongly recommended instead of fibrinolytics (in the absence of marked delayed presentation), with a number needed to treat (NNT) of 16 patients to prevent 1 death, nonfatal reinfarction, or stroke (Table 1).[9,10] The benefit of coronary stenting (versus balloon angioplasty and thrombectomy alone) at the time of primary PCI, however, is predominantly an improvement in long-term angina and quality of life,[11] as stenting has been shown to reduce the need for subsequent revascularization but not reduce mortality.[12] In the setting of an acute non-STEMI (NSTEMI), several studies have shown that a routine invasive strategy is generally superior to an ischemia-guided or selectively invasive strategy.[13,14] Use of a routine invasive versus ischemia-guided therapy is associated with a modest improvement in both long-term mortality (3.8% vs 4.9%, with an NNT of 91) and long-term angina and health status (~ 4-point improvement in Seattle Angina Questionnaire Angina Frequency [SAQ AF] domain scores at 1 year).[15]

STENTING IN THE SETTING OF STABLE CORONARY ARTERY DISEASE

Coronary stenting for stable CAD has been an area of recurrent study, as many cardiologists and patients continue to believe that opening an artery with stenting must be better than medical management.[16,17] The recommendation for revascularization in the setting of stable CAD is based on studies comparing coronary artery bypass graft (CABG) surgery to medical therapy in the 1970s and 1980s, before effective medical therapy was even used. The benefit of revascularization was mostly seen in patients with left main CAD, although there was also a modest effect in patients with 3-vessel CAD.[18] With the advent of angioplasty and then coronary stenting, the use of revascularization has continued to expand down the spectrum of risk–the persistent guiding principle being that an open artery is better. Through the 1980s and 1990s, coronary stenting for asymptomatic

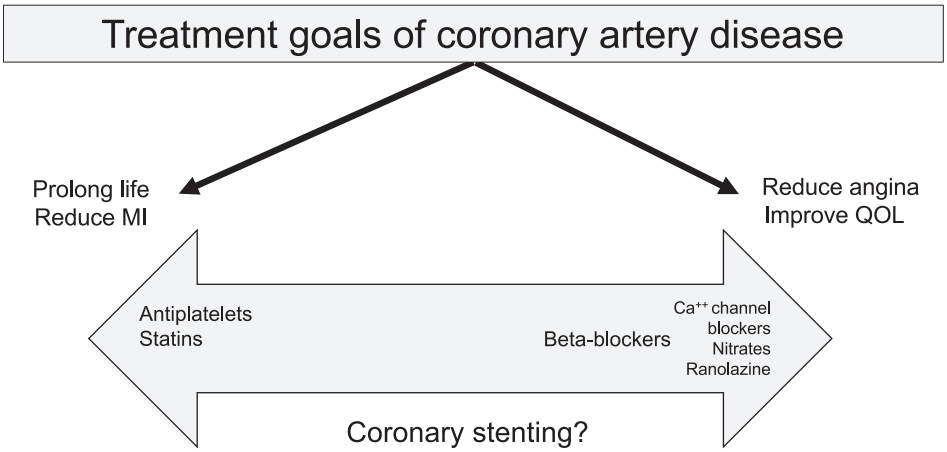

Figure 1.
The role of treatments for coronary artery disease. MI: myocardial infarction; QOL: quality of life

or minimally symptomatic stable CAD remained common practice, comprising nearly half of all elective PCI procedures.[19] To date, however, there is little evidence that coronary stenting reduces morbidity or mortality outside of a few narrow indications.

The Clinical Outcomes Using Revascularization and Aggressive Drug Evaluation (COURAGE) trial was the first major trial to challenge the practice of routine PCI for stable CAD. Sponsored by the Department of Veterans Affairs, the trial randomized 2,287 patients with stable angina to receive optimal medical therapy alone or PCI plus medical therapy between 1999 and 2004. The primary finding was that there was no difference in the incidence of mortality or acute MI,[20] although there was a small but significant improvement in angina and health status with PCI (~ 4-point improvement in SAQ AF domain scores at 1 year) that decreased over time. Despite these findings, the trial generated a number of valid criticisms that kept physicians from making widespread changes to their practice patterns. For example, critics argued that the results were not generalizable to contemporary clinical practice, high-risk patients were not enrolled by physicians, only 6% of screened patients were randomized, the PCI technique was substandard with a very low rate of drug-eluting stent use, too many patients were enrolled from Veterans Affairs and Canada, and adherence to optimal medical therapy was not achievable in the real world.[21] However, when these results were compared with an

	SURVIVAL BENEFIT	SYMPTOM BENEFIT
ST-elevation myocardial infarction	Large: NNT 16	Modest: 6-point SAQ AF at 6 months but no significant difference at 1 year
Non–ST-elevation myocardial infarction	Modest: NNT 91	Modest: 4-point SAQ AF at 1 year
General		Modest[a]: 4-point SAQ AF at 1 year
Proximal LAD disease	Limited data but no evidence of effect	
Low ejection fraction	Limited data but no evidence of effect	
Low ischemic burden	Possible harm	
High ischemic burden	Possible benefit	

NNT: number needed to treat; LAD: left anterior descending artery; SAQ AF: Seattle Angina Questionnaire Angina Frequency domain, a disease-specific health status measure that quantifies the patient's frequency of angina and correlates well with daily angina diaries.[41] A 10-point difference is the minimal clinically important difference within an individual. A ~ 5-point difference is thought to be clinically relevant at the population level.

[a] Greater benefit in patients with high symptom burden prior to PCI

Table 1.
Data for benefit of coronary stenting by indication.

unselected cohort of patients who underwent elective PCI at the Mayo Clinic during a similar timeframe, the clinical characteristics and long-term mortality were similar to COURAGE,[22] which may indicate that the COURAGE results are more generalizable than some had criticized. Furthermore, similar results were observed in the BARI-2D trial of patients with diabetes and stable CAD, where there was no significant benefit of revascularization over medical therapy in terms of morbidity or mortality.[23]

Crossovers from medical treatment to PCI, which are inherent in any strategy trial, have also raised concerns about the validity of the COURAGE results (diluting the benefits of revascularization). Crossover was permitted for refractory angina or acute events and occurred in one-third of patients in the medical arm within the first year (of note, 21% of patients in the PCI arm had repeat PCI during the first year). In an analysis comparing patients who crossed over to PCI with patients who were randomized to PCI, there was no difference in the rate of MI or death between the groups.[24]

PROXIMAL LEFT ANTERIOR DESCENDING ARTERY DISEASE

A number of studies have attempted to identify subgroups of high-risk patients with stable CAD who might benefit from revascularization. Patients with obstructive atherosclerosis in the proximal left anterior descending artery (LAD) were one area of keen interest. In the Coronary Artery Surgery Study registry of medically treated patients, survival rates decreased with greater burden of obstructive CAD, but the addition of proximal LAD disease decreased the likelihood of survival even further.[25] For example, the 5-year survival rate for patients with one-vessel disease was 91% versus 83% if the proximal LAD was involved. This also was observed in a subanalysis of the COURAGE trial, where more-severe obstruction in the proximal LAD was associated with increased risk of death or acute coronary syndrome. Importantly, however, PCI in this case did not modify the risk[26]; therefore, PCI for survival benefit in the setting of proximal LAD disease has only a IIb indication in the guidelines.[27] Similarly, while left ventricular systolic dysfunction is also associated with increased risk of death, PCI was not shown to modify that risk in COURAGE.[26]

HIGH ISCHEMIC BURDEN

The burden of ischemia has been another area of intense investigation. In a large retrospective study of > 10,000 patients, a greater burden of ischemia detected on stress imaging was associated with a higher risk of short-term mortality. Furthermore, when the burden of ischemic myocardium was > 10%, early revascularization was associated with a reduction in mortality compared with medical therapy.[28] As with any observational study, this analysis is subject to selection bias since the patients who were sent for revascularization were inherently different from those who were recommended for medical therapy. The authors did attempt to account for this with propensity matching, but this analytic strategy can only account for patient characteristics that were measured within the study, making the potential for unmeasured confounding a real concern.

In contrast to the retrospective data, a substudy of patients in the COURAGE trial found PCI to have no benefit over medical therapy for reducing MI or death among 468 patients with moderate-to-severe ischemia through 6 years of follow-up.[29] This lingering question about the clinical importance of ischemia and the role of revascularization in modifying its risk formed the basis of the NIH-funded International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial. Beginning in 2012, ISCHEMIA has randomized more than 4,000 patients who have stable CAD and at least moderate ischemia on stress imaging to revascularization plus medical therapy versus medical therapy alone, with results expected in 2019. While some of the same issues that raised concerns about the COURAGE study have also plagued ISCHEMIA—including selective referrals for screening of only lower-risk patients, incomplete revascularization particularly with chronic total occlusions, low rate of U.S. patients—this trial will provide the best evidence to date on whether performing revascularization for ischemia reduces the risk of adverse cardiovascular events.

STENTING FOR SYMPTOM RELIEF

While there is little evidence that PCI reduces the risk of morbidity and mortality in the majority of patients with stable CAD (with the issue of high-risk ischemia still outstanding), PCI can greatly improve the symptoms, functional limitations, and quality of life decrement associated with ischemia. Chronic angina affects roughly half of the 15.4 million U.S. adults with ischemic heart disease, substantially worsens patients' quality of life, and increases the costs of healthcare.[30-33] As such, treatments that improve angina can have a marked impact on a patient's well-being. In COURAGE, PCI was associated with 10- to 20-point improvements in SAQ AF, quality of life, and physical limitations scores at 1 year—improvements that were most prominent among patients with more severe baseline angina.[34] However, medical therapy also can be associated with large improvements in symptoms, such that the difference between medical therapy and PCI in COURAGE at 1 year was only 3 to 4 points, and there was only a modest difference between the proportion of patients who were angina-free (medical vs PCI: 50% vs 57%, $P = .005$). Interestingly, this is in contrast to the older CABG studies, where there was a marked difference in angina-free rates between treatments at 1 year (medical vs CABG: 30% vs 66%, $P < .001$).[35] This likely

reflects both improvements in medical therapy over time and, to a lesser extent, better angina relief with CABG versus PCI.[36] Medical therapy in antianginal trials is also associated with marked improvements in angina and quality of life. In the Efficacy of Ranolazine in Chronic Angina (ERICA) Trial, patients with stable angina who were randomized to ranolazine for 6 weeks had an average improvement of 22.5 points on the SAQ AF domain,[37] similar to what was observed with PCI in COURAGE. Importantly, patients randomized to placebo had an average improvement of 18.5 points on the SAQ AF domain. While patients randomized to ranolazine had a significant improvement above and beyond placebo of ~ 4 points, these antianginal medication trials highlight the importance of the placebo effect.

It is well established that antianginal medications must prove effectiveness beyond placebo, which has repeatedly had a strong impact on angina.[37-39] Although patients undergoing PCI most often have a marked improvement in angina, it is not yet known how much of that improvement is due to PCI versus the placebo effect. Obviously, conducting a blinded and controlled trial of an invasive procedure is more challenging, but these types of sham studies can be particularly enlightening. A classic example in cardiology is percutaneous transmyocardial revascularization, which had been shown to be a markedly effective treatment for refractory angina in patients without good revascularization options, with substantial improvement in Canadian Cardiovascular Society class and exercise capacity (but interestingly, no change in ischemia on perfusion imaging).[40] However, in a randomized patient- and evaluator-blinded placebo-controlled trial, there were no differences in improvements in exercise duration or angina burden between patients who were treated with percutaneous myocardial laser revascularization and those treated with a similar sham procedure.[41] All three groups had similar improvements in angina (~ 20-point improvements in SAQ AF domain scores) that persisted for up to 12 months after the procedure.[41] Recently, the Objective Randomised Blinded Investigation With Optimal Medical Therapy of Angioplasty in Stable Angina (ORBITA) trial compared PCI with a sham procedure for the treatment of stable angina, specifically looking at improvements in angina to try and identify how much of the effect is due to placebo. They found no additional benefit of PCI on top of medical therapy for exercise duration or angina relief. While there are many valid criticisms of this trial, including small sample size and short duration of follow-up, this trial has questioned the role of PCI for symptom benefit in stable angina and also highlighted the power of a placebo procedure.[42]

SUMMARY

The current indications for coronary stenting—whether for survival benefit or symptom improvement—depend on the clinical situation. For patients who present with a STEMI, primary PCI clearly has a survival benefit, but coronary stenting beyond angioplasty and thrombectomy is primarily done to improve symptoms after discharge. For NSTEMI patients, coronary stenting has a more modest benefit on both survival and symptoms—effects that are most notable in high-risk patients. For patients with stable CAD, there is little evidence of any survival benefit for coronary stenting outside of a few narrow indications, and data are lacking for a strong benefit in the age of modern medical treatment. Whether or not coronary stenting in the setting of high-risk ischemia has an impact on morbidity and mortality is still unknown. The ISCHEMIA trial has been designed to answer this question, but if the outcome is negative, criticism of the trial will likely prevent full acceptance of the results, similar to what was seen with COURAGE. Although observational studies in this area are inherently biased, it is likely that these data will continue to fuel our practice patterns. Finally, while it is generally accepted that PCI relieves angina and improves quality of life in stable CAD, a question remains as to how much of this relief is due to a placebo effect (given similar magnitudes of benefit in medication trials), and an ongoing trial will provide insight in this area. Atherosclerotic vascular disease is a systemic process, which makes medical therapy a key piece of any treatment plan for CAD. How revascularization, and specifically coronary stenting, fits into this plan is continuing to evolve as we learn more about the benefits and limitations of this technology.

KEY POINTS

- Coronary stenting in the setting of myocardial infarction has a positive impact on both survival and quality of life, with more modest effects in patients with NSTEMI.
- Coronary stenting for stable coronary disease has not been shown to reduce the morbidity and mortality associated with coronary disease outside of a few narrow indications (with the question of high-risk ischemia still outstanding).
- Coronary stenting for stable coronary disease markedly improves symptoms of ischemic heart disease; however, the impact of PCI on angina relief above and beyond medical therapy is rather modest in the long term and may also be subject to the placebo effect.
- Strategy trials testing PCI for stable CAD have limitations (selective enrollment of lower-risk patients, less-than-ideal revascularization) that raise questions about the generalizability of the results, but they provide the best evidence for how to optimally manage these patients, as observational data are inherently biased, and statistical methods to try and address these biases will be insufficient.

Conflict of Interest Disclosure:
The author has completed and submitted the *Methodist DeBakey Cardiovascular Journal* Conflict of Interest Statement and none were reported.

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coronary stenting, revascularization, percutaneous coronary intervention, ischemic heart disease, angina, coronary artery disease

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