Treatment of Higher-Risk Patients With an Indication for Revascularization
Evolution Within the Field of Contemporary Percutaneous Coronary Intervention

ABSTRACT: Patients with severe coronary artery disease with a clinical indication for revascularization but who are at high procedural risk because of patient comorbidities, complexity of coronary anatomy, and/or poor hemodynamics represent an understudied and potentially underserved patient population. Through advances in percutaneous interventional techniques and technologies and improvements in patient selection, current percutaneous coronary intervention may allow appropriate patients to benefit safely from revascularization procedures that might not have been offered in the past. The burgeoning interest in these procedures in some respects reflects an evolutionary step within the field of percutaneous coronary intervention. However, because of the clinical complexity of many of these patients and procedures, it is critical to develop dedicated specialists within interventional cardiology who are trained with the cognitive and technical skills to select these patients appropriately and to perform these procedures safely. Preprocedural issues such as multidisciplinary risk and treatment assessments are highly relevant to the successful treatment of these patients, and knowledge gaps and future directions to improve outcomes in this emerging area are discussed. Ultimately, an evolution of contemporary interventional cardiology is necessary to treat the increasingly higher-risk patients with whom we are confronted.

Coronary artery disease (CAD) is a leading cause of morbidity and mortality in the developed world, affecting 15.5 million adults in the United States, with 635,000 Americans projected to have a new coronary event (either first hospitalized myocardial infarction or CAD death) this year.1 The profound burden of CAD, coupled with these high event rates, underscores the need to identify and offer treatment to patients with CAD at higher risk for these adverse clinical events. Unfortunately, despite the availability and implementation of disease-modifying guideline-directed medical therapy (GDMT; eg, lifestyle modification, aspirin, statins, and control of risk factors such as blood pressure and diabetes mellitus), a significant proportion of patients still present with prognostically important and anatomically severe CAD as their initial manifestation of CAD.2

For these higher-risk CAD patients, coronary revascularization (in addition to GDMT) can both improve quality of life and reduce adverse clinical events.3-6 A strategy of offering revascularization to patients with high-risk clinical presentations (acute coronary syndromes or stable ischemic heart disease with high-risk anatomy or refractory symptoms) is supported in current clinical practice guidelines and appropriate use documents.7-10 Nonetheless, the rate of revascularization

Correspondence to: Ajay J. Kirtane, MD, SM, 161 Fort Washington Ave, 6th Floor, New York, NY 10032. E-mail akirtane@columbia.edu

Key Words: angioplasty ◼ coronary artery disease ◼ coronary occlusion ◼ heart failure ◼ percutaneous coronary intervention

© 2016 American Heart Association, Inc.
procedures, especially for stable ischemic CAD, has declined considerably over the past decade. Several factors have been identified as contributing to this decline. More effective implementation of GDMT after the publication of randomized trials examining the role of revascularization strategies for patients with stable CAD, more judicious CAD screening protocols, and concerns about inappropriate percutaneous coronary intervention (PCI) have likely resulted in more selective use of diagnostic and revascularization procedures. Declines in revascularization because of these factors are entirely appropriate. However, it is possible that the decline in the rate of revascularization may be out of proportion to clinically inappropriate use. On the basis of a comprehensive analysis of the US CathPCI Registry frequently cited as evidence for the overuse of PCI in the midst of this decline, <5% of all urgent and electively performed PCIs were rated as inappropriate using appropriate use criteria. Thus, although revascularization may have been overused in lower-risk patients, within the overall decline in volume is the possibility of underuse of invasive testing and revascularization procedures in other subgroups of patients such as those at higher risk for adverse events.

A patient population among the least likely to be offered PCI but with a clinical indication for revascularization consists of patients with CAD who also are at higher or extreme (inoperable) surgical risk. Although complete revascularization through PCI is a less invasive alternative to surgical revascularization and may therefore offer advantages to patients at high risk for surgery, early experiences with PCI conducted in the balloon angioplasty and early stent eras demonstrated lower success rates and higher rates of complications with PCI in this group of patients. Nonetheless, with improved patient selection, in conjunction with advances in interventional techniques and technologies, complete revascularization through PCI may allow appropriate patients to safely benefit from revascularization procedures that otherwise might not have been possible or were unwise to offer in the past. Here, we attempt to characterize these patients, increasingly referred to as the “complex higher-risk (and indicated) patient” population, on the basis of growing interest within the field of interventional cardiology. We also examine the potential unmet need for revascularization in this patient subset and discuss the evolution in treatment paradigms essential for the effective care and treatment of these patients.

CANDIDACY FOR REvascularization: AN UNMET NEED FOR PCI

Risk assessment with established and evolving contemporary risk models is an integral component for appropriately identifying and selecting patients for coronary revascularization. Objective risk assessment also can provide patients and referring providers with information to allow them to make shared and informed decisions about treatment. The risk selection algorithm for the advanced CAD patient should be an integrated process aimed at determining the risks of all potential therapies that can be offered to the patient: surgical, percutaneous, or GDMT alone. Large, multicenter, randomized trials have generally demonstrated superior outcomes with coronary artery bypass grafting (CABG) compared with PCI or GDMT in patients with complex multivessel/left main CAD and complex anatomy as identified through an intermediate to high SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) score. However, patients who are deemed either inoperable or at higher risk (eg, >5% estimated risk of mortality for a surgical revascularization procedure) are potential candidates for a percutaneous approach. An additional group of patients for whom percutaneous revascularization is frequently considered is composed of patients who have already had a CABG procedure, especially those for whom the left internal mammary has already been used as a conduit.

Contemporary data demonstrate that patients with higher-risk CAD (such as those with comorbidities or presentations with heart failure) are among the least likely to undergo or even be offered revascularization via a percutaneous approach. There are several possible reasons why this group of patients may not be offered PCI. Some patients may have comorbidities that are too extensive for a (potentially futile) revascularization procedure to make an appreciable difference in outcome. For other patients at high surgical risk, other practical obstacles can lead to the underuse of PCI. For most interventional cardiologists, the percutaneous treatment of these high-risk patients represents a challenge that is often avoided, given a lack of widespread technical expertise, the perception of low procedural success, and confusion about accepted indications for PCI in this population. Physicians may intuitively (and perhaps incorrectly) think that these patients have such far advanced CAD to preclude any meaningful clinical benefit. This is, no doubt, compounded by a relative scarcity of data on the efficacy of revascularization in this population. Public reporting of adverse outcomes can also serve as a deterrent to PCI among higher-risk patients.

At the present time, it is not known precisely how many of these higher-risk patients who might potentially benefit from revascularization are not ultimately offered it. The difficulty in approximating this number stems from the fact that many of these patients may never come to the attention of interventionalists or cardiac surgeons. Additionally, higher-risk patients are almost uniformly excluded from most clinical trials. Many of these patients do not even undergo the diagnostic testing necessary to...
make the diagnosis of severe CAD.24,32 Furthermore, a misalignment exists in the use of cardiac catheterization in many patients relative to their predicted probability of severe CAD in which the use of catheterization appears to target patients who would derive less benefit from revascularization, consistent with a treatment-risk paradox.21

PCI may be considered a beneficial option for the subgroup of patients with severe CAD in whom the revascularization hypothesis (of incremental benefit compared with GDMT alone) may in fact be demonstrable, assuming that these patients can safely undergo revascularization. Even among patients who may be candidates for surgical revascularization, some patients may be willing to accept a higher rate of repeat revascularization with PCI if it minimizes stroke risk compared with CABG, whereas other patients may be willing to accept a longer perioperative recovery from a CABG in hopes of avoiding the need for repeat revascularization and potentially shorter overall longevity with PCI. If CABG is not an option or not desired by the patient, complete revascularization through PCI in many of these patients would require specialized technical and cognitive skills not readily possessed by most coronary interventionalists. Nevertheless, if complete revascularization can be safely and effectively achieved, these patients are among the most likely to derive a robust clinical benefit. Therefore, effective treatment of these patients falls into a true “higher risk, higher reward” paradigm.

DEFINING THE STABLE ISCHEMIC CAD PATIENT AT HIGHER RISK FOR ADVERSE OUTCOMES WITH REvascularization THERAPIES

Accurate risk stratification is critical in the evaluation and management of patients with stable ischemic CAD who are candidates for revascularization therapies. The clinical characteristics and presentation, noninvasive testing including functional testing, and anatomic delineation of CAD all inform the overall risk assessment of CAD patients, and diagnostic and therapeutic strategies usually are tailored by weighing the anticipated benefits of treatment against an individual’s predicted risk for adverse events. Among patients who might benefit from revascularization, a careful assessment of anticipated procedural benefits and estimated procedural risk is critical, and communication of these benefits and risks to the patients, their family, and any physicians comanaging them is essential. Despite the presence of procedural risk calculators for both CABG and PCI, formal consensus on the exact definition of high procedural risk still remains somewhat of an art.33–35 This may be in part due to factors not currently captured in validated risk calculators,36,37 combined with the observation that in higher-risk patients, conventional risk calculators that estimate 30-day mortality across both elective and emergent patients may be wanting, particularly for stable patients undergoing higher-risk interventions.34 In addition, there may be individual variability in levels of accepted or tolerated risk (by both patients and providers/institutions, and depending on the clinical scenario).

All proposed definitions of risk for revascularization procedures incorporate features specific to 3 clinical spheres: patient risk factors and comorbid conditions (including those that preclude surgical or percutaneous revascularization); location and complexity of coronary anatomy (including adequacy of vessels for PCI or for surgical targets); and hemodynamics, ventricular function, and concomitant valvular disease (Figure). It is the composite risk derived from the integration of each of these 3 areas that leads to the cumulative procedural risk profile of any individual CAD patient for whom revascularization is considered.

Comorbid characteristics and adverse patient risk factors can result in increased mortality, decreased functional capacity, inferior quality of life, and greater cost and resource use, including rehospitalization. Epidemiologic data demonstrate that the odds of having multiple cardiovascular comorbidities in CAD patients has increased significantly over time.38 In addition, certain comorbidities may disproportionately modify procedural risk for CABG compared with PCI. In particular, patients with oxygen-dependent chronic obstructive pulmonary disease, severe liver disease, carotid artery disease, prior stroke, frailty, or even prior CABG have...
been shown to have increased risk with CABG compared with PCI.\textsuperscript{33,39-41} Other factors such as the presence of a hostile chest (eg, resulting from anatomic deformities or prior radiation therapy), severe aortic calcification (porcelain aorta), and other factors specifically increasing surgical risk may also weigh into the decision making for revascularization strategies in CAD.

When a revascularization strategy is being considered for patients with CAD, anatomic considerations such as the presence of unprotected left main CAD, complex bifurcation and trifurcation lesions, chronic total occlusions, and heavily calcified lesions, as well as high SYN-TAX score, also can factor heavily into the estimation of risk, particularly for patients for whom PCI is being considered.\textsuperscript{42} Each of these factors can influence the degree of difficulty of a complex PCI procedure. There also is a disparate set of anatomic considerations that affect the risk and potential success of CABG, including suitability of conduits (arterial and venous) and the adequacy of distal targets within the native coronary arteries, especially because this may affect the suitability of left internal mammary placement to a diseased left anterior descending coronary artery. A fundamental assumption before consideration of higher-risk revascularization procedures is that the territories being revascularized are both ischemic and viable. In patients with severe left ventricular dysfunction or regional wall motion abnormalities, performance of either noninvasive testing to confirm ischemia/viability or fractional flow reserve to determine the physiologic significance of lesions should be considered to ensure that a meaningful degree of myocardium subtended by the vasculature to be intervened on is recoverable.

Poor hemodynamic status, impaired ventricular function, and the presence of concomitant valvular heart disease are the final critical components of the assessment of procedural risk. Patients with abnormalities in this sphere typically have low physiologic reserve and are at high risk for hemodynamic decompensation during either PCI or CABG. Revascularization in these patients also requires careful planning, with preprocedural hemodynamic optimization and consideration of the use of hemodynamic support before intervention in selected cases and continuing through the immediate postprocedural time period. An additional (often unrecognized) subgroup of patients at high risk for adverse outcomes are those with pulmonary hypertension or right ventricular failure; surgical outcomes in this group in particular are among the poorest.\textsuperscript{43}

**MULTIDISCIPLINARY TEAM-BASED APPROACH TO HIGHER-RISK CAD PATIENTS**

Given the complexity of managing higher-risk patients with CAD, a collaborative team-based model is essential for appropriate patient selection, treatment, and subsequent care of these patients. The coordinated approach of a dedicated heart team has the potential to lead to enhanced decision making, superior outcomes, and ultimately exceptional overall patient care.\textsuperscript{7-9} although institutional protocols encapsulating heart team decision making algorithms may sometimes be substituted for formal heart team deliberations in an institution with well-established and high-quality practice patterns.\textsuperscript{44} Patients should be considered potentially for PCI or surgical revascularization if they have ongoing symptoms despite GDMT and are thought by the heart team to derive a likely meaningful clinical benefit from revascularization. A thorough assessment of the extent of CAD burden, hemodynamics, and global cardiac function should be undertaken. The optimal revascularization strategy, timing, and alternative approaches then should be closely mapped out within the constructs of the heart team. Given the nuances of clinical decision making in these patients and scenarios in which there may be clinical equipoise, the collective experience of the multidisciplinary heart team is vital to optimizing patient outcomes.

Beyond the decision making for a revascularization strategy, when patients with higher-risk CAD are treated, input from primary treating physicians, interventional cardiologists, cardiothoracic surgeons, heart failure specialists, multimodality imaging specialists, intensivists, and even electrophysiologists (for patients with depressed ventricular function or concomitant arrhythmias) may become relevant (Table 1). For example, heart failure or critical care specialists with a dedicated interest in the acute care of decompensated congestive heart failure should be engaged when issues related to candidacy for advanced heart failure therapies or cardiac transplantation are being considered. Additionally, imaging experts with specific knowledge of applied imaging as an adjunct to interventional vascular procedures would be best suited to participate in discussions of the cause and management of concurrent valvular heart disease (eg, ischemic mitral regurgitation). Furthermore, it is important to explicitly state that all patients with CAD should have their medical regimen optimized before proceeding with any revascularization procedure. Optimization should include a thorough assessment of implementation and adherence to GDMT, related to both disease modification and symptom relief. A careful and systematic review of both medical and adjunctive lifestyle-modifying therapies can reveal significant opportunities for improvements in overall cardiac care. Finally, careful optimization of hemodynamic status and adjunctive periprocedural therapies (eg, management of kidney dysfunction, including optimization of hydration, in conjunction with low-contrast protocols, prophylaxis for contrast allergy as needed) can be critical to ensuring that a patient undergoes a safe procedure.
improved among operators trained in specialized technology, and PCI techniques and devices, the success in functionally based revascularization, adjunctive pharmacology, and PCI techniques and devices is a prerequisite (Table 2). The experience and clinical judgment required to perform these procedures in most cases will be beyond that obtained in traditional single-year interventional cardiology fellowships in which the exposure to the most complex patient and lesion subsets may be limited. Moreover, the nuances of case selection and clinical judgment necessary to become an expert interventional cardiologist require time and an accumulated case load.

The development and eventual success of this field are, however, predicated on appropriately identifying and treating the correct patient population and ensuring that the desired outcomes can be achieved. Although performing PCI in patients who are either ineligible or too high risk for surgical revascularization makes empirical sense, a movement toward the performance of PCI in these populations is not to be taken lightly. Given the procedural complexity and the patient comorbidities associated with an intrinsically high-risk population, the potential for considerable harm exists if potentially unprepared interventionalists are given free rein to perform the highest-risk procedures for contemporary PCI in a potentially vulnerable population. There is a difference between complex intervention and higher-risk intervention. Whereas complex intervention requires advanced and specialized techniques, not all of these confer increased risk to an individual patient. For example, although a patient with an ejection fraction of 10% and a focal noncomplex LAD lesion might not at first blush appear to be at significantly higher risk for an interventional procedure, if the patient had pulmonary artery pressures of 75 mm Hg with a pulmonary capillary wedge pressure of 35 mm Hg and a pulmonary artery saturation of 30%, that patient might indeed be at higher risk than a patient with a complex distal left main coronary artery lesion and normal ventricular function. Therefore, successful establishment of specialized programs must incorporate training/expertise in both complex techniques (eg, treating the distal left main bifurcation) and the adequate assessment of procedural risk (eg, through knowing when to perform right-sided heart catheterization before undertaking PCI).

In many respects, a focused core curriculum for interventionalists performing procedures in these patients is therefore essential. Such a curriculum could focus not only on how to safely and skillfully treat these patients from a technical standpoint but also on the cognitive development necessary for preprocedural screening and evaluation in conjunction with an understanding of the rationale and goals for revascularization. Having a dedicated and case-based curriculum could additionally help to ensure a shared level of expertise and knowledge among interventional cardiologists performing

Table 1. Roles and Team Members Who May Be Called on in a Multidisciplinary Approach to Patients With Higher-Risk, Severe CAD

<table>
<thead>
<tr>
<th>Role</th>
<th>Member</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient/family</td>
<td>Patient and family members</td>
</tr>
<tr>
<td>Physicians</td>
<td>Primary care physician, Primary cardiologist, Advanced heart failure/critical care specialist (experience in advanced therapies, transplantation)</td>
</tr>
<tr>
<td>Formulating revascularization strategy</td>
<td>Specialized coronary interventionalalist, Cardiothoracic surgeon</td>
</tr>
<tr>
<td>Managing concomitant structural heart disease</td>
<td>Multimodality imaging specialist, Structural heart interventionalist (for concomitant valvular disease)</td>
</tr>
<tr>
<td>Managing concomitant rhythm therapies</td>
<td>Electrophysiologist</td>
</tr>
<tr>
<td>Postprocedural care</td>
<td>Cardiac intensivist, primary cardiologist</td>
</tr>
<tr>
<td>Staff</td>
<td>Nurse or advanced practice provider to assist in preprocedural/postprocedural optimization, Social worker/services</td>
</tr>
</tbody>
</table>

CAD indicates coronary artery disease.

SPECIALIZED COGNITIVE SKILLS AND TECHNICAL SKILLS REQUIREMENTS

To treat patients safely and effectively, there needs to be a cadre of interventional cardiologists who possess the skill sets necessary to perform complete revascularization safely and effectively in the most complex and high-risk patients. In the current era of PCI with advances in functionally based revascularization, adjunctive pharmacology, and PCI techniques and devices, the success rates for treating the most complex lesion subsets have improved among operators trained in specialized techniques but have remained significantly lower among everyday interventionalists. Armed with the knowledge of how and when to use these techniques, dedicated interventionalists with expertise in treating these patients could be more apt to choose the optimal treatment strategies and, most important, improve overall outcomes in these patients.

For those interventionalists who wish to evolve beyond those performing conventional contemporary PCI, adequate technical training complemented by an adequate procedural volume of complex cases (eg, chronic total occlusions, calcified vessels, complex bifurcation disease, cases requiring hemodynamic support) and specific techniques and devices is a prerequisite (Table 2). The experience and clinical judgment required to perform these procedures in most cases will be beyond that obtained in traditional single-year interventional cardiology fellowships in which the exposure to the most complex patient and lesion subsets may be limited. Moreover, the nuances of case selection and clinical judgment necessary to become an expert interventional cardiologist require time and an accumulated case load.

The development and eventual success of this field are, however, predicated on appropriately identifying and treating the correct patient population and ensuring that the desired outcomes can be achieved. Although performing PCI in patients who are either ineligible or too high risk for surgical revascularization makes empirical sense, a movement toward the performance of PCI in these populations is not to be taken lightly. Given the procedural complexity and the patient comorbidities associated with an intrinsically high-risk population, the potential for considerable harm exists if potentially unprepared interventionalists are given free rein to perform the highest-risk procedures for contemporary PCI in a potentially vulnerable population. There is a difference between complex intervention and higher-risk intervention. Whereas complex intervention requires advanced and specialized techniques, not all of these confer increased risk to an individual patient. For example, although a patient with an ejection fraction of 10% and a focal noncomplex LAD lesion might not at first blush appear to be at significantly higher risk for an interventional procedure, if the patient had pulmonary artery pressures of 75 mm Hg with a pulmonary capillary wedge pressure of 35 mm Hg and a pulmonary artery saturation of 30%, that patient might indeed be at higher risk than a patient with a complex distal left main coronary artery lesion and normal ventricular function. Therefore, successful establishment of specialized programs must incorporate training/expertise in both complex techniques (eg, treating the distal left main bifurcation) and the adequate assessment of procedural risk (eg, through knowing when to perform right-sided heart catheterization before undertaking PCI).

In many respects, a focused core curriculum for interventionalists performing procedures in these patients is therefore essential. Such a curriculum could focus not only on how to safely and skillfully treat these patients from a technical standpoint but also on the cognitive development necessary for preprocedural screening and evaluation in conjunction with an understanding of the rationale and goals for revascularization. Having a dedicated and case-based curriculum could additionally help to ensure a shared level of expertise and knowledge among interventional cardiologists performing
these procedures. If this curriculum could be robustly developed and broadly applied, it could truly be transformative in defining what it means to be an advanced coronary specialist in an era of continued differentiation within the field of interventional cardiology.

The specialized techniques needed for effective treatment of higher-risk patients with indications for revascularization simply cannot be taught in an abridged course or without some element of hands-on training. Thus, a considerable investment in time and effort likely would be needed for physicians to become truly proficient. The development of formalized training programs, observerships, or even proctorships could help with some of the practical hands-on skills necessary, particularly for practitioners who lack the procedural experience and support to begin to tackle more complex procedures with the goal of complete revascularization. In addition, we could envision specific training and mock scenarios administered within the cardiac catheterization laboratory and intensive care units to ensure adequate training by staff in both areas. It is imperative, however, that designated specialists and programs continue to use their accumulated skills set on a regular basis because outcomes are undoubtedly likely to suffer if appropriate volume thresholds are not maintained. Finally, further work is required to address the ideal reimbursement and cost structures for these complex procedures that can often lead to substantial variances in time, equipment costs, and hospital use.

**Table 2. Technical Skills and Training/Infrastructure Requirements (for Physicians, Staff, and Institutions) for the Care and Revascularization of Patients With Higher-Risk, Severe CAD**

<table>
<thead>
<tr>
<th>Patient/Lesion Subsets</th>
<th>Techniques/Devices</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic total occlusions</td>
<td>Dual access and injections</td>
</tr>
<tr>
<td></td>
<td>Antegrade and retrograde techniques, including dissection/re-entry devices</td>
</tr>
<tr>
<td></td>
<td>Specialty wires, microcatheters, devices for increasing guide/catheter support,</td>
</tr>
<tr>
<td></td>
<td>externalization techniques</td>
</tr>
<tr>
<td>Left main stenosis/</td>
<td>Single- and 2-stent strategies (both primary and for provisional/bailout use)</td>
</tr>
<tr>
<td>bifurcations</td>
<td>Intravascular imaging</td>
</tr>
<tr>
<td>Calcific disease</td>
<td>Rotational/orbital atherectomy</td>
</tr>
<tr>
<td></td>
<td>Intravascular imaging</td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>Coronary physiological studies (eg, fractional flow reserve)</td>
</tr>
<tr>
<td></td>
<td>Intravascular imaging</td>
</tr>
<tr>
<td>Poor hemodynamic</td>
<td>Left/right ventricular percutaneously implanted support devices</td>
</tr>
<tr>
<td>status/ventricular function</td>
<td>Intra-aortic balloon counterpulsation</td>
</tr>
<tr>
<td>coexisting with complex anatomy</td>
<td>Extracorporeal membrane oxygenation</td>
</tr>
<tr>
<td></td>
<td>Large-vessel access/closure management</td>
</tr>
<tr>
<td></td>
<td>Transradial expertise (when both femoral arteries are used)</td>
</tr>
<tr>
<td></td>
<td>Alternative access considerations (axillary, transfacial)</td>
</tr>
<tr>
<td>Stent underexpansion/</td>
<td>Intraocular imaging</td>
</tr>
<tr>
<td>restenosis</td>
<td>Aggressive noncompliant and plaque-modification balloons</td>
</tr>
<tr>
<td></td>
<td>Atherectomy (laser, rotational)</td>
</tr>
<tr>
<td></td>
<td>Vascular brachytherapy</td>
</tr>
<tr>
<td>Complication management</td>
<td>Echocardiography-guided pericardiocentesis</td>
</tr>
<tr>
<td></td>
<td>Covered stents, coils, beads</td>
</tr>
<tr>
<td></td>
<td>Snares/snaring techniques</td>
</tr>
<tr>
<td></td>
<td>Dual guide techniques</td>
</tr>
<tr>
<td></td>
<td>Dissection/re-entry to salvage distal flow</td>
</tr>
<tr>
<td></td>
<td>Endovascular rescue</td>
</tr>
</tbody>
</table>

CAD indicates coronary artery disease.

**KNOWLEDGE GAPS AND FUTURE DIRECTIONS**

There are still many unanswered questions related to the evolving population of higher-risk PCI patients. The exact size of the patient population that can benefit from higher-risk PCI procedures remains unknown because these patients have historically been underrepresented in clinical trials and registries, and many patients who could be eligible for revascularization never come to the attention of interventional cardiologists or cardiothoracic surgeons. There have also been no trials comparing PCI with GDMT in this patient population. Moreover, in patients with complex coronary anatomy at very high (but not inoperable) surgical risk, it is unknown whether PCI is truly a viable alternative to CABG over the long term. Whereas surgical ineligibility can confer risk independently for patients undergoing high-risk PCI, no risk models can calculate the differential risk of PCI appropriately compared with optimal GDMT. As a result, providers inappropriately may ascribe too high or too low a risk to PCI and adversely affect the decision about revascularization. Lastly, it is not known how many patients fall into an area of futility where no benefit can be achieved by revascularization.

To begin to answer some of these questions, it is critical to start gathering systematic disease-based data on patients with complex and severe CAD and the current treatments offered to these patients. Various research priorities within this space are listed in Table 3. One of the first steps in investigating this patient population would involve the formation of a large,
research priorities in the higher-risk CAD population potentially eligible for PCI

<table>
<thead>
<tr>
<th>Research Priority/Question</th>
<th>Study Design/Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>What is the prevalence of severe (and nonrevascularized) CAD?</td>
<td>Disease-based (as opposed to solely procedure-based) registries</td>
</tr>
<tr>
<td>What are the outcomes of PCI in higher-risk CAD patients (eg, nonsurgical patients), and are there specific operator/institution volumes that are required to achieve the best procedural outcomes?</td>
<td>Procedural registries</td>
</tr>
<tr>
<td>What are the costs associated with revascularization in higher-risk CAD patients?</td>
<td>Disease-based registries with embedded procedural data Potential randomized trials</td>
</tr>
<tr>
<td>What are the outcomes with PCI, surgical revascularization, and medical therapy among higher-risk patients with an indication for revascularization?</td>
<td>Disease-based registries with embedded procedural data</td>
</tr>
<tr>
<td>What is the variability in care patterns for patients meritind consideration of revascularization?</td>
<td>Procedure- and disease-based registries</td>
</tr>
<tr>
<td>To what extent are contemporary interventionalists trained and skilled to perform complete revascularization across complex lesion subsets?</td>
<td>Randomized trials, possible comparative-effectiveness assessments</td>
</tr>
<tr>
<td>To what extent can PCI achieve surgery-like outcomes in higher-risk CAD patients?</td>
<td></td>
</tr>
</tbody>
</table>

CAD indicates coronary artery disease; and PCI, percutaneous coronary intervention.

multicenter registry that could allow the systematic tracking of short- and long-term outcomes for higher-risk patients already undergoing more complex procedures. This has already started within the chronic total occlusion space. The data from similarly developed and more broadly based registries would be hypothesis generating but could help shape guidelines for the management of these patients. These registries ultimately could lead to the creation of a preliminary database infrastructure that could be used to construct formalized prospective studies (even randomized trials) within this population. Such registries and any subsequent studies also may be mined to develop finally an accurate risk model to help guide physicians in the decision making process for revascularization in this population. Ultimately, the recognition of the evolution in risk profiles among patients undergoing PCI concept may lead to the collective improvement in the quality of PCI as a whole because patients may be more apt to undergo PCI by well-trained interventionalists possessing the breadth and depth of technical and cognitive skills to treat them safely and effectively.

CONCLUSIONS

Patients with severe CAD who are candidates for PCI but at high risk for established coronary revascularization procedures such as CABG because of patient comorbidities, complexity of coronary anatomy, and/or poor hemodynamic status represent an understudied and potentially underserved patient population. The characterization of a new field of coronary interventional procedures aims to fulfill an unmet need to better define this population and to focus the use of PCI in these patients who potentially have the most to gain from coronary revascularization procedures. The most critical requirements at present relate to training adequately a dedicated cadre of coronary interventionalists who possess the cognitive and technical skills to manage these patients. The impact of these procedures on the hospital level and health system must be formally assessed, but it is our belief that this treatment paradigm has the potential to maximally benefit patients judiciously and safely.

ACKNOWLEDGMENT

We thank Dominic P. Francese, MPH, for assistance in formatting and preparing this manuscript.

DISCLOSURES

Dr Kirtane reports institutional research grants to Columbia University from Boston Scientific, Medtronic, Abbott Vascular, Abiomed, St. Jude Medical, and Eli Lilly. Dr Doshi reports an educational grant from Abiomed Inc. Dr Karpaliotis reports serving on the speakers’ bureau for Abbott Vascular, Boston Scientific, Medtronic, and Asahi. Dr Leon reports serving on the advisory board for Boston Scientific and Medtronic. Dr. Lasala reports speaker fees from Abiomed, St. Jude Medical, Eli Lilly, Boston Scientific, and Daiichi Sankyo; serving on the advisory board for Abiomed and Boston Scientific; and being a stockholder in Abiomed. Dr Ohman has received grant support from Gilead Sciences and Daiichi-Sankyo/Eli Lilly and Co, as well as consultant fees from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Janssen Pharmaceuticals, Liposcience, The Medicines Company, Merck/Schering Plow, Pozen, Roche, Sanofi-Aventis, and WebMD. Dr Shroff has been a consultant for Medtronic, Abiomed, Terumo Medical, and The Medicines Company. Dr Cohen has been on the speakers’ bureau for Medtronic; has been a consultant for AstraZeneca, Abiomed, Daiichi Sankyo, and Terumo Medical; and has received research support from Boston Scientific and Abbott Vascular. Dr Uriel has been a consultant for Thoratec, Heartware, Abiomed, and Medtronic and has received grant support from Thoratec and Heartware. Dr Kapur reports serving on the speakers’ bureau for Abiomed, Maquet, and Heartware; being a...
consultant for Abiomed, Cardiac Assist, Maquet, and Thoratec; and receiving research support from Abiomed, Cardiac Assist, and Maquet. Dr Dangas reports institutional research grant support from The Medicines Company, Bristol-Myers Squibb/Sanofi, and Eli Lilly and Co/Daiichi-Sankyo, as well as consulting fees from Abbott Vascular, AstraZeneca, Boston Scientific, Covidien, Janssen Pharmaceuticals, Regado Biosciences, Mayo Medical, Merck & Co, and The Medicines Company. Dr Lombard has served as a consultant to Abbott Vascular, Boston Scientific, and Abiomed; has been on the advisory board for Abbott Vascular and Boston Scientific; is an employee (spouse) of Spectranetics; and holds equity in Bridgepoint Medical Systems. Dr Parikh reports serving on the speakers’ bureau for Abbott Vascular, Medtronic, CSI, and Boston Scientific and on the advisory board for Abbott Vascular, Medtronic, and Philips. Dr Moses reports consulting fees from Boston Scientific and Abiomed. The remaining authors report no conflicts.

AFFILIATIONS
From Herbert and Sandi Feinberg Interventional Cardiology and Heart Valve Center, Columbia University Medical Center/New York-Presbyterian Hospital, New York, NY (A.J.K., D.D., M.B.L., D.K., M.A.P., G.W.S., J.W.M.); Cardiovascular Research Foundation, New York, NY (A.J.K., D.D., M.B.L., D.K., M.A.P., G.W.S., J.W.M.); Washington University in St Louis, St Louis, MO (J.M.L.); The Program for Advanced Coronary Disease, Duke University Medical Center, Durham, NC (E.M.O.); Henry Ford Hospital, Detroit, MI (W.W.O.); University of Illinois, Chicago (A.S.); University of Miami Miller School of Medicine, Miami, FL (M.G.C.); Massachusetts General Hospital, Harvard Medical School, Boston (I.F.P.); Mount Sinai Medical Center, Miami, FL (N.B.); University of Chicago, Chicago, IL (N.U.); Tufts Medical Center, Boston, MA (N.K.K.); University of Washington Medical Center, Seattle (W.L.); and Mount Sinai Medical Center, New York, NY (G.D.D.).

FOOTNOTES
Received February 14, 2016; accepted June 22, 2016. Circulation is available at http://circ.ahajournals.org.

REFERENCES


22. Harskamp RE, Wang TY, Bhatt DL, Wiviott SD, Amsterdam EA, Li S, Thomas L, de Winter RJ, Roe MT. Hospital patterns of med-
Treatment of Higher-Risk Patients With an Indication for Revascularization: Evolution Within the Field of Contemporary Percutaneous Coronary Intervention


_Circulation_. 2016;134:422-431
doi: 10.1161/CIRCULATIONAHA.116.022061

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2016 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/134/5/422

Data Supplement (unedited) at:
http://circ.ahajournals.org/content/suppl/2016/07/27/CIRCULATIONAHA.116.022061.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org/subscriptions/
Caroline: Welcome to Circulation on the Run, your weekly podcast summary and backstage pass to the journal and its editors. I’m doctor Caroline Lahm, associate editor from the National Heart Center and Duke National University of Singapore. Joining on me in just a moment are two guests to discuss a very exciting new category of papers, known as the white paper. The topic for today is an evolution within the field of current day percutaneous coronary intervention that of the treatment of higher risk patients with an indication for revascularization. But first, here is your summary of this week's journal.

The first study is from first author doctor Jolis and corresponding author doctor Grainger, from the duke clinical research institute in Durham, North Carolina. These authors describe the American Heart Association Mission: Lifeline, STEMI Systems Accelerator. This exciting project represents the largest effort ever attempted in the United States to organize ST segment elevation myocardial infarction care across multiple regions, including 484 hospitals, 1,253 emergency medical services across sixteen regions and involving more than 23,800 patients.

Indeed, this project aims to organize coordinated regional reperfusion plans so as to increase the proportion of patients treated within guideline goals, that is a first medical contact to devise time of less than 90 minutes for STEMI patients directly presenting to PCI capable hospitals and less than 120 minutes for transferred patients.

The authors observed that during the study period of July 2012 to December 2013, there was a significant increase in the proportion of patients meeting these guideline goals, including an increase from 50% to 55% of STEMI patients directly presenting via emergency services and from 44% to 48% of those transfer patients. The authors concluded that these improvements, while modest, suggest the potential for reductions in total ischemic time and happily observe corresponding trends towards lower in-hospital mortality compared with the national data towards the end of the measurement period. Indeed, the tickle message is that the findings support continued efforts to implement regional STEMI networks.

The next study is by first author doctor Hidari and corresponding author doctor Kuang from the Brigham and Women’s Hospital in Boston, Massachusetts. They describe the OMEGA-REMODEL randomized clinical trial. This is a multi-center, double-blinded, placebo control trial of 358 participants presenting within acute myocardial infarction who are randomized to six months of high dose omega-3 fatty acids at four grams daily versus placebo.

Cardiac magnetic resonance imaging was used to assess cardiac structure and tissue characteristics at baseline and following therapy with the primary study in point being a change in left ventricular systolic volume index. Indeed, the authors reported that compared to placebo, patients who received four grams daily omega-3 fatty acids experienced significant improvements in both left ventricular and systolic volume and surrogate measures of non-infarct myocardial fibrosis during the six months of treatment.
These remodeling benefits further followed a dose response relationship with the rise in the in vivo omega-3 fatty acid levels as quantified by your red blood cell index. They concluded that four grams daily of omega-3 fatty acid is a safe and effective treatment in improving cardiac remodeling in patients receiving current guideline based post-myocardial infarction therapies. Indeed, this does warrant perspective clinical studies.

The third study is by first author doctor Liu and corresponding author doctor Sia from University of Texas, Houston Medical School and Colleagues, who sought to understand the molecular basis underlying adaption to high altitude hypoxia. By conducting both human high altitude and most genetic studies, the authors identified a novel functional role of CD73-dependent elevations in extracellular adenosin signolin in response to high altitude hypoxia.

This led to sequential activation of a readthrough site AMP-activated protein kinase, which in turn resulted in increased 2,3-bisphosphoglyceric production and enhanced oxygen release capacity to peripheral tissues. Thus, reducing tissue hypoxia, inflammation and pulmonary injury. These findings have significantly added to our understanding of the molecular mechanisms underlying adaption to hypoxia. Thereby, opened novel therapeutic possibilities for the prevention and treatment of hypoxia related conditions.

The final study is from first author doctor Yen and corresponding author doctor Chen from the National Taiwan University and Colleagues, who aimed to determine the effect of betel nut chewing and paternal smoking on the risks of early metabolic syndrome in human offspring. The author studied more than 13,000 parent-child trios identified from more than 238,000 Taiwanese aged 20 years or older screened in two large community based screening cohorts.

The main finding was that pre-fatherhood habits of both betel nut chewing and cigarette smoking led to a 77% and 27% increase in risk of early metabolic syndrome in their offspring respectively. In fact, they even observed a dose-response relationship where the risk was higher with an increase in duration of exposure as well as with earlier age of starting exposure. These findings interestingly suggest that genetic or epigenetic changes due to exposure to both betel nut and cigarette smoking before birth can contribute to early occurrence of metabolic syndrome in offspring. In fact, these findings really support education for avoidance of these habits or cessation of these habits.

That was your weekly summary. Now, for our feature paper. Our feature paper this week is a white paper regarding the treatment of higher risk patients with an indication for revascularization and evolution within the field current-day percutaneous coronary intervention. To join me in this discussion, I'll have the first and corresponding author doctor Ajay Kirtane from Colombia University Medical Center, New York Presbyterian hospital, as well as doctor [Manus Brelaques 00:08:22], associate editor from UT Southwestern. Welcome, Ajay and Manus.
Ajay: Thanks so much for having us.

Manus: Thanks Caroline.

Caroline: Great. Manus, I would love if we could start by talking about the concept of the white paper and what circulation is looking in these white papers.

Manus: Of course. It is a very exciting part of the new circulation which is for topics that are very timely and important, but at the same time there's not enough populous data and populous literature to be able to address it in a more formal systematic review way. The concept is that establish the leaders in the field. I'm going to provide their perspectives which have derived through their clinical practice and be able to inform us of what the current issues are, how can they best be addressed and what are the next steps forward.

Caroline: That's great, and what a great example to start with with this paper by Ajay. Ajay, maybe I could just start by asking you to make it crystal clear to us the kind of patients you're referring to in this higher risk and the context and the scope of the problem that you're talking about in your paper.

Ajay: Absolutely. First of all, I'm honored that you would consider that's both timely and important and that this will be one of the new papers in the series on behalf of all the [cohorts 00:09:44] is we're really pleased to be able to discuss it. I think the reason that we find this really critical at this juncture is because what we're sort of saying is an evolution in current-day practice. There are many patients now who were seen that have either been turned down for cardiac surgery or have highly complex disease that we know merit revascularization.

In other words, medical therapy has failed for them either from the symptomatic standpoint or because it puts them at too high risk given the complexity of their coronary anatomy and where these lesions are located. Yet at the same time, in order to be able to treat these patients effectively, we need to grasp not only advanced techniques in terms of how to do it, but also need to be able to select the patients appropriately so that they can undergo these procedures safely and to drag the benefit that we'd like to be able to offer them.

Just one brief thing to mention is that we certainly know that over the past 10 years or so, there's been a lot of criticism of the PCI procedures they could perform, particularly here in the United states. Some of them were perhaps unnecessary or some of them were not necessarily benefiting patients. The good news is we've curtailed a lot of that, but yet at the same with that curtail we've sort of seen a decline in these types of cases that we refer to in the paper where patients really could benefit from revascularization, but for whatever reason or not being offered it.
Caroline: Listeners might be wondering though, what is the difference between what you're talking about high risk, and we read a lot of papers about complex procedures and complex PCI, you want to make that differentiation just slightly clearer?

Ajay: Sure. I think that complex PCI has been something that carries the historical definition and usually involves lesion subsets like the left main, chronic total occlusion, bifurcations, that require more than just a simple predilatation stent implantation. The concept of procedural risk though while it overlaps with complexity, to some extent actually has other inputs. For instance, the ventricular function of the patient whether or not the other circulation is also compromised, so it's a larger ischemic territory, and similarly some things that were previously complex with an evolution of techniques actually don't offer or confer that much greater risk on patients.

I would say when I did my fellowship training, left main was something that my heart rate got up for and we were worried about the patient in that respect. Now when we do left mains, it's actually something where we view it as one of the more simple things that we do relative to for instance the retrograde approach to a CTO revascularization. There's been an evolution and there's an overlap of what's complex and what's high risk.

Caroline: Very nicely put. Could you tell us a little bit about how your paper is structured? I really like for example the way your tables are laid out and so on, but maybe just give an overview?

Ajay: Absolutely. I think we start off with just setting the scope of the problem. Basically, looking at coronary heart disease and the fact that there are subsets of coronary diseases for which has prognosticked the importance to revascularize. For instance, the publication of this ten-year result for the first trial [inaudible 00:12:45] revascularization as a whole. We talk a little bit about the assessment of procedural risk and then we sort of move on in the end to the various areas that interventionalists need to become better trained in order to deal with these types of patients. I have to give credit where credit is due. The tables that you like so much were actually the suggestion of the editors. Because of the new theory, Manus had a lot to do with this. I think it's very important for people to understand, at least for this paper the role, the back-and-forth conversation between not only us, but also the editors and the reviewers play in bringing this manuscript to its final form. I really give them credit for it. What's in the tables are not only descriptions of the types of multidisciplinary teams that are needed in order to [affect 00:13:27] that we take of these patients. Also, the techniques that would be useful for interventionalists to know how to use and be [inaudible 00:13:33] to take care of these patients. Finally, a table looking at future directions because it's all good and fine for us to say this is a new area and we're moving into it, but we need to sort of generate the research and the evidence base to really support the treatment that we're trying offer or saying we can offer in the manuscript.
Caroline: Manus, you have to this describe some of this back-and-forth conversation that went on.

Manus: Ajay, I wish that every author took the comments as well as you did because that's definitely not the case. I must admit that it was a pleasure working with you because again you were so open to all the comments and suggestions even though some were tough ones. I think the interaction and being so open I think made the paper better and we're very, very appreciative for your response to those.

Ajay: I think at the end of the day when you have a new editor team taking over, there are going to be changes and some changes you learn how to grow through and other changes you basically adopt what the previous editors were doing. At least my experience, not to [despair 00:14:29], is the prior circulation editors at all, I actually had a great experience with them as well, but this was novel, and I think it's something that for many authors will find quite nice to experience because there was a lot of back and forth. Some parts were contemptuous, but these were all resolved. I wrote in my response back to the reviewers I really do feel the paper was better as a result.

Manus: I think that's the idea that [inaudible 00:14:51] the language and the whole editorial team is trying to enforce and we're very happy with it and enjoyed.

Caroline: I couldn't agree more. Actually, Manus I was also going to ask the title is provocative. It says this is an evolution and even in the conclusion of the paper that this could be a new field of coronary interventional procedures. I really love your thoughts. Is this a beginning of a whole new field?

Manus: I personally do believe and many people I think do believe that there's a tremendous evolution that is going on right now, continue to go on in the field compared to the early days of [inaudible 00:15:26] where we did simple angioplasty I think it has come a long way. But I think there is gap between what can be done right now in terms of technical possibilities, in terms of equipment we'll have and improved patients' quality and quantity of life.

Actually, what is being done because as you heard from Ajay, many of those patients who could benefit do not. Within the environment of trying to stop in a [inaudible 00:15:51] procedure, which is very appropriate, what happened exactly is that those more complex and high risk cases because of the fear of complications or sub-optimal outcomes led to offering less treatment to those complex patients.

I do believe it's an evolution in the field. I do believe that having access to these techniques, equipment and offering options to the patients and explaining there is benefit ratio can bring the patient's life, make them better and bring the field forward to the next step.

Caroline: Ajay, do you think you could elaborate a little bit more then on what those next steps you think are and what are the future areas of research?
Ajay: Yeah, I'd certainly be happy to do so. I couldn't agree with Manus more. I know he and I share a lot of beliefs in terms of this. One of the things that's important to recognize is while we can all assess procedural risk, some of these advanced techniques are not commonly shared by all interventionalists here in the United States, particularly if you look at the overall case volumes of many interventionalists in the United States, there are folks who are just not going to have the requisite volume to be able to do complex CTO revascularization with a retrograde approach. For instance, they would bring procedural success rates up around 90%.

I think that some of this is education. You have to sort of understand what can and cannot be done, what can and cannot be done [faithfully 00:17:08] and what techniques you use or are necessary in order to be able to improve this rate of success. If for instance I can't do the procedure myself, then I need to be familiar with somebody who actually can because if the patient merits revascularization, in other words they could benefit from having a procedure done, they're not a surgical candidate and they could be helped by PCI, then rather than saying, "We should just do medical therapy because I can't do the procedure." The appropriate thing to do is to actually refer the patient to somebody who actually could do the procedure in a safe way and therefore ensure benefit for the patient.

That's an educational aspect. Some of it relates to training, but I think conceptually we do need to start understanding now that there is a sub-specialization within coronary intervention of interventionalists who are able to offer things that many interventionalists cannot. That's somewhat of a fundamental step many people have to take, but I think it's time to take that step and that was the whole point in writing this paper.

Caroline: I think that is a very effective first step that now you've brought it to light and we're so proud and privileged to be publishing this paper. Thank you so much Ajay, thank you so much Manus.

Ajay: Thanks so much for having us.

Manus: Thanks Caroline.

Caroline: And thank you listeners. You've been listening to Circulation on the Run. Please tune in next week for more highlights and discussions.