Review

Patients With Coronary Artery Disease Unsuitable for Revascularization: Definition, General Principles, and a Classification

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ABSTRACT

In the present report, we review the phenotypes of coronary artery disease (CAD) patients unsuitable for revascularization procedures. We then analyze these phenotypes and propose a simple angiographic-based classification for patients with CAD unsuitable for revascularization. Under this classification, the following four distinct angiographic phenotypes are proposed: (1) suspected cardiac syndrome X; (2) limited territory at risk; (3) diffuse thread-like coronary atherosclerosis; and (4) end-stage CAD. It is hoped that such a classification system, as well as the general principles described in this report, will help to standardize the collection of epidemiological data on patients with refractory angina (RFA) and advanced CAD. It is also hoped that this system will be useful to extend the principles of clinical equipoise to the development of clinical trials of innovative therapies or devices for the treatment of RFA. Finally, we anticipate that the elaboration of this system, the first of its type in the literature, will stimulate discussion of what we feel to be a subject that has received insufficient attention in the literature, and ultimately to improved management of a challenging patient population.

With improvements in medical therapies, a growing number of patients with coronary artery disease (CAD) survive to a point where conventional therapeutic options have been exhausted. In the field of refractory angina (RFA), the concept of “no-option” is a complex relationship between cardiac pain, myocardial ischemia, and unsuitability for revascularization. Cardiac ischemia, and unsuitability for revascularization (Fig.1). The later component is a poorly defined notion that combines anatomical and clinical elements.

In patients with refractory symptoms, the decision to not pursue further revascularization is difficult and varies depending on patient-specific characteristics and available medical expertise. For this reason, a consensus as to why or when a patient is unsuitable for revascularization is often difficult. These patients can vary significantly with respect to the extent of their CAD, comorbidities, and respective risk profiles. Because of this variability, the concept of noneligibility for revas-
Rationale for a Classification System

The need for a classification system is supported by several reasons. Epidemiologically, more restrictive phenotypes will allow for refinement of the data available for each patient subset and help to actually constitute an identifiable population of people who are unsuitable for revascularization and living with RFA. Precise estimates of the prevalence of RFA are not available, leading to the potential for gross over- or underestimation of an affected population. Likewise, there is relatively little reliable information on the natural history and long-term outcomes of patients with CAD unsuitable for revascularization. Available reports indicate wide variability in the annualized death rates, ranging from to 3% to 21% in randomized clinical trials and from 2% to 17% in clinical registries. This variability likely reflects the lack of a systematic and valid classification scheme for this heterogeneous group of patients. Without standardized and reliable epidemiological reports, it will remain difficult to obtain precise and comparable mortality and morbidity figures, which are required to raise awareness and mobilize resources around the problem of RFA. Still, RFA could rapidly become endemic. It is currently estimated that 500,000 Canadians are living with unresolved angina and these data are likely an underestimate due to a reliance on self-report measures.

A classification could allow matching patients with an appropriate level of investigational risks in trials testing new devices and therapies. Angina is a chronic stable condition that does not pose immediate threat to life. Consequently, angina cannot be used alone to justify testing potentially hazardous therapies in clinical trials. Investigational therapies should not be offered if the anticipated hazards exceed the natural mortality and morbidity rates expected for study participants. While this point seems straightforward, departures from this ethical principle have been observed in the recent past; worrisome complications and even procedural deaths have been observed as a result of investigational devices intended to treat RFA. With transmyocardial laser revascularization for instance, procedural deaths ranging between 3% and 5% have been observed in randomized controlled trials enrolling patients with chronic RFA, with perioperative mortality of up to 16% reported in patients with unstable angina undergoing transmyocardial laser revascularization. Paradoxically, a mortality risk above 5% is frequently cited by competent authorities as a reasonable cutoff to justify withholding high-risk percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery in selected populations.

Few contemporary RFA trials have disclosed the reason why study participants were not eligible for revascularization (see Supplemental Table S1). Some RFA trials actually justified enrolment by stating that “PCI or CABG were not indicated,” but provided no additional details. In cases where a PCI or a CABG was deemed inappropriate due to procedural risk, the facts surrounding actual risk assessment were never disclosed. A minority of trials commented on the extent of CAD seen in their enroled participants. The lack of precise information on the natural history of patients with CAD unsuitable for revascularization is a major challenge precluding uptake of new therapies. For example, only 1 antianginal drug has been approved in Canada in 20 years. RFA randomized controlled investigations are notoriously difficult to conceive. Without precise data, potentially efficacious therapy may not survive the initial phases of clinical development because of unrealistic targets or inappropriate sample size estimates. An appropriate classification scheme would therefore help reduce sample heterogeneity among temporized ‘subgroups’ often used in clinical trials for RFA.

Proposed Phenotypes of Patients Unsuitable for Revascularization

Definition of CAD unsuitable for revascularization

In order to propose specific phenotypes, we first offer the following operational definition of CAD unsuitable for coronary revascularization: A patient is deemed unsuitable for revascularization in the presence of a CAD due to 1 or several significant epicardial stenoses and/or to microvascular dysfunction where PCI or bypass surgery cannot be reasonably attempted or is not expected to improve myocardial perfusion. When appropriate, the diagnosis of coronary disease unsuitable for revascularization should be based on a consensual agreement involving a specialized medical team of at least an interventional cardiologist and a cardiac surgeon with interest in the field of RFA. The decision, which must be based on a recent
angiogram, is temporary and must therefore be reassessed periodically due to the dynamic nature of CAD and function. This definition of unsuitability for revascularization is meant to complement definitions of RFA previously proposed, including the definition formulated by the joint Canadian Cardiovascular Society/Canadian Pain Society working group in 2011, where: “RFA is a persistent, painful condition characterized by the presence of angina caused by coronary insufficiency in the presence of CAD which cannot be controlled by a combination of medical therapy, angioplasty, and coronary bypass surgery.”

General principles

Three key principles should be observed before a patient can be deemed unsuitable for revascularization.

1. The status of unsuitability for revascularization can be temporary. The “no-option” label may be difficult to remove once it has been affixed to a patient. CAD is a progressive disease and the decision not to attempt revascularization is clinically relevant at a particular moment but should be reassessed regularly, especially in the context of a change in clinical status. Hence, patients once deemed noneligible for revascularization may become candidates for PCI or CABG, either because of disease progression in a bypass graft or another coronary artery, or because comorbidity has evolved (for instance, chronic renal insufficiency now undergoing dialysis). The ratio of risks vs expected benefits is also fluid due to patient-related factors as well as external elements, including available technologies, and local expertise. Revascularization rates up to 25% have been reported among cohorts of patients enrolled in “non-revascularizable” RFA trials with longer-term follow-up. In these cohorts, frequently evoked reasons for revascularization were the appearance of a new lesion in a previously unaffected coronary artery or bypass graft, the resolution of a comorbid condition, or the availability of novel techniques or expertise. Importantly, the development of unstable symptoms or acute coronary syndrome may drive subsequent revascularization in up to 11% of patients. The decision to proceed or not with a coronary revascularization should rely on a recent angiogram (≤ 1 year).

2. The decision should be the result of multidisciplinary dialogue. The concept of multidisciplinary dialogue (ie, heart team approach) is increasingly being discussed in the medical community. For patients with complex CAD, the importance of the multidisciplinary team for the choice of an appropriate revascularization strategy has recently been brought forward as a class 1C recommendation by a joint task force of the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery. Multidisciplinary dialogue is particularly important in the context of clinical trials, especially if potentially hazardous new therapies are being investigated. The multidisciplinary approach constitutes the best opportunity to assure an adequate informed consent process.

3. What constitutes an optimal medical therapy should be explicitly detailed. While traditional therapies including β-adrenoceptor blockade, long-action nitrates, and calcium channel blockers are widely available, there is a great deal of variability in regional availability of more recent antiangina medications, even within countries of the Western hemisphere. For instance, ranolazine (available in the United States), and nicorandil and trimetazidine (available in Europe) cannot be prescribed in Canada at present outside a special access program. In RFA trials, a frequently cited description of optimal medical therapy is the use of maximal tolerable doses of 2 or more traditional antiangina agents. Clinically, optimal medical therapy is more frequently defined as the use of 3 or more antianginal drugs at maximally tolerated doses including 1 heart rate-limiting agent and a coronary vasodilator. Interestingly, less than 30% of the recent RFA trials actually detailed their optimal medical therapy criteria (Supplemental Table S1).

Classification of phenotypes unsuitable for revascularization

Patients unsuitable for revascularization can be regrouped under 4 anatomopathological phenotypes (Table 1). These phenotypes are based on readily accessible coronary angiographic features. The classification focuses on chronic stable atherosclerotic disorders and excludes unstable presentations such as acute coronary syndromes, spontaneous coronary dissection, emboli, and/or spasm. These phenotypes also exclude nonatherosclerotic causes of coronary artery narrowing such as congenital coronary artery anomalies, coronary fistula, and myocardial bridging. Finally, symptoms caused by external compression of coronary arteries, and hematologic diseases associated with coronary thrombosis without underlying atherosclerotic plaque (such as thrombocytopenic purpura and polycythemia vera), are also excluded.

Phenotype A. Suspected cardiac syndrome X. The syndrome of stress-induced chest pain with normal coronary arteries has been known since the early days of coronary arteriography and has been described by Arbigast and Bourassa and Kemp et al. introduced the concept of cardiac syndrome X to describe patients with angina and objective evidence of myocardial ischemia despite normal coronary angiograms. In the late 90s, dysfunction of the coronary microvascular beds was identified as a principle mechanism of ischemia in patients with cardiac syndrome X. Microvascular dysfunction is thought to result from an autonomic imbalance (enhanced adrenergic drive vs impaired parasympathetic tone) and from coronary endothelial dysfunction.

Of the phenotypes proposed in this classification, syndrome X and microvascular angina (MVA) are possibly the best characterized in terms of prognostic and long-term information. Contrary to what was initially conveyed, MVA does not necessarily have a benign prognosis. Just like obstructive CAD, dysfunction of the microcirculation results in ischemia and is therefore associated with adverse long-term outcome. In the Women’s Ischemia Syndrome Evaluation (WISE) study, endothelial-independent microvascular dysfunction was associated with a small yet significantly increased hazard of experiencing a major adverse event (hazard ratio 1.20; 95% confidence interval [CI], 1.05-1.38; \( P = 0.008 \)). Similar conclusions were reached with endothelium-dependent dysfunction. While the association between syndrome X and adverse long-term outcome is significant, the absolute number of hard events such as myocardial infarction and coronary deaths remain low in this population. Instead, recurrent...
Frequent association between MVA and sensitive heart syndrome. While possibly confounded by a referral bias, the mortality rate observed in this subgroup was 29.4% over a follow-up of 3.2 years (annualized mortality rate: 9.2%).

Angina symptoms cause major impairment of functional capacity and quality of life. The persistence of chest pain in patients with normal coronary arteries has been associated with a higher prevalence of mood disorders, including depression and panic disorder.

MVA is most frequently evoked in patients with normal coronary angiogram but is frequently present in patients with advanced CAD, including patients with prior CABG surgery. In a case series of patients with angina referred for bypass graft angiography at the Mayo Clinic Catheterization Laboratory, 170 were not eligible for further revascularization, 78 of which had adequately functioning grafts to all major epicardial territories. The lack of correlation between the extent of CAD and the severity of anginal symptoms has been recognized for almost a century. As such, patients with relatively minor ischemic burden can be severely symptomatic. The patients included in the phenotype B category could be described as having CAD significant enough to cause symptoms, complex enough not to be amenable to PCI, and not severe enough to warrant a first or a redo CABG surgery. Phenotype B should not be characterized by coronary angiography alone; the phenotype is patient-specific as a given lesion which is assumed responsible for symptoms in 1 patient may not be enough to trigger symptoms in other patients. Cases of limited territory at risk are possible among patients with and without prior CABG surgery. These 2 groups should be carefully differentiated.

In patients with prior CABG surgery, classic examples of phenotype B are those patients with chronic total occlusions in a single vessel such as the left circumflex or the right coronary artery (Fig. 2, B). Other examples are side branch stenoses or distal coronary stenoses. In such cases, PCI is often unsuccessful despite the use of advanced techniques and repeated attempts. Alternatively, PCI may not be appropriate because of size or morphology of a distal artery or branch. While technically possible, CABG surgery is rarely considered a reasonable option, either because the expected survival benefit is insufficient (eg, in the case of a small area of jeopardized myocardium) and/or because complete revascularization is technically not achievable. In the presence of a patient with a limited territory at risk, the heart team should acknowledge that in the absence of ischemia in the territory of the proximal left anterior descending (LAD) coronary artery, the survival benefit of CABG surgery is unlikely to exceed the mortality risk.

In patients with prior CABG surgery, examples of phenotype B are single saphenous vein graft occlusions to the left circumflex or the right coronary artery. Other possibilities are

### Table 1. Phenotypes of patients unsuitable for revascularization

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Specifications</th>
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<tbody>
<tr>
<td>A. Suspected CSX</td>
<td>1. Normal coronary angiogram with suspected CSX.</td>
</tr>
<tr>
<td></td>
<td>• Objective evidence of myocardial ischemia in absence of significant epicardial stenosis.</td>
</tr>
<tr>
<td></td>
<td>• Can result from microvascular dysfunction or exceptionally from inborn errors of metabolism in association with infiltrative cardiomyopathy.</td>
</tr>
<tr>
<td></td>
<td>• Natural history; prognosis not necessarily benign but absolute number of hard events such as mortality remain low.</td>
</tr>
<tr>
<td></td>
<td>2. Suspected CSX with prior CABG surgery.</td>
</tr>
<tr>
<td></td>
<td>• Objective evidence of myocardial ischemia despite adequately functioning grafts to all major epicardial territories.</td>
</tr>
<tr>
<td></td>
<td>• Likely results from microvascular dysfunction.</td>
</tr>
<tr>
<td></td>
<td>• Natural history: annualized mortality rates reported at 9.2% (over 3.2 years).</td>
</tr>
<tr>
<td>B. Limited territory at risk</td>
<td>1. Limited territory at risk with no prior CABG surgery.</td>
</tr>
<tr>
<td></td>
<td>• Significant epicardial coronary stenosis not amenable to PCI, sufficiently severe to cause angina, but not associated with high-risk features at noninvasive stratification.</td>
</tr>
<tr>
<td></td>
<td>• Can result from non-LAD single vessel CTO or side branch stenosis or distal stenosis.</td>
</tr>
<tr>
<td></td>
<td>• Natural history: annualized mortality rates ranged from 1.8% to 2.4% for 1 and 2 vessel disease treated medically (over 5 years).</td>
</tr>
<tr>
<td></td>
<td>2. Limited territory at risk with prior CABG surgery.</td>
</tr>
<tr>
<td></td>
<td>• Significant epicardial coronary stenosis not amenable to PCI, but not sufficiently severe to justify redo CABG.</td>
</tr>
<tr>
<td></td>
<td>• Can result from single saphenous vein graft occlusion or incomplete revascularization at the time of the index CABG surgery.</td>
</tr>
<tr>
<td></td>
<td>• Natural history: annualized mortality rates reported at 2.4% (over 5 years).</td>
</tr>
<tr>
<td>C. Diffuse thread-like coronary atherosclerosis</td>
<td>1. Diffuse atherosclerotic atherosclerosis from proximal to distal beds leading to a thread-like appearance with small (&lt; 1 mm) distal run-off.</td>
</tr>
<tr>
<td></td>
<td>• Usually involves simultaneously the 3 coronary arteries. Focal plaques possible but typically part of a diffuse process. Frequently associated with diabetes mellitus, and South Indian origin.</td>
</tr>
<tr>
<td></td>
<td>• Distinction between prior vs no prior CABG surgery not applicable (usually not considered an option).</td>
</tr>
<tr>
<td></td>
<td>• Natural history: unknown.</td>
</tr>
<tr>
<td>D. End-stage CAD</td>
<td>1. A state of coronaropenia that combines stenosis in proximal coronary segments and a diffuse atherosclerosis of the distal coronary beds. A furnished network of coronary collaterals is typically visible in viable territories.</td>
</tr>
<tr>
<td></td>
<td>• Most frequently seen on patients with prior, degenerated CABG.</td>
</tr>
<tr>
<td></td>
<td>• Natural history: annualized mortality above 5% (ranging from 5.1% to 33%).</td>
</tr>
</tbody>
</table>

CABG, coronary artery bypass graft; CAD, coronary artery disease; CSX, coronary syndrome X; CTO, chronic total occlusion; CABG, coronary artery bypass surgery; PCI, percutaneous coronary intervention; redo CABG, coronary reoperation.
incomplete surgical revascularization at the time of the index surgery because of an anatomically inaccessible coronary artery. When a PCI is technically impossible, a coronary reoperation (redo CABG) remains a theoretical option. However, the benefits of repeating the surgery on patients with patent grafts are not well characterized. The risks associated with reoperation are 2 to 4 times higher than initial surgery. Consequently, an extensive amount of jeopardized myocardium is expected before reoperation is considered. This is particularly the case when a patent internal mammary artery (IMA) has been grafted to the LAD. When a PCI is technically impossible, a coronary reoperation (redo CABG) remains a theoretical option. However, the benefits of repeating the surgery on patients with patent grafts are not well characterized. The risks associated with reoperation are 2 to 4 times higher than initial surgery. Consequently, an extensive amount of jeopardized myocardium is expected before reoperation is considered. This is particularly the case when a patent internal mammary artery (IMA) has been grafted to the LAD. When a PCI is technically impossible, a coronary reoperation (redo CABG) remains a theoretical option. However, the benefits of repeating the surgery on patients with patent grafts are not well characterized. The risks associated with reoperation are 2 to 4 times higher than initial surgery. Consequently, an extensive amount of jeopardized myocardium is expected before reoperation is considered. This is particularly the case when a patent internal mammary artery (IMA) has been grafted to the LAD.

What constitutes a sufficiently large amount of myocardium in jeopardy to consider a first or redo CABG surgery varies according to patient-related factors, such as diabetes mellitus or depressed left ventricular systolic function. Patients within phenotype B without prior CABG surgery frequently may not have major comorbidities and therefore show relatively low surgical risk. Table 2 lists the high-risk features seen at noninvasive stratification that are associated with an annual mortality > 3%. These features (or lack thereof) can be used as landmarks to justify revascularization. By definition, no phenotype B patient should have high-risk features on noninvasive stratification. In the specific case of patients with single vessel disease, the European guidelines advocate against revascularization to improve prognosis except for patients with a proximal LAD stenosis generating an ischemic region > 10% of the left ventricle. Coronary revascularization with either PCI or CABG surgery has demonstrated survival benefit only for proximal LAD stenoses. The Appropriateness Criteria for Coronary Revascularization does not comment on the appropriateness of CABG surgery for non-LAD single or double vessel disease. However, the American College of Cardiology/American Heart Association PCI guidelines advocate that PCI, when feasible, is the preferred revascularization choice in such cases.

Population-based studies suggest that patients with coronary stenoses > 95% in 1 or 2 vessels have 5-year survival rates of 91% and 88%, respectively, when the proximal LAD is not involved. Information is lacking on the morality rates associated with phenotype B patients with prior CABG. A cohort study from Cleveland Clinic has suggested that in the presence of a patent IMA to the LAD with myocardial jeopardy in the distribution of the circumflex or right coronary arteries, med-

Figure 2. Angiographic representations of phenotypes unsuitable for revascularization. (Phenotype A) Left coronary circulation (left panel) and right coronary artery (right panel) showing no significant epicardial stenosis. The arrowhead points to a stent previously implanted in the proximal left anterior descending artery. The patient has had persistent chest pain after the stent implantation with objective evidence of myocardial ischemia in the left anterior descending territory. (Phenotype B) Left coronary circulation (left panel) and right coronary artery (right panel) showing a chronic total occlusion of the left circumflex artery. The arrowheads point to site of the chronic total occlusion. Prior percutaneous recanalization attempts failed twice and the lesion was deemed not amenable to a retrograde recanalization. The patient had normal left ventricular ejection fraction and no other significant comorbidities. Ischemia was detected in 8% of the left ventricle on cardiac imaging. (Phenotype C) Left coronary circulation seen on caudal incidence (left panel) and lateral incidence (right panel) showing a diffuse atherosclerotic infiltration spreading from the proximal to the distal coronary beds. All the vessels including the side branches appear equally diseased. No focally calcified plaque is prominent. The noninvasive imaging suggested 3-vessel disease. (Phenotype D) Left coronary circulation (left panel) and right coronary circulation (right panel) showing severe epicardial stenoses proximally with a more diffuse infiltration distally. A sequential vein graft perfuses the circumflex artery.
Phenotypes Unsuitable for Revascularization

Figure 3. Right internal mammary artery bypass. Angiographic reconstruction of a right internal mammary artery bypassed to a diagonal branch. Not only the bypass crosses the thoracic midline, it was shown to be fixed and adherent to the thoracic wall. This patient had had 3 other bypasses that were all occluded.

diabetic therapy alone was associated with survival at 1, 5, 10, 15, and 20 years of 97%, 88%, 72%, 56%, and 42%, respectively.29 Compared with medical therapy alone, revascularization by PCI or redo CABG was associated with worse early mortality with no catch-up on longer-term follow-up.

Phenotype C. Diffuse thread-like coronary atherosclerosis. Phenotype C refers to a diffuse atherosclerotic infiltration spreading from the proximal to the distal coronary segments (Fig. 2, C). Angiographically, these coronary arteries have a thread-like appearance. The coronary arteries are steadily infiltrated from the ostium to the distal beds, but the lesions are rarely occlusive. The calibre of the arteries is diffusely reduced in the distal segments of severe epicardial atherosclerotic plaque. Proximal segments of normal or near normal calibre arteries are interrupted by severe advanced CAD. In the proximal to mid coronary segments, a more diffuse infiltration is possible (Fig. 2, D). An extensive network of coronary collaterals is frequently visible on angiogram.

The distinction between phenotype C and D hold mainly on how diffuse the infiltration process is. In phenotype D, segments of coronary artery with a normal calibre are still present. Normal or near normal calibre arteries are interrupted by segments of severe epicardial atherosclerotic plaque. Proximal

Table 2. High-risk features of noninvasive ischemic stratification

| 1. Severe resting left ventricular dysfunction (LVEF < 35%) |
| 2. High-risk Duke treadmill score (score: 11) |
| 3. Severe exercise left ventricular dysfunction (exercise LVEF < 35%) |
| 4. Stress-induced large perfusion defect (particularly if anterior) |
| 5. Stress-induced multiple perfusion defects of moderate size |
| 6. Large, fixed perfusion defect with LV dilation or increased lung uptake (thallium-201) |
| 7. Stress-induced moderate perfusion defect with LV dilation or increased lung uptake (thallium-201) |
| 8. Echocardiographic wall motion abnormality (involving greater than 2 segments) developing at low dose of dobutamine (≤ 10 mg/kg/min) or at a low heart rate (< 120 beats/min) |
| 9. Stress echocardiographic evidence of extensive ischemia |

LV, left ventricle; LVEF, left ventricular ejection fraction.

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to mid vessel chronic total occlusions are frequent. Because the disease in segmental, the artery recovers a normal calibre distal to the lesion. This is rarely the case with phenotype C.

Frequently, patients with type D phenotype have had prior CABG which has allowed them to survive despite a slow but inexorable progression of atherosclerosis. The accelerated progression of atherosclerosis in the grafted coronary vessels is a well-known contributory phenomenon. Likewise, disease progression in nongrafted native vessels can occur at a rate up to 40% over a decade. Not uncommonly, patients are sustained by a single conduit which perfuses the entire heart via an extensive collateral network. Phenotype D may represent an exception to the notion that status of unsuitability for revascularization after CABG is temporary.

Data are scarce on the prevalence and natural history of patients with phenotype D, mainly because, historically, series presenting “no-option” patients have regrouped heterogeneous populations. Ten years ago, Mukherjee et al. estimated that 100,000 to 200,000 Americans deemed unsuitable for revascularization may be eligible each year for new investigative devices to treat angina. In a population-based study from Olmsted County (Minnesota), an estimated 17.9 patients per 100,000 population presented with significant coronary lesion not amenable to revascularization after CABG. This incidence translated into approximately 50,000 (95% CI, 40,000-61,000) patients in the United States. A strong proportion of these patients were male (65%), had diabetes (37%), and chronic renal failure (40%). In a subgroup of patients classified as being technically impossible to revascularize by conventional percutaneous or surgical means, the estimated all-cause mortality and cardiac mortality were 34.7% and 21.7% respectively, over a median follow-up of 3.2 years. The angiographic reasons why patients were not considered suitable for PCI or CABG included chronic total occlusion (93%), poor distal targets (73%), degenerated saphenous vein graft (68%), disease beyond graft insertion (53.9%), and multiple restenosis (7%).

In a contemporary series from Minneapolis (Minnesota), 7% of the consecutive patients with angina undergoing angiography had significant CAD with evidence of myocardial ischemia but were no-option candidates for revascularization. The angiographic reasons why patients were not considered suitable for further revascularization included chronic total occlusion (70%), diffuse disease (46%), collateral dependent perfusion (42%), multiple restenoses (6%), and poor distal targets (3.0%). Interestingly, the presence of significant comorbidities was evoked as a principal reason not to proceed with revascularization for only 12% of patients. The overall all-cause mortality was 15.2% at 3 years, translating into an annualized rate of 5.1%. This mortality rate has been considered consistent with the 3.5% annualized mortality rate observed among patients from a dedicated RFA clinic in the same area. This observed mortality rate is substantially lower than the 15%-17% annualized mortality historically reported in the United States, and 33% mortality at 1 year reported in Europe for patients with advanced CAD not amenable to revascularization.

Limitations of the Classification

The present phenotypic classification scheme relies exclusively on anatomical features identified on coronary angiogram. It does not take into account other clinical factors that can affect the decision to proceed with revascularization. Non-anatomical factors such as comorbidities, available local expertise, or procedural risk have been intentionally left out of the classification because they are difficult to capture, subject to personal interpretation, and affected ethnic origin. Clinically, these factors are an important in the decision-making process and can be combined with the phenotypic classification proposed in this report. Depending on whether CABG or PCI is considered, several nonanatomical reasons not to proceed with revascularization have been reported (see Table 3). In addition, many predictive models and scoring systems are available to assess risk associated with revascularization procedures. These tools can be used to complement phenotypic classification in order to achieve comprehensive assessment of revascularization options.

While our proposed classification scheme attempts to assign unsuitable patients to distinct categories, it is possible that some patients may present with overlapping phenotypic features in different coronary beds. In case of overlapping phenotypes, the most severe coronary phenotype seen within viable territories should be used to classify each patient (ie, A < B < C < D). More globally, RFA could also translate in exertional dyspnea, fatigue, and other symptoms. While the classification represented RFA with a strong pain perspective, other anginal equivalents should be considered when appropriate. Finally, this classification must be validated before it gains clinical acceptance and before its utility can be realized.

Conclusions

The heterogeneity of epidemiological data in RFA reflects the need for the phenotypic classification system proposed in this report. This classification system is simple but requires validation and endorsement by a scientific society before being used by clinicians and investigators. We believe that it can serve as a starting point toward a more precise understanding of the natural history of patients with RFA. Our classification may also pave the way to more comprehensive and appropriate risk-benefit analyses for participants of future trials testing new RFA therapies and devices. Ultimately, it is our hope that a better

### Table 3. Nonanatomic reasons used to justify nonsuitability to revascularization

<table>
<thead>
<tr>
<th>Percutaneous coronary intervention</th>
<th>Coronary artery bypass grafting</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Excessive comorbidities, including chronic renal insufficiency, and bleeding diathesis</td>
<td>1. Excessive comorbidities, including chronic renal insufficiency and severe chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>2. Multiple coronary restenoses</td>
<td>2. Old age—often in combination with comorbidities</td>
</tr>
<tr>
<td>3. Poor compliance to medication, including anti-platelet therapy</td>
<td>3. Multiple previous coronary artery bypass grafting or valve surgery</td>
</tr>
<tr>
<td>4. Absent vascular access</td>
<td>4. Severely calcified aorta</td>
</tr>
<tr>
<td>5. Medical conditions with adverse long-term prognosis (cancer)</td>
<td>5. Lack of surgical conduits</td>
</tr>
</tbody>
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understanding of patients with RFA, via phenotyping, will translate into superior trial designs and accelerated development of much needed therapeutic innovations for this heavily burdened patient group.

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Disclosures

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**Supplementary Material**

To access the supplementary material accompanying this article, visit the online version of the Canadian Journal of Cardiology at www.onlinecjc.ca, and at doi: 10.1016/j.cjca.2011.10.015.