Reasonable Incomplete Revascularization and the Role for Adjunct Medical Therapy in Ischemic Heart Disease

Irfan Hameed, MD, Vankeepuram S. Srinivas, MD
Division of Cardiology, Montefiore Medical Center, New York, NY

The goal of complete revascularization in multivessel coronary artery disease is the elimination of all ischemia-producing lesions, either through coronary artery bypass grafting or percutaneous coronary intervention. However, a substantial proportion of patients receiving contemporary revascularization undergo incomplete revascularization, often with residual ischemia. Currently, the decision of whether to pursue a complete or a limited revascularization strategy is determined by the interventional cardiologist, often in consultation with referring physicians and taking into consideration patient preference. Although there are no guideline-specific recommendations regarding completeness of revascularization, there are passionate arguments supporting the value of complete revascularization by some and the equivalence of incomplete revascularization by others. This article focuses on the evidence that underlies the controversy regarding completeness of revascularization. When interpreting current evidence in patients with multivessel coronary artery disease, decision making regarding treatment strategy should take into account four concepts: (1) incomplete revascularization is more common in clinical practice than complete revascularization; (2) the definition of incomplete revascularization is not uniform; (3) completeness of revascularization is not always superior to incomplete revascularization; and (4) all incomplete revascularization scenarios are not equivalent. We believe that a reasonable incomplete revascularization strategy needs to include a consideration of adjunctive anti-ischemic medications (in particular effective anti-ischemic therapies such as ranolazine), and active monitoring of its effectiveness in reducing residual ischemia.

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KEY WORDS

Incomplete revascularization • Multivessel coronary artery disease • Adjunct medical therapy

In the setting of multivessel coronary artery disease (CAD), complete revascularization is considered a necessary goal by some and an optional strategy by others. The goal of complete revascularization is the elimination of all ischemia-producing lesions either through coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI). Existing literature supports CABG over medical treatment in a specific subset of patients with multivessel disease: those with three-vessel CAD with reduced left ventricular function, and those with two-vessel CAD with proximal left anterior descending artery involvement.[1,2] The survival benefit in these studies, published in the 1980s and 1990s, has led to a widespread belief conflating completeness of revascularization as the only cure and as a standard of care. In these claims, the putative benefits of complete revascularization include freedom from recurrent cardiac events and improved survival over medical therapy, in addition to better relief of angina. Although multiple studies have identified limitations of PCI-based revascularization in reducing future myocardial infarction (MI) and improving survival in patients with stable ischemic heart disease (SIHD), there is no denying the efficacy of PCI in relieving angina symptoms. In fact, as operator comfort has increased and with technical advances, PCI is no longer confined to single-vessel CAD.[3] A substantial proportion of patients undergoing PCI have multivessel disease and, in these patients, the desire to accomplish complete revascularization becomes an essential decision element. Currently, this decision of whether to pursue a complete revascularization strategy or a limited revascularization strategy is determined by the interventional cardiologist, often in consultation with referring physicians and taking into consideration patient preference. Although the current guidelines make no recommendations regarding the completeness of revascularization, there has been a growing body of literature that has generated intense debate within the cardiology and cardiovascular surgery communities.[4,5] Further complicating this discourse are current improvements in medical therapy that relieve angina symptoms more effectively and technologies that allow real-time assessment of hemodynamic significance of coronary lesions. Under these circumstances, the debates about completeness of revascularization with PCI center on the following questions: (1) Should complete revascularization be the standard for all revascularization? (2) Under what circumstances is incomplete revascularization acceptable and/or preferred? and (3) What is the role of contemporary antianginal therapies, such as ranolazine, in patients receiving incomplete revascularization? This article focuses on four paradigms that, in our opinion, provide a framework for decision making in these complex patients.

Paradigm 1: There Is No Single Definition of Complete Revascularization

Counterintuitive as it may seem, complete revascularization with PCI is often *in the eye of the beholder*. Over the years, both cardiovascular surgeons and interventional cardiologists have developed different standards to define complete revascularization. The earliest definition of complete revascularization was based on the initial cardiac surgical experience and determined by the caliber of vessels that were deemed appropriate for grafting.[1,6-10] Although it was adopted into the PCI experience, its limitations became quite evident early on. For example, vessel sizes that may have been acceptable for bypass grafting (≥ 1.5 mm in diameter) are not often acceptable for PCI; vessel sizes considered suitable for stent implantation are ≥ 2.25 mm in diameter. The growing recognition that not all coronary lesions are hemodynamically significant when assessed with physiologic testing, such as fractional flow reserve (FFR), or ischemia-producing on myocardial perfusion imaging, led to the concept of functional complete revascularization strategy. Recent studies such as the Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME),[11] the Fractional Flow Reserve–Guided PCI Versus Medical Therapy in Stable Coronary Disease (FAME 2),[12] and others have validated the concept of functional revascularization.[11-16] As a result, the various studies that examine completeness of revascularization use different definitions of complete and incomplete revascularization, thus complicating comparisons across studies.[17] A summary of the criteria and definitions used in different trials for complete versus incomplete revascularization, based on a comprehensive review of this topic by Ong and Serruys,[17] is shown in Table 1.

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TABLE 1

Criteria and Definitions Used in Different Trials for Complete Versus Incomplete Revascularization

Revascularization	Definition
Incomplete anatomic revascularization	
Unconditional	All stenotic vessels are revascularized irrespective of size and territory supplied
Conditional	All stenotic vessels greater than a defined diameter are revascularized, or all stenotic main-branch vessels are revascularized
Complete functional revascularization	All ischemic myocardial territories are reperfused; areas of old infarction with no viable myocardium are not required to be reperfused
Complete numeric revascularization	The number of stenotic vessels must equal the number of distal anastomoses applied
Complete revascularization by a predetermined scoring cutoff value	Scoring of stenoses in different vessels at different locations (weightings may be used); the overall extent of disease is a continuous variable, the treatment is another variable, and the posttreatment score determines completeness of revascularization
Anatomic	Irrespective of viable myocardium
Functional	Jeopardy score: the postrevascularization score is calculated on the basis of the amount of remaining myocardium at risk

Adapted from Ong and Serruys.[17]

Paradigm 2: Incomplete Revascularization With PCI Is Common

Patients (and/or the referring physician) and operating physicians have different expectations of the revascularization procedure.[18] Whereas patients believe that the revascularization strategy improves survival and avoids future MI, the interventional cardiologist often performs such revascularization in patients with SIHD with the intent of ameliorating symptoms in most cases and reducing cardiovascular events in some. In some circumstances, patients—in the mistaken belief that revascularization is curative—may also fail to appreciate the need for potentially lifelong secondary prevention therapies. However, rarely is the completeness of revascularization, or lack thereof, a topic of discussion in the informed consent process for either CABG or PCI. Because incomplete revascularization by its very nature is associated with the presence of residual CAD, with potential for incomplete relief of symptoms and future events, the likelihood for misunderstanding and the resultant dissatisfaction with intended revascularization is not uncommon.

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In patients undergoing PCI for multivessel CAD, incomplete revascularization (using anatomic criteria) is extraordinarily common. In a recent systematic review followed by a meta-analysis, we examined the current literature on this topic.[19] A common feature of all studies chosen in this meta-analysis was that they were observational in nature. To date, there has been no randomized comparison of a strategy of intentional complete versus incomplete revascularization. Based on a predetermined set of criteria, we identified a total of nine studies that met criteria for inclusion: contemporary PCI with stent implantation with clear written criteria describing completeness of revascularization and declared clinical endpoints. The first and most striking finding in our meta-analysis was that the vast majority of patients (50% to 82%) were receiving incomplete revascularization.

There were significant differences in clinical and anatomic factors between patients that received complete revascularization and incomplete revascularization. Indeed, among patients receiving PCI for multivessel disease, complete revascularization was often achieved

in those with two-vessel disease, whereas incomplete revascularization was more frequent in patients with three-vessel disease. Other reasons for incomplete revascularization with PCI included higher patient risk, such as those deemed high-risk for CABG, and circumstances in which complete revascularization with PCI increased risk (eg, patients with chronic kidney disease in whom large contrast loads may result in worsening renal function, and patients unable to tolerate dual antiplatelet therapy, thereby limiting drug-eluting stent use). Anatomic factors also influenced the frequency of complete revascularization. Among the various technical challenges (heavily calcified lesions, diffuse disease, small vessels, high thrombus burden, one or more chronic total occlusions), the presence of chronic total occlusions has remained a particularly strong predictor of incomplete revascularization. Although there have been substantial improvements in chronic total occlusion technology and success, they continue to remain an important lesion subset that leads to incomplete revascularization. Finally, there are clinical scenarios in which complete revascularization is unnecessary, such as when lesions supply areas of nonviable myocardium or because functional complete revascularization is adequate.

Paradigm 3: Complete Revascularization Is Always Better Than Incomplete Revascularization

There is a pervasive belief that completeness of revascularization is always necessary (all or nothing). However, this belief is predicated on inadequate information that also carries substantial limitations. All studies that have examined completeness of revascularization are based on registries or post hoc analysis of clinical trials and, more importantly, without the guidance of randomized clinical trials. Completeness of revascularization has never been tested in a randomized clinical trial. A trial design to assess this issue would be difficult owing to the wide variety of unique anatomic and physiologic scenarios that would have to be taken into account during randomization. In our meta-analysis of the contemporary experience of completeness of revascularization,[19] patients who were selected for complete revascularization had better outcomes; there was an 18% reduction in all-cause mortality, a 33% reduction in nonfatal MIs, and a 30% reduction in CABG rates (Figure 1) compared with patients selected for incomplete revascularization. Impressive as these results are, it must be recognized that, in these registries, selection bias could not be avoided as patients were selected a priori for incomplete or complete revascularization by physicians, resulting in distinctly different patient populations. This is reflected in the substantial differences in the clinical characteristics of patients undergoing complete revascularization versus those that had incomplete revascularization (Table 2). Because the decision favoring incomplete revascularization does

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Figure 1. Pooled analysis of the effect of completeness of revascularization on all-cause mortality, recurrent MI, and subsequent CABG. CABG, coronary artery bypass grafting; CR, complete revascularization; IR, incomplete revascularization; MI, myocardial infarction. Adapted with permission from Aggarwal V et al.[19]

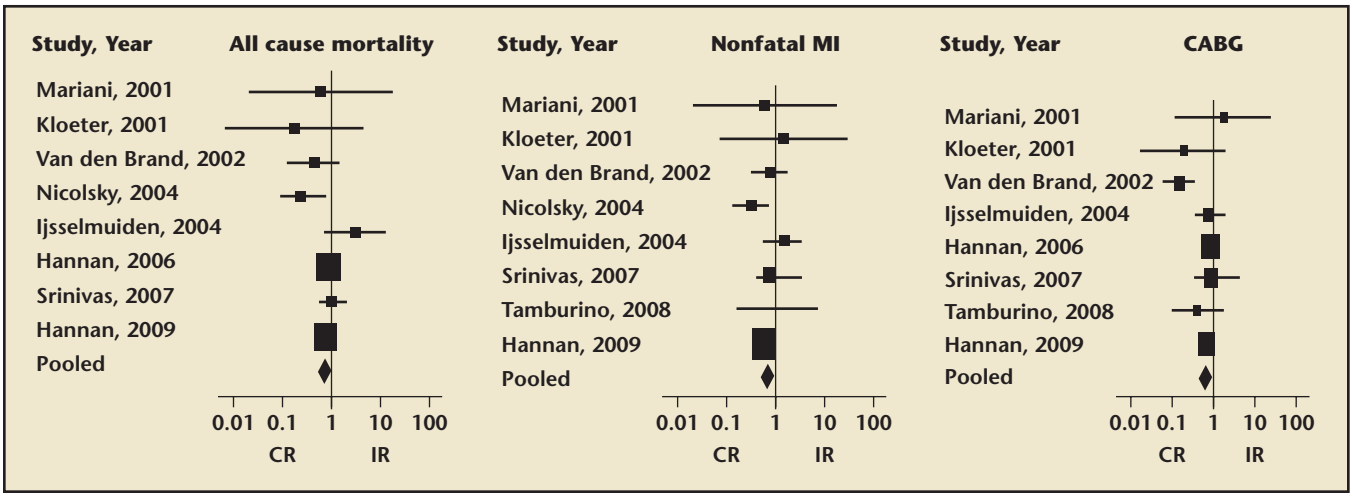

TABLE 2

Differences in Baseline Characteristics in Complete and Incomplete Revascularization

	Mariani G et al[33] (n = 207)		Hannan EL et al[4] (n = 11,294)		Nikolsky E et al[35] (n = 352)		Kloeter UC et al[34] (n = 250)		van den Brand MJ et al[5] (n = 219)		Tamburino C et al[39] (n = 508)		Srinivas VS et al[38] (n = 1781)	
	CR	IR	CR	IR	CR	IR	CR	IR	CR	IR	CR	IR	CR	IR
Sample size (%)	23.7	76.3	31	69	26.7	73.3	40.4	59.6	49.3	50.7	41.7	58.3	17.7	82.3
Mean age (y)	63.7	63.9	—	—	62	62	57	61	62	61.7	61	63	61.9	64.1
Female sex	26.5	17	33.2	32.9	27.8	26.9	17	18	24	26	21	21	28.6	34.5
Prior MI	37	47	28.8	37.6	27.3	37.1	63	57	41	44	23	33	20.6	32.9
Hypertension	—	—	—	—	49.2	45.4	47	50	32	37	55	67	67.2	68.9
DM (%)	26	14.5	28.3	34.3	100	100	8	20	11	17	32	35	29.8	33.3
PAD (%)	—	—	5.1	8.3	—	—	—	—	—	—	7	6	6.7	7.6
≥ 1 CTO (%)	14	41	0	35.2	—	—	21	31	5.4	19.4	23	51	21	31.6
3-vessel disease (%)	45	51	9.9	31.6	41.9	50	15	24	3	9	15	54	11.7	36.5
Mean EF	—	—	—	—	—	—	64	61	—	—	51	49	54.3	55.1
EF < 40%	0	11	7.7	12.6	12.6	18.6	—	—	—	—	11	18	—	—

CR, complete revascularization; CTO, chronic total occlusion; DM, type 2 diabetes mellitus; EF, ejection fraction; IR, incomplete revascularization; MI, myocardial infarction; PAD, peripheral artery disease.
Adapted from Aggarwal V et al.[19]

not occur in a vacuum, despite robust statistical adjustments, there is no way to entirely eliminate residual confounding or capture all the elements that drove the decision making, particularly in large administrative registries. Therefore, one could just as easily conclude that the outcomes are a reflection of the patient selection rather than revascularization strategy. Underscoring the bias inherent in the patient population was our finding that, in sensitivity analysis, the results favoring complete over incomplete revascularization were driven largely by the results from one observational cohort, the New York State PCI registry. Although the results of our meta-analysis was based on anatomic complete versus incomplete revascularization, as will be evident from the subsequent discussion, the field of revascularization has been upended by the recognition that functional revascularization is a better predictor of outcome than anatomic completeness of revascularization.

Paradigm #4: Not All Incomplete Revascularization Strategies Are Equal

Many trainees present and past would recall hearing such aphorisms as, "No one ever dies from branch vessel disease," or "Nothing is more stable than a chronic total occlusion." Such statements reflect the observations of interventional cardiologists, over the years, that not all lesions and vessels are created equal. Therefore, revascularization decisions, particularly in the setting of multivessel CAD, often require a careful consideration of the consequence of the stenosis rather than the severity of the stenosis alone. Accordingly, the concept of reasonable incomplete revascularization was born. This concept was first advocated by surgeons at the University of Leipzig (Leipzig, Germany),[20] who observed that in the presence of left internal mammary artery to left anterior descending artery bypass, reasonable incomplete revascularization of the circumflex or right coronary artery territory did not adversely affect early or long-term survival in patients with multivessel CAD. It has been enthusiastically welcomed by some in the interventional community,[21] but not by others.[22]

What is considered reasonable incomplete revascularization in the context of PCI and how does one identify whether a revascularization strategy is reasonable or not? One way of examining reasonable incomplete revascularization is to judge it through the prism of anatomic complete revascularization. Thus, although the Synergy Between PCI with Taxus and

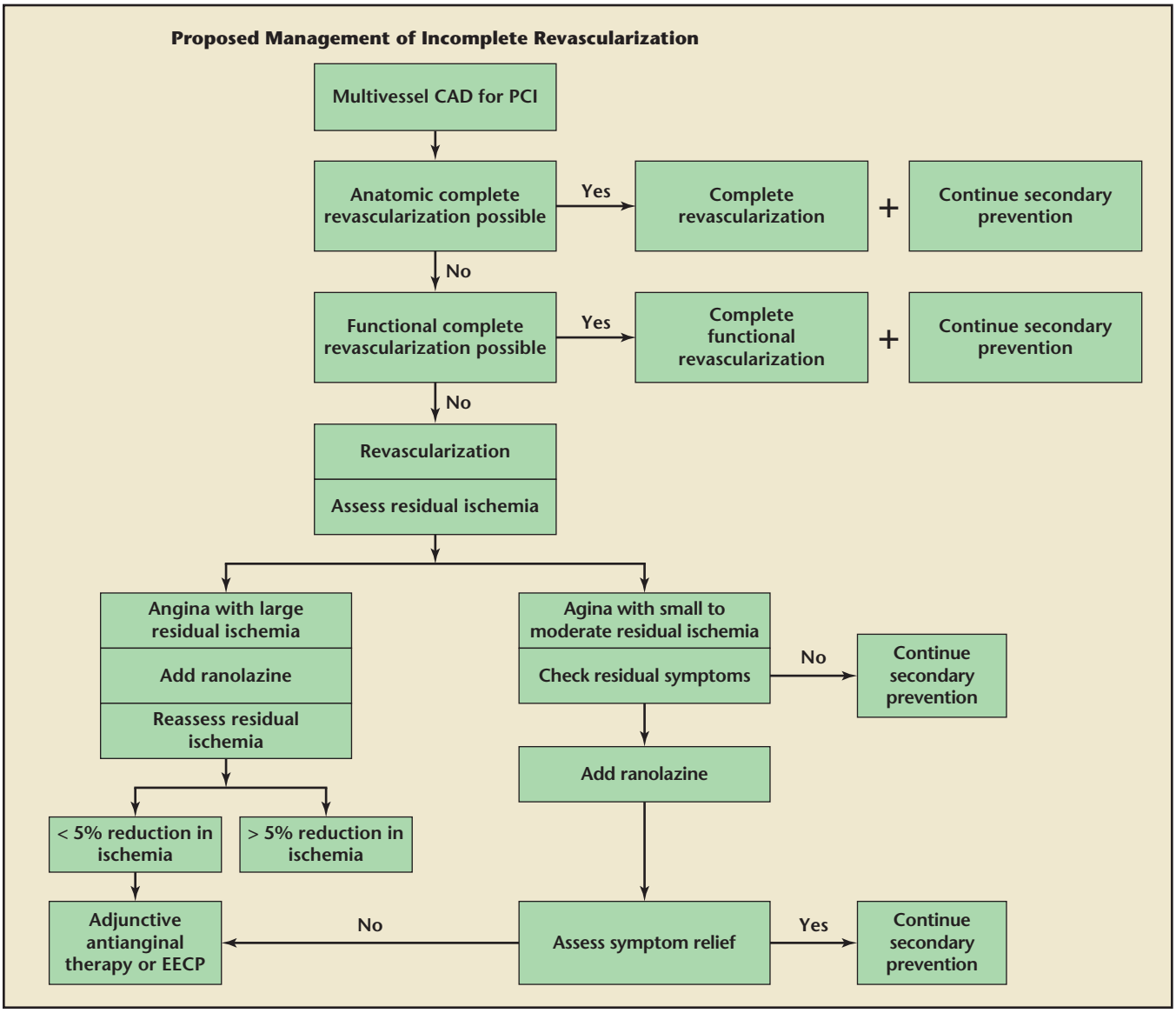

Figure 2. Proposed schema for the management of patients with multivessel CAD in whom a strategy of reasonable incomplete revascularization is considered. CAD, coronary artery disease; EECP, enhanced external counterpulsation; PCI, percutaneous coronary intervention.

Cardiac Surgery (SYNTAX) study[23] was a comparison of equivalent levels of revascularization—with revascularization requiring vessels agreed upon prior to randomization by a Heart Team that included a clinical cardiologist, interventional cardiologist, and a surgeon—incomplete revascularization was frequent, albeit more so with PCI than CABG (43.3% vs 36.8%). Furthermore, incomplete revascularization after PCI had worse major adverse cardiac and cerebrovascular complications (hazard ratio [HR] = 1.55, 95% confidence interval [CI], 1.15-2.08; $P = .004$) compared with incomplete revascularization with CABG.[24] Rates of late survival and survival free of MI appear to be similar in patients with and without complete revascularization after PCI. Nevertheless, the need for subsequent CABG is usually higher in those whose initial revascularization procedure was incomplete (compared with those with complete revascularization) after PCI.[25-27] Thus, it would appear that the type of revascularization might matter with regard to incomplete revascularization. This is probably a result of the amount of potentially ischemic myocardium following incomplete revascularization, an area in which bypass surgery often demonstrates superiority over PCI. In fact, if one were to measure the extent of incomplete revascularization, it might shed light on this perspective. In a substudy from the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) clinical trial,[28] Schwartz and colleagues compared outcomes of patients with type 2 diabetes mellitus undergoing complete revascularization and

classified incomplete revascularization into mildly incomplete and moderate to severely incomplete revascularization using the myocardial jeopardy index. Complete revascularization was achieved in 37.9%, mildly incomplete revascularization in 46.6%, and moderate to severely incomplete revascularization in 15.4% of patients. Adjusted event-free survival was 14% higher in patients with more complete revascularization compared with the rest.[28] There was a graded increase in the likelihood of the death, MI, or stroke over an average follow-up of 5 years observed for patients receiving mildly incomplete or moderate to severely incomplete revascularization (HR 1.87 and 2.21, respectively; $P = .002$) compared with complete revascularization. Therefore, at least in BARI 2D, the degree of incomplete revascularization was an important predictor of outcome. This naturally leads to the question of whether it is enough to just identify all the potentially ischemic segments anatomically, as was done in the BARI 2D analysis, or whether one should only address the more clinically meaningful coronary lesions, the so-called functional revascularization. A functional revascularization strategy is an ischemia-guided strategy wherein only ischemia-producing lesions are considered targets for revascularization.[11-16] This concept was best examined in the FAME 2 trial.[12] In FAME 2, a total of 888 stable CAD patients with ischemia demonstrated by FFR < 0.80 at the time of cardiac catheterization were randomized to medical therapy alone versus PCI plus medical therapy. Patients with FFR > 0.80 were placed into a medical treatment registry. The primary endpoint (death, MI, or urgent revascularization) occurred in 4.3% in the PCI group and 12.7% in the medical therapy group, mainly due to lower rates of urgent revascularization triggered by MI or objective ischemia. Additional evidence for the potential benefit of a functional revascularization strategy has included evidence from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) nuclear substudy[29] that demonstrated that, not only did PCI result in greater reduction in ischemia compared with medical therapy, but also that presence of residual ischemia conferred higher risk for later events. Unfortunately, a functional revascularization strategy using FFR could not take place in patients with chronic total occlusions because an FFR could not be measured. In place, one could use stress testing to assess the functional relevance of that occluded vessel.

It would seem that a reasonable incomplete revascularization strategy is one that not only leans toward a functional revascularization strategy, but incorporates the following caveats: (1) All things being equal, the PCI strategy does not exclude the patient from receiving a more complete revascularization with surgery; (2) the revascularization strategy must be guided by physiologic testing (preferably FFR, or myocardial perfusion imaging); and (3) the amount of ischemic myocardium following revascularization is minimized.

Therefore, although assessing complete revascularization by alternative modalities and guidance with FFR are important before revascularization, minimizing the amount of ischemic myocardium requires an assessment of residual ischemia. This can only be done either with myocardial perfusion imaging or by calculating anatomic scores such as the myocardial jeopardy score of the more commonly used SYNTAX score.[15]

In the presence of unrevascularized segments causing ischemia, it is equally important that a strategy of treating these patients with adjunct pharmacology be promoted. It could be argued that, in the setting of residual ischemia, a potent first-line agent with potential for reducing myocardial ischemia (such as ranolazine) should be an important consideration, as it is well tolerated in populations in whom the use of alternative agents are contraindicated or cause adverse events, and is effective in reducing the frequency of angina and increasing the time to the development of angina with exercise.[30-32]

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Role of Ranolazine in Incomplete Revascularization

This important issue of how to treat the residual ischemia following successful revascularization of selected targets has prompted the Ranolazine for Incomplete Vessel Revascularization Post-Percutaneous Coronary Intervention (RIVER-PCI) trial (http://clinicaltrials.gov/ct2/show/NCT01442038). This ischemia-guided approach to revascularization is also being tested in the International Study of Comparative Health Effectiveness With Medical and Invasive Approaches (ISCHEMIA) (http://www.clinicaltrials.gov/ct2/show/NCT01471522). Although results of both studies to help guide therapy will not be available for several years, physicians

managing patients with multivessel disease and considering a reasonable incomplete revascularization strategy need an approach that incorporates the best available evidence into their practice now. Therefore, we have developed a schema included as a putative approach when considering a strategy of reasonable incomplete revascularization. This framework builds on the existing evidence, but nevertheless has flexibility such that it may be modified as new evidence becomes available. The essential elements of this reasonable incomplete revascularization strategy are the use of functional testing to achieve functional complete revascularization. When functional complete revascularization is not achieved, the adjunct medical therapy to treat ischemia (or its consequent angina symptoms) is based on the extent and severity of the ischemia. With large areas of ischemia, or any symptoms consistent with residual angina after incomplete revascularization, a first line anti-ischemic agent such as ranolazine could be a consideration, along with appropriate secondary prevention therapy. The primary role of ranolazine is based on its proven efficacy as an anti-anginal agent, its ability to modulate myocardial ischemia, and its potential to reduce possibly life-threatening arrhythmias.

Conclusions

Although complete anatomic revascularization is accomplished infrequently with PCI for multivessel CAD, increasingly more patients are receiving complete functional revascularization. Despite the increase in functional revascularization, incomplete revascularization is associated with worse long-term outcomes. Although some of this risk reflects the higher risk from patient type (eg, older age, more disease), some of this risk is mediated by residual ischemia. Therefore, we believe that a reasonable incomplete revascularization strategy with PCI ought to not only carefully assess the need for adjunctive anti-ischemic medications, but also actively monitor its effectiveness in reducing such ischemia. Figure 2 outlines a proposed schema for the management of patients with multivessel CAD in whom a strategy of reasonable incomplete revascularization is considered. However, it must be acknowledged that this strategy has not yet been shown to improve outcomes, and clinical trials are underway that will test this hypothesis. ■

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MAIN POINTS

- When interpreting current evidence in patients with multivessel coronary artery disease, decision making should take into account four concepts: (1) incomplete revascularization is more common in clinical practice than complete revascularization; (2) the definition of incomplete revascularization is not uniform; (3) completeness of revascularization is not always superior to incomplete revascularization; and (4) all incomplete revascularization scenarios are not equivalent.
- Reasons for incomplete revascularization with percutaneous coronary intervention (PCI) included higher patient risk, and circumstances in which complete revascularization with PCI increased risk (eg, patients with chronic kidney disease and patients unable to tolerate dual antiplatelet therapy); anatomic factors also influenced the frequency of complete revascularization.
- Residual ischemia following successful revascularization of selected targets should be treated with adjunct pharmacology; a potent first-line agent with potential for reducing myocardial ischemia (such as ranolazine) should be an important consideration, as it is well tolerated in populations in whom the use of alternative agents are contraindicated or cause adverse events, and is effective in reducing the frequency of angina.

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