Atherosclerotic coronary artery disease (CAD) may manifest in numerous ways, from being asymptomatic, to stable ischemic heart disease (SIHD; with or without ischemia or symptoms), to acute coronary syndrome (ACS; unstable angina, non–ST-segment–elevation myocardial infarction [MI], or ST-segment–elevation MI), or sudden cardiac death. Anatomically, the extent of CAD may remain stable over time (or rarely regress) or progress slowly or rapidly, with or without symptoms. Risk stratification in patients with SIHD is essential to guide treatment decisions. In this regard, whether coronary anatomy, physiology, or plaque morphology is the best determinant of prognosis (and driver an effective therapeutic risk reduction) remains one of the greatest ongoing debates in cardiology. In the present report, we review the evidence for each of these characteristics and explore potential algorithms that may enable a practical diagnostic and therapeutic strategy for the management of patients with stable ischemic heart disease.

Abstract: Risk stratification in patients with stable ischemic heart disease is essential to guide treatment decisions. In this regard, whether coronary anatomy, physiology, or plaque morphology is the best determinant of prognosis (and driver an effective therapeutic risk reduction) remains one of the greatest ongoing debates in cardiology. In the present report, we review the evidence for each of these characteristics and explore potential algorithms that may enable a practical diagnostic and therapeutic strategy for the management of patients with stable ischemic heart disease.

Key Words: coronary artery disease ■ fractional flow reserve ■ multidetector computed tomography ■ myocardial ischemia ■ plaque, atherosclerotic
On this basis 2 ongoing prospective studies, PROSPECT II/PROSPECT ABSORB (Providing Regional Observations to Study Predictors of Events in the Coronary Tree; ClinicalTrials.gov Identifier: NCT02171065) and SECRITT-2 (vShield Evaluated at Cardiac Hospital in Rotterdam for Investigation and Treatment of TCFA) are exploring therapeutic mechanical interventions in high-risk plaques detected by invasive imaging.

With this background, the present report analyzes 2 conceptual approaches for prognostic and therapeutic decision making in patients with SIHD. The first approach (universally applied in contemporary practice) treats coronary anatomy, physiology, and plaque morphology as competing and mutually exclusive concepts and aims to identify which of the 3 parameters is most likely to determine future events and thus constitute the basis of treatment. The second approach proposes that coronary anatomy, physiology, and plaque morphology are inter-related and should be integrated to improve the accuracy of risk assessment and identification of patients most likely to benefit from coronary revascularization.

Anatomy

Coronary Anatomy and Prognosis

Coronary atherosclerotic burden measured using invasive and noninvasive anatomic imaging modalities has been consistently demonstrated to be a powerful independent prognostic determinant of risk for MACE. Specific anatomic measures such as diameter stenosis severity and location, aggregate coronary plaque volume, and the overall extent of disease substantially contribute to individual cardiovascular risk, beyond that related to standard risk factors, physiological measures of ischemia, and currently available biomarkers. The worsening natural history of patients with involvement of an increasing number of coronary artery territories with severe stenosis (>70%) on invasive coronary angiography formed the basis for landmark trials documenting the significant mortality reduction provided by coronary artery bypass graft (CABG) performed for severe coronary stenosis. Recent studies utilizing coronary computed tomographic angiography (CTA) confirmed the prognostic value of lumen stenosis in more contemporary, lower-risk populations referred for noninvasive imaging. For example, within the CONFIRM registry (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter registry) of >23,000 patients who underwent coronary CTA, the number of vessels with stenosis of ≥50% was the most robust predictor of outcomes, beyond that provided by traditional risk factors and left ventricular ejection fraction (Figure 1A). Because atherosclerosis is the substrate of most myocardial infarctions, sudden deaths, and strokes, even commonly identified nonobstructive lesions (<50% diameter stenosis) portend additional risk when compared with the excellent prognosis known to be associated with the absence of coronary atherosclerosis on coronary CTA (Figure 1B). Finally, among 621 patients in the COURAGE trial, atherosclerotic burden as determined by an independent core laboratory was a strong determinant of the 7-year occurrence of death, MI or non–ST-segment-elevation ACSs, whereas the quantitative measure of baseline ischemia by SPECT was not.

Cardiac death and MI. Nonetheless, the conflicting results of observational registries and randomized trials seeking to improve patient prognosis through revascularization based on these indices motivate re-examination of the prognostic determinants in SIHD. For example, although it is well established that the presence of obstructive CAD (anatomy) heralds worsening prognosis,2,3 in the COURAGE (Clinical Outcomes Using Revascularization and Aggressive Drug Evaluation)4 and BARI 2D (Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes)5 trials, routine revascularization guided by anatomic stenosis alone did not result in reduction of major adverse cardiovascular events (MACE) compared with optimal medical therapy (OMT; with revascularization reserved for refractory symptoms). In contrast to anatomy-driven therapy, more studies support ischemia-based treatment decision making. Various observational registries have illustrated that revascularization contributes to a reduced relative hazard for mortality when compared with OMT in the presence of myocardial perfusion imaging–verified moderate-severe of myocardial ischemia.6–8 The randomized FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) and FAME 2 trials9–12 have demonstrated fractional flow reserve (FFR)–guided therapy to be superior to both angiography-guided therapy and OMT, respectively. The actively enrolling National Heart, Lung, and Blood Institute (NHLBI)–sponsored ISCHEMIA (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches) trial is testing whether prognosis is improved by a routine strategy of angiography and revascularization in patients with SIHD and mild symptoms but with moderate or severe ischemia. In addition, it has become increasingly clear that it is not the lesion stenosis alone but the composition of the plaque that is the basis of adverse events in atherosclerotic disease. High-risk plaques are positively (or outwardly) remodeled and contain a large lipid-rich necrotic core covered by an attenuated (thinned) and inflamed fibrous cap.13 Numerous imaging14–22 and postmortem studies23–27 have established that most MI and acute events are caused by plaques with vulnerable features, especially when they expand in size and become luminally occlusive.1,26

Nonstandard Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>ACS</td>
<td>acute coronary syndrome</td>
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<tr>
<td>BVS</td>
<td>bioresorbable vascular scaffold</td>
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<tr>
<td>CABG</td>
<td>coronary artery bypass graft</td>
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<td>CAD</td>
<td>coronary artery disease</td>
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<td>CTA</td>
<td>computed tomography angiography</td>
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<td>FFR</td>
<td>fractional flow reserve</td>
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<td>IVUS</td>
<td>intravascular ultrasound</td>
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<td>MACE</td>
<td>major adverse cardiovascular events</td>
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<td>MI</td>
<td>myocardial infarction</td>
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<td>MLA</td>
<td>minimal lumen area</td>
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<td>NIRS</td>
<td>near-infrared spectroscopy</td>
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<td>OMT</td>
<td>optimal medical therapy</td>
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<td>PCI</td>
<td>percutaneous coronary intervention</td>
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<td>SIHD</td>
<td>stable ischemic heart disease</td>
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<td>TCFA</td>
<td>thin-cap fibroatheroma</td>
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ACS, acute coronary syndrome; BVS, bioresorbable vascular scaffold; CABG, coronary artery bypass graft; CAD, coronary artery disease; CTA, computed tomography angiography; FFR, fractional flow reserve; IVUS, intravascular ultrasound; MACE, major adverse cardiovascular events; MI, myocardial infarction; MLA, minimal lumen area; NIRS, near-infrared spectroscopy; OMT, optimal medical therapy; PCI, percutaneous coronary intervention; SIHD, stable ischemic heart disease; TCFA, thin-cap fibroatheroma.
Should Anatomy Direct Revascularization Decisions?

Given the robust prognostic power of the coronary anatomy for future events, a common sense and commonly used approach would be to treat patients with stable obstructive CAD with either elective percutaneous coronary intervention (PCI) or CABG, as appropriate. In the large-scale CONFIRM registry, among 15,233 SIHD patients undergoing coronary CT angiography with established CAD, a survival benefit at a median follow-up time of 2.1 years was observed if early revascularization was performed in those with high-risk anatomy (defined as 2-vessel CAD with proximal left anterior descending artery involvement, 3-vessel CAD, or left main CAD), but not in patients with lesser degrees of coronary atherosclerosis. However, the COURAGE trial revealed that an initial approach of OMT was equally effective as PCI plus OMT in preventing death or MI, and that revascularization could be safely deferred in approximately two thirds of patients with SIHD (although symptoms were more rapidly reduced with PCI). With 4.6 years of median follow-up, the rate of the primary end point of all-cause death or MI was 19% in both the PCI plus OMT arm and the OMT alone arm (P=0.62). Similar rates of survival between the initial strategy of PCI plus OMT and OMT alone from COURAGE have now been reported out to 15 years. However, the NHLBI-sponsored BARI 2D trial in patients with stable CAD and type 2 diabetes mellitus, routine early revascularization did not improve 5-year survival compared with medical treatment (88% in both groups, P=0.97). With the caveat that neither of these studies utilized contemporary interventional devices or adjunct pharmacotherapy, no current randomized trial data support the concept that coronary anatomy alone should dictate therapeutic strategy in SIHD. An exception may be patients with ischemic cardiomyopathy in whom improved survival with CABG compared with OMT alone was recently reported from the 10-year extension of the NHLBI-sponsored Surgical Treatment for Ischemic Heart Failure (STICH) trial. Benefit of the doubt may also be given to patients with obstructive disease of the left main coronary artery, in whom 2 small randomized trials in the 1970s demonstrated a marked survival benefit for CABG compared with medical therapy (although the latter was clearly suboptimal by today’s standards, predating even the statin era).

Overall, coronary anatomy provides prognostic utility beyond traditional risk factors and risk estimate scores. However, anatomy alone, in most cases, might not help clinicians guide revascularization decisions if improving survival and freedom from MI is the major goal.

Physiology

Coronary Ischemia and Prognosis

In both the US and European guidelines, the indications for coronary revascularization in the patient with SIHD depend on the symptoms, the extent and severity of ischemia, and the anatomic complexity of disease. Candidates for revascularization include those who are (1) prognostically high risk with certain anatomic patterns (e.g., significant left main stenosis) or (2) symptomatic despite failed OMT. It is important to note that in both COURAGE and BARI 2D, minimal eligibility criteria were used based on stress testing findings. Neither COURAGE nor BARI 2D provide reliable guidance as to whether the presence or degree of ischemia should be considered when determining the potential benefits of prompt revascularization.

Numerous stress imaging studies have demonstrated a gradient between the extent and the severity of ischemia and subsequent cardiac event risk. Thus, enrollment of patients with lower levels of ischemia in the published stable CAD trials may, in part, explain why revascularization did not improve prognosis. Moreover, patients were enrolled in COURAGE and BARI 2D with the investigators having knowledge of baseline exercise test results and coronary angiography, possibly biasing enrollment toward lower-risk
patients. Indeed, in the COURAGE nuclear substudy, the average amount of ischemia was only 8.2% of the left ventricle (with 10% usually accepted as representing moderate ischemia).\textsuperscript{41} Observational evidence suggests that there may be a variable therapeutic benefit from revascularization based on the extent and severity of ischemia.\textsuperscript{6,42} In several reports from the Cedars-Sinai registry ($n=10627$), patients with $\approx 10\%$ or more (ie, moderate-severe) ischemic myocardium had a nearly doubling of mortality when treated medically as compared with a demonstrable reduction in death among patients undergoing coronary revascularization ($P<0.001$).\textsuperscript{6,7,42} This result was also validated among 4629 patients with ischemia in the J-ACCESS registry ($P=0.006$).\textsuperscript{8} However, studies can be found supporting the contention that ischemia has a poor relationship to either prognosis or differential outcomes after revascularization, especially in the era or contemporary OMT, representing a state of equipoise.\textsuperscript{53}

**Should Noninvasive Evidence of Ischemia Direct Revascularization Decisions?**

A meta-analysis of 3 modest-sized randomized trials in 1557 total patients with SIHD and stabilized ACS and ischemia at baseline noted a 48% reduction in mortality with revascularization.\textsuperscript{44} To date, however, definitive data are unavailable that revascularization improves the prognosis of patients with SIHD and noninvasively detected ischemia. To overcome many of the limitations of previous study, the ISCHEMIA trial was designed and funded by NHLBI to determine whether revascularization in patients with SIHD, mild symptoms and moderate or greater ischemia reduces the composite rate of cardiovascular death or MI.\textsuperscript{45} Up to 8000 patients will be enrolled in ISCHEMIA after stress testing (and confirmation of obstructive non–left main CAD by blinded coronary CTA), but before angiography to reduce enrollment bias, and randomized to OMT with angiography reserved for refractory symptoms versus OMT plus early angiography with revascularization (PCI or CABG) as appropriate. Currently, the trial is in its fourth year of enrollment with $>3000$ patients recruited.

**Should Abnormal FFR Direct Revascularization Decisions?**

Gould et al\textsuperscript{46} demonstrated that progressive narrowing of a canine coronary artery produced a predictable decline in coronary flow reserve. However, in clinical studies, the relationship between anatomy and physiology has been far from perfect.\textsuperscript{37,48} Given the fundamental limitations of coronary imaging, no set of anatomic parameters, including those obtained by direct intracoronary visualization (eg, intravascular ultrasound [IVUS] and optical coherence tomography [OCT]), can accurately determine blood flow across an individual stenosis at rest and during stress.\textsuperscript{59}

To overcome the fundamental limitations of anatomic imaging, intracoronary pressure and flow measurements using sensor guide wires were developed. The physiological importance of a stenosis may be characterized by its effect on poststenotic pressure (and flow) transmission. In a diseased artery, energy is required to overcome the resistance to coronary blood flow. Energy loss is translated into poststenotic pressure loss. The poststenotic pressure is a function of the stenosis flow and resistance specific to the unique morphological features that include minimal lumen area (MLA), lesion length, the stenosis entrance and exit orifice configurations, and the shape and size of the normal reference vessel segment.\textsuperscript{50} Moreover, the trans-stenotic pressure drop is inversely proportional to the fourth power of the lumen radius and contributes significantly to the specific curvilinear pressure–flow relationship that defines the physiological importance of any lesion.\textsuperscript{51} As a consequence, a relatively small change in luminal diameter, caused by active or passive vasomotion or transient obstruction by thrombus, can produce marked hemodynamic effects with a significant impact on coronary perfusion. Because of the complex relationship between anatomy and physiology, it is not surprising that 2-dimensional vascular imaging cannot predict the hemodynamic effect of a given stenosis, especially in the moderately severe ranges (40%–80% diameter narrowing).

Early studies suggested that intracoronary Doppler flow velocity measurements could determine coronary lesion significance.\textsuperscript{52} However, these approaches were never adopted into clinical practice because of (1) difficulty of obtaining a valid flow velocity signal and (2) the unknown status of the microcirculation in interpreting an abnormal coronary flow reserve. However, using the fundamental assumption that coronary pressure distal to a stenosis is linearly related to blood flow when measured at minimal and constant vascular resistance (ie, maximal hyperemia), Pijs et al\textsuperscript{35} established a pressure-derived estimate of the percentage of normal coronary blood flow expected in a stenotic artery, termed the FFR. FFR, the ratio of poststenotic pressure:aortic pressure obtained at maximal pharmacologically induced hyperemia, reflects both antegrade and collateral myocardial perfusion. It closely correlates to indices of ischemia more than a resting trans-stenotic pressure gradient. Because its derivation was based on pressure at maximal flow and excluded the microcirculatory resistance, FFR (unlike coronary flow reserve) was largely independent of changes in basal flow, systemic hemodynamics, or contractility\textsuperscript{53} although an intact microcirculation is required for the hemodynamic effects of full hyperemia to be established. FFR thresholds for hemodynamic significance were established by comparisons to ischemic stress testing modalities and subsequently validated in numerous clinical outcome studies. Compared with traditional angiographic PCI guidance, FFR-guided decisions have demonstrated clinical and economic superiority in numerous single- and multicenter interventional trials.\textsuperscript{5,11,12,55–57} In the FAME trial, an FFR-guided PCI strategy was superior to an angiography-guided PCI therapy in reducing both stent use and the rates of future urgent revascularization because of unstable angina and MI.\textsuperscript{54} In the FAME 2 trial, FFR-guided revascularization resulted in lower rates of progressive ischemic symptoms and the need for urgent or elective revascularization within 2 years, compared with OMT alone.\textsuperscript{55} FFR use also resulted in fewer postdischarge MIs. However, these trials were not blinded, and the rates of death or MI were not significantly reduced with revascularization. Nonetheless, the totality of the evidence supports the strong guideline-based recommendations for the use of FFR to guide PCI revascularization decisions.\textsuperscript{59,60}
Of note, although tomographic imaging techniques provide an extra dimension beyond angiography in assessing plaque geometry and extent, such techniques are still not accurate correlates of ischemia. For example, MLA assessed by intravascular imaging (IVUS and OCT) correlates better with FFR than with simple diameter stenosis measured by angiography. However, among 25 studies that compared IVUS or OCT imaging to FFR, the best cut-off value for MLA ranged from 1.8 to 4.0 mm² (excluding the left main for which the best cut-off values were 4.8–5.9 mm²), with areas under the curve ranging from 0.63 to 0.90. However, although MLA of >4 mm² in non–left main lesions predicted an FFR of >0.80 in 91% of cases, MLA of <4 mm² correlated poorly to FFR, with most studies reporting FFR of <0.8 in ≈50% of cases. IVUS thresholds are also dependent on lesion location, whereas the FFR threshold is not. The major reason why location strongly influences the IVUS/FFR relationship is that both the size of the reference vessel and the flow volume of the myocardial bed subtended by the stenotic vessel are important variables needed to compute the trans-stenotic pressure loss. Thus, IVUS is not a replacement for FFR as a valid measure of ischemia.

Despite the fact that FFR has become the de facto standard for physiological lesion assessment in the catheterization laboratory, its adoption by the clinical community has not been widespread for reasons that are multifactorial. One issue is the requirement of pharmacological hyperemia that engenders additional time, cost, and patient discomfort. Based on the sophisticated coronary pulse wave analysis of Davies et al and Sen et al, a basal pressure index termed the instantaneous wave-free ratio may be computed. Coronary blood flow into the myocardium is largely determined by the prominent coronary suction wave of LV relaxation at the beginning of diastole followed by a brief wave-free period of diastole wherein coronary resistance is low and constant, wherein flow and pressure are linearly related as was assumed for the FFR derivation. Clinical studies comparing instantaneous wave-free ratio to FFR demonstrate concordance in ≈80% of cases. Instantaneous wave-free ratio has the potential to reduce the use of pharmacological hyperemia for lesion assessment, and may be prone to fewer artifacts than FFR. Several large-scale outcome trials of instantaneous wave-free ratio versus FFR for PCI guidance are in progress. Finally, there are numerous causes of ischemia beyond a fixed stenosis, including diffuse small vessel and microvascular disease, primary endothelial dysfunction, and coronary spasm. In this regard, either invasive or noninvasive assessment of coronary flow may be complementary to translational pressure measurement.

Plaque Morphology

High-Risk Plaque and In Vivo Detection

Early pathological studies in 1976 and in vivo studies in 1980 demonstrated that most fatal ischemic events were caused by ruptured atherosclerotic plaques. Plaque rupture complicated by thrombosis was identified in 75% of ST-segment–elevation MI autopsies and in 60% of sudden cardiac deaths. In a large review of 18 autopsy studies, fatal coronary thrombi were associated with plaque rupture in 1114 of 1460 (76%) cases of acute MI and sudden deaths. A thin fibrous cap with active inflammation and a large lipid core were associated with disrupted plaques, and these pathological substrates with an intact fibrous cap (thin-cap fibroatheroma [TCFA]) were considered vulnerable to rupture. In ≈25% of cases of MI and sudden cardiac death, coronary thrombi have been associated with surface erosion of plaques with either an intact or indistinct fibrous cap. A detailed understanding of the morphology of the vulnerable plaque has motivated the development of imaging tools for in vivo detection.

Inflammation is an intrinsic contributor to atherogenesis, plaque progression, and instability. Inflammation (which varies according to activity, immunophenotype, and type of cytokine/mediator-release) affects the intima, media, and adventitia, as well as periadventitial spaces, where inflammatory cells can cluster in lymph node–like aggregates (Figure 2A and 2B). Plaque inflammatory cells typically include CD68-positive macrophages (siderophages, foam cells, and dendritic cells with antigen-presenting properties), less frequently lymphocytes (mostly T cells) and mast cells, and rarely granulocytes and multinucleated giant cells. B cells are more prevalent in adventitial clusters surrounding nerves and vascular structures. An abundance of inflammatory cells in the structurally weak thin areas of the fibrous cap contributes to plaque rupture through the release of collagenolytic enzymes such as cathepsins and metalloproteases. When activated, intimal inflammatory cells and endothelial cells are reciprocally regulated. Inflammation exerts prothrombotic effects, and the thrombus in turn contributes to proinflammatory effects (Figure 2C and 2D).

Angioneogenesis is common in atherosclerotic plaques and is not normally seen in normal coronary vessels. These vessels may arise from the adventitial capillary network, and circulating CD34 cells enter the plaque through the intima. Angioneogenesis is likely triggered by the chronic hypoxia of the thickened arterial wall and the expanding necrotic core. In addition, inflammatory cells contribute to angioneogenesis as suggested by its proximity to inflammation (Figure 2E).

The neoangiogenic vessels lack smooth muscle envelope and pericytes, allowing macromolecules (including erythrocytes) to leak from these permeable vessels into the plaque. The cell membranes of the erythrocytes are rich in free cholesterol and contribute to growing necrotic core volume and cholesterol crystals. The fragility of the neoangiogenic vessels results in plaque hemorrhage, which is now recognized as an important contributor to plaque vulnerability.

Noninvasive and intravascular imaging modalities are able to distinguish the morphological structure, physical characteristics, and chemical components of high-risk plaques. Noninvasive coronary CTA is able to detect low attenuation plaque, a marker of necrotic core, and positive remodeling at the lesion site. In addition to being highly prevalent in culprit sites, positive remodeling, and low attenuation plaque have been associated with the subsequent development of acute ACSs. ACS developed in 22.2% of patients with coronary lesions with these 2 features compared with only 0.5% in patients with neither of the 2 features.

Invasive IVUS, OCT, and near-infrared spectroscopy (NIRS) are able to detect distinct features of high-risk plaques.
Three prospective natural history studies, PROSPECT,23 VIVA (VH-IVUS in Vulnerable Atherosclerosis),24 and AHEROREMO,82 have demonstrated the utility of IVUS with radiofrequency analysis (virtual histology IVUS) in identifying patients and specific lesions likely to rapidly progress and give rise to future MACE. In the multicenter PROSPECT study,23 the highest risk plaques were an IVUS-classified TCFA with a large plaque burden (≥70%) and MLA of ≤4 mm². Plaques with these 3 characteristics had a 18.2% likelihood of causing an event within 3.4-year follow-up (hazard ratio, 11.1; 95% confidence interval, 4.4–27.8; P<0.001). The relationship between plaque burden and subsequent events arising from untreated lesions in PROSPECT was particularly striking14; the event rate rose exponentially with increasing plaque burden and was 9.5% in lesions with ≥70% plaque burden. No such events arose from several thousand plaques with burden <40%, and the 3-year event rate arising from lesions with plaque burden ≥40% to <60% was <1%. The mean angiographic diameter stenosis of lesions responsible for future events was only 32% at baseline, but progressed rapidly during follow-up to a mean 65% diameter stenosis, usually with thrombus. Most patients presented with unstable angina requiring urgent revascularization, likely because of effective treatment with dual antiplatelet therapy and guideline-directed medical therapy in most (although sudden cardiac death occurred in ≈3% of patients without angiography, also possibly because of coronary thrombosis). The PROSPECT study thus demonstrated that although angiographically mild, vulnerable plaques are actually severe stenoses with large plaque burden and sizable necrotic cores.82

Despite these positive results, radiofrequency IVUS has not been widely adopted for high-risk plaque identification because of several limitations. Plaque contours must be accurately drawn, and automated edge detection software to assist in this task has not been developed. Pattern recognition of plaque phenotype is not always simple. The radiofrequency signals for necrotic core and dense calcium overlap, adding imprecision, and the current classification tree does not recognize thrombus. Finally, the axial resolution of IVUS is only 150 to 200 μm, and thus stable lesions could be misclassified as TCFA. OCT has overcome some of the limitations of IVUS-based imaging. It is the only available technique capable of identifying a pathologically thin cap (<65 μm) although the depth of penetration is not sufficient to assess plaque burden. NIRS has been validated to identify lipid-rich plaques in humans83 and provides an automated quantitative assessment of lipid burden. NIRS has identified greater lipid content in target lesions responsible for ACS than in stable ischemic syndromes.84 However, unlike radiofrequency IVUS, neither OCT nor NIRS have been prospectively validated to identify patients or lesions at risk for future ACS.

In the ongoing PROSPECT-II study, a NIRS-IVUS catheter is being used that affords coregistration of the NIRS chemogram signal with a gray scale-IVUS image, allowing the simultaneous assessment of plaque burden, MLA, and lipid content. Approximately 900 patients with ACS after successful PCI are undergoing 3-vessel quantitative coronary angiography and NIRS-IVUS imaging at 16 centers in Sweden, Denmark, and Norway. The NIRS component of the image is electronically blinded although the gray-scale IVUS image is viewable. As in the ongoing PROSPECT-II study, untreated nonculprit lesions will be prospectively characterized, and events during follow-up will be adjudicated to these baseline lesions, with the goal of determining the utility of NIRS-IVUS imaging to identify vulnerable plaque and patients. The primary end point of patient-level MACE in PROSPECT-II will be analyzed at 2 years, and as a part of SCAAR (the Swedish Coronary Angiography and Angioplasty Register) patients will be followed up for up to 15 years.
Although PROSPECT, VIVA, and ATEROREMO confirmed the biological importance of TCFA for future MACE, pathological studies have suggested that fibrous cap thickness may be the best discriminator of ruptured plaque. Therefore, OCT-identified TCFA is used as the basis of plaque vulnerability in the SECRITT-I and SECRITT-II studies, as described below.

**Should High-Risk Plaque Morphology Direct Revascularization Decisions?**

Despite advances in primary and secondary prevention, MACE continue to occur in patients with SIHD. The in vivo identification of high-risk plaques has enabled investigation of pharmacological and mechanical treatments aimed at their passivation. Although systemic therapy is the cornerstone of treatment for patients with CAD, the prospective identification of specific lesions with event rates of >10% in PROSPECT suggest that focal therapy may also be beneficial. However, some authors have questioned the concept of the vulnerable plaque and the potential for focal therapy, and several unknowns that must be elucidated before such an approach can be recommended. The temporal stability of vulnerable plaque is not well understood and may vary in patients whose disease is evolving.

![Image of modification of the natural history of coronary disease by local implantation of a bioresorbable scaffold.](http://circres.ahajournals.org/)

**Figure 3.** Modification of the natural history of coronary disease by local implantation of a bioresorbable scaffold. From left to right: Intimal thickening (a), intimal xanthoma (b), pathological intimal thickening (c), fibroatheroma (d), thin-capped fibroatheroma (e) (reprinted from Garcia-Garcia et al with permission of the publisher. Copyright © 2009, Europa Digital & Publishing). As coronary disease progresses, does the endothelial function worsen. After the implantation of the scaffold, it can be seen that the 3-dimensional (3D) structure of the device can be delineated by means of optical coherence tomography (OCT) (f). In histology, it can be appreciated the polymeric struts overlying on the vessel wall (black arrow). On the 2D OCT image, the squared-shape struts are translucent and therefore their whole thickness can be appreciated (f'). At 5 o clock, the metallic marker can be seen (*). Invasive imaging by means of angiography and OCT allows the reconstruction of the scaffolded artery (f''). Thereafter, blood flow simulation was performed on the luminal surface and around struts at baseline and the local shear stress conditions were measured. As times goes by, the struts are integrated into the vessel wall and cover by neointima (g and g'). When the shear stress at baseline is portrayed into the follow-up OCT images (g''), it became apparent that the low shear stress areas at baseline (blue) correlate with thicker neointima thickness at follow-up as compared to high shear stress areas (on top of struts in red color), which showed thinner neointima thickness (reprinted from Bourantas et al with permission of the publisher. Copyright © 2014, American College of Cardiology Foundation. Published by Elsevier Inc.). Eventually, the polymeric struts will disappear (h) and somewhat vessel wall thinning is observed (i). As the bioresorbable vascular scaffold (BVS) integrates and dissolves, there is some vasomotion restoration (reprinted from Serruys et al with permission of the publisher. Copyright © 2014, American College of Cardiology Foundation. Published by Elsevier Inc.). EL indicates extracellular lipid; FC, fibrous cap; NC, necrotic core. BVS is a product of Abbott Vascular, Santa Clara, CA.
Figure 4. Overview of the current state of the field with regards to various determinants of coronary artery disease. The FOCUS of interest in each group (obstructive lesions [anatomy], lesions-specific ischemia, myocardial perfusion imaging [MPI]–verified myocardial ischemia [physiology], and high-risk features [pathology]), the pros and cons of various diagnostic and therapeutic modalities for each focus are demonstrated. The established and upcoming trials with focus of each determinant are represented. ACS indicates acute coronary syndrome; CAD, coronary artery disease; CCTA, coronary CTA; FFR, fractional flow reserve; IVUS, Intravascular ultrasound; LAP, low attenuation plaque; MI, myocardial infarction; NIRS, near-infrared spectroscopy; NRS, napkin ring sign; OCT, optical coherence tomography; OMT, optimal medical therapy; and PR, positive remodeling.

Figure 5. There are 8 possible plaque types when considering various possibilities with regards to presence or absence of significant luminal obstruction, ischemia, and high-risk features. Note that plaques that are nonobstructive, nonischemic without high-risk features are not represented in this diagram. The possibility of future events, based on the currently available literature, for each type of plaque estimated and represented by the box color (red: high risk, orange: medium risk, and green: low risk) and the number of + (low risk:+ to high risk: ++++). *Type 2 plaques: obstructive, nonischemic lesions with high-risk features are relatively rare types, as most of obstructive lesions with large necrotic core are ischemic as well.
with ACS and SIHD.99,100 The proportion of future events attributable to vulnerable plaques identified at a single point in time is uncertain. Whether the accuracy of core laboratory-based image characterization can be replicated at clinical sites is a real concern. And the risks of focal therapy, such as periprocedural MI, stent thrombosis, and restenosis, must be less than the disease itself. As such the long-term consequences of any intervention (including the imaging procedure used for screening) must be shown to provide net clinical benefit to the patient, requiring adequately powered randomized trials.

Local mechanical passivation has been studied with balloon angioplasty and dedicated metallic stents. In 1995, Meier and Ramamurthy91 described plaque sealing by coronary angioplasty, noting that “the smooth inner lining of the intimal proliferation virtually precludes endothelial rupture and thrombosis and thereby preventing plaque rupture and occlusive thrombosis impacts on the occurrence of myocardial infarction and death.” Coronary plaque modification has also been achieved by means of a paclitaxel-eluting balloon. A new layer of neointima and thickening of the fibrous cap overlying the necrotic core was noted (potentially turning a TCFA to thick-cap fibroatheroma; Figure 3).92–94

The pilot SECRITT trial assessed the feasibility and safety of using a self-expandable bare metal stent (vShield) for focal treatment of TCFA.96 This study showed an increase in the average fibrous cap thickness from 48±12 μm to 201±168 μm at 6-month follow-up, with no MACE associated with the device.96 However, a permanent metallic stent may have deleterious consequences, such as increased risk of stent thrombosis or late restenosis caused by either late acquired malapposition, strut fracture, or formation of neoatherosclerosis. Bioresorbable scaffolds may avoid many of these long-term risks. After implantation of the Absorb bioresorbable vascular scaffold (BVS), a 150- to 200-μm growth of neointima is observed, which was accommodated by outward remodeling and preservation of the lumen area97; changes that cannot occur with permanent metallic stents. The main component of the neointima after BVS implantation is fibrous tissue, whereas fibrin and granulomatous cells are scarce.98 Thickening of the de novo fibrous cap occurred simultaneously with the integration of the bioresorbable struts within the vessel wall. By 3 years, the polymeric material has been fully replaced by proteoglycans, and by 4 years, the initial location of the struts in the vessel wall is no longer identifiable by histology or OCT.

Incorporated into the PROSPECT-II study is PROSPECT-ABSORB, a multicenter randomized trial evaluating the safety and efficacy of PCI with the Absorb BVS to stabilize vulnerable plaque. Among the 900 patients undergoing 3-vessel NIRS-IVUS imaging, it was estimated from PROSPECT-I that ≈300 patients would have an angiographically mild nonculprit lesion with a gray-scale IVUS plaque burden ≥25% not otherwise indicated for PCI using current criteria. Such lesions, which sustained a 3-year MACE rate of ≈7% in PROSPECT-I, are being randomized 1:1 to treatment with an ABSORB BVS or control, with all patients receiving intensive guideline-directed medical therapy. All randomized patients will undergo 2-year follow-up angiography with 3-vessel repeat NIRS-IVUS imaging, affording evaluation not only of scaffold healing and plaque regression but also of lesion progression at untreated sites representing a natural history substudy not undertaken in PROSPECT-I. The primary objective of PROSPECT-ABSORB is to determine whether the BVS can safely enlarge luminal dimensions at 2 years, thereby informing a pivotal randomized trial to demonstrate improved clinical outcomes with focal plaque therapy. In addition, the upcoming SECRITT-II study will prospectively assess whether bioresorbable scaffolds are able to speed up the process of de novo fibrous cap formation in comparison with pharmacological treatment (ie, high-dose statin treatment).

Discussion

Anatomy, physiology, or plaque morphology all variably contribute to worsening prognostic outcomes among patients with SIHD. These 3 determinants have often been treated as mutually exclusive competing concepts. All previous and ongoing studies of SIHD management, such as COURAGE and BARI 2D (anatomy: obstructive lesions), FAME 1 and FAME 2 (physiology: FFR-verified ischemia), ISCHEMIA (physiology: stress test verified ischemia), and PROSPECT-II (morphology: vulnerable plaque), have approached the problem from this perspective (Figure 4). The physiology-based revascularization approach has been the most successful strategy to date. However, all strategies relying solely on an anatomic, physiological, or morphological lesion characterization have been associated with low positive predictive value for predicting future events that can lead to unnecessary revascularization in a high percentage of patients. Only a minority of obstructive lesions (≈20% in 5 years),4 ischemia-inducing lesions (≈9% in 2 years),12 and plaques with high-risk morphological features (≈16%–20% in 5 years)99 have resulted in death or ACS if treated with OMT alone. Relying on a single feature to discriminate high- versus low-risk plaque and patients also discard valuable prognostic and therapeutic information that the other 2 nonchosen features might have contributed.5,12,27

A rationale may be proposed for combining all 3 features (anatomy, physiology, and plaque morphology) for prognostication and therapeutic decision-making guidance (Figure 5). In this regard, it is important to recognize that each of obstructive, ischemic, and pathologically high-risk groups are a mix of both benign and malignant lesions, amenable to further risk stratification. Any given lesion could have combinations of high-risk features that pertain to anatomy, physiology, and morphology, and therefore the attempt to predict the lesion’s prognosis based on only one of these features leads to an incomplete assessment. For example, an obstructive plaque with high-risk morphological features most likely has a different likelihood of causing an event compared with an obstructive plaque with the same degree of luminal narrowing but without the high-risk morphological features.26 Similarly, a plaque with vulnerable features (eg, consistent with a TCFA) that also has a large plaque burden and causes luminal obstruction is more likely to result in a future MACE than in a plaque with similar histological features that is not obstructive and has small plaque burden.23,26,27 Moreover, lesions with high-risk morphological features by CTA can be subdivided into a very high-risk group, which underwent plaque progression and became obstructive (27% of which resulted in ACSs in 5
years), whereas lesions with high-risk morphological features but no significant plaque progression had no ACS in the similar timeline.99

Although the presence of ischemia is likely to be indicative of severe anatomic stenosis, there is not a perfect relationship between the 2.27 Although some severely stenotic lesions may not result in detectable ischemia (stenosis without ischemia), others with only a mild-moderate degree of angiographic stenosis may result in ischemia (ischemia without stenosis).100,101 Features other than the degree of luminal stenosis, such as lesion length, entrance angle, exit angle, size of the reference vessel, and absolute flow relative to the territory supplied, are important in determining FFR-verified lesion-specific ischemia50 and might explain the discordance between anatomy and physiology in some cases. Recently, it has been shown that the presence of high-risk plaque features, especially large low attenuation plaque, a CTA surrogate for necrotic core, is strong predictor of FFR-verified ischemia independent of degree of luminal stenosis.102,103 Local impairment of the vessel to dilate at the site of a stenosis with either a large plaque burden or necrotic core, a hallmark of vulnerable plaque, may contribute to ischemia independent of the degree of luminal narrowing. In this regard, plaques with large necrotic cores are often significantly positively remodeled, even if the lumen is not significantly narrowed. Similar to the Glagovian limit104 in the high-risk plaques, the vessel section at the lesion site is in its maximally stretched state and cannot dilate any further. The large lipid-rich necrotic core may cause local endothelial dysfunction secondary to presence of inflammation and oxidative stress.100,105–107 As a corollary, FFR-negative lesions are more likely to be devoid of both large necrotic core and severe stenosis. Therefore, FFR may indirectly be a sensitive (but not specific) detector of stenotic lesions that have a large plaque burden and necrotic core.101 This may explain why FFR-negative lesions are safe to defer to medical therapy despite a significant degree of luminal narrowing; a 0.2% 2-year prediction of PCI for stenosis with either a large plaque burden or necrotic core, a hallmark of vulnerable plaque, may contribute to ischemia independent of the degree of luminal narrowing. In this regard, plaques with large necrotic cores are often significantly positively remodeled, even if the lumen is not significantly narrowed. Similar to the Glagovian limit104 in the high-risk plaques, the vessel section at the lesion site is in its maximally stretched state and cannot dilate any further. The large lipid-rich necrotic core may cause local endothelial dysfunction secondary to presence of inflammation and oxidative stress.100,105–107 As a corollary, FFR-negative lesions are more likely to be devoid of both large necrotic core and severe stenosis. Therefore, FFR may indirectly be a sensitive (but not specific) detector of stenotic plaques with large volume necrotic core.101 This may explain why FFR-negative lesions are safe to defer to medical therapy despite a significant degree of luminal narrowing; a 0.2% 2-year rate of MI arising from FFR-negative lesions was observed in the FAME study despite 104 lesions having 70% to 90% luminal narrowing.10,101 A related intriguing question that needs to be addressed is whether all FFR-positive plaques have the same prognosis, and thus do all require revascularization? Based on the FAME 2 data, only 8.2% of FFR-positive plaques that were randomized to medical therapy resulted in death or MI within 2 years.12,101 We propose that identification of FFR-positive lesions that have a large plaque burden and necrotic core may further risk stratify SHD patients with the highest likelihood of future MACE, those who would benefit most by revascularization (Figure 5). As the ischemic potential and morphological characteristics of lesions have not been simultaneously studied in any natural history study to date, this hypothesis requires future validation in appropriately conducted prospective studies.

Disclosures

None.

References


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