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THE PRESENT AND FUTURE

REVIEW TOPIC OF THE WEEK

The Risk Continuum of Atherosclerosis and its Implications for Defining CHD by Coronary Angiography

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ABSTRACT

Patients undergoing coronary angiography for suspected coronary heart disease who are found to have coronary atherosclerotic disease with <50% diameter stenosis may carry a risk of adverse cardiac events similar to that in patients with single-vessel obstructive disease. Yet clinical practice guidelines offer no direction for managing symptomatic patients with nonobstructive coronary atherosclerosis because current diagnostic criteria for coronary heart disease are not met. Accordingly, secondary preventive measures are not endorsed, and their role is not defined in this setting. Available data suggest that we are missing the opportunity to provide effective preventive measures in millions of patients with nonobstructive coronary heart disease. The emergence of noninvasive coronary angiography in patients with suspected coronary heart disease provides the opportunity to transition from a categorical perspective on the presence or absence of coronary heart disease to accepting the risk continuum from atherosclerosis and its implications for diagnosis and management. (J Am Coll Cardiol 2016;68:2467–78)

A 43-year-old woman presents to a physician's office complaining of intermittent chest discomfort that is not related to identifiable triggers. She carries a history of arterial hypertension and achieved good blood pressure control on a diuretic agent/angiotensin-receptor-antagonist combination. Her physical examination is unremarkable, except for mild obesity. A baseline electrocardiogram is normal. Her serum cholesterol and low-density lipoprotein levels are in a low-risk range. She underwent exercise stress testing with myocardial imaging, which did not provoke symptoms or reveal evidence of myocardial ischemia. The patient's symptoms persisted, and she eventually underwent computed tomography (CT) coronary angiography to conclusively rule out coronary heart disease (CHD). CT angiography revealed noncalcified atherosclerotic disease in her proximal left anterior descending artery (LAD) with an approximately 40% lumen diameter stenosis (Figure 1). Very mild atherosclerotic disease was also noted in her left circumflex and right coronary arteries, both with <30% lumen narrowing. Although her symptoms may or may not be related to these angiographic findings, the question of whether preventive measures (e.g., aspirin and statin therapy) are indicated to lower her risk of adverse cardiac events arises.

DEFINING THE ISSUE

The case example illustrates several problems with our present concept of defining CHD using coronary angiography. According to current practice guidelines, the diagnosis and management of CHD center

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ABBREVIATIONS AND ACRONYMS

CHD = coronary heart disease

CT = computed tomography

FFR = fractional flow reserve

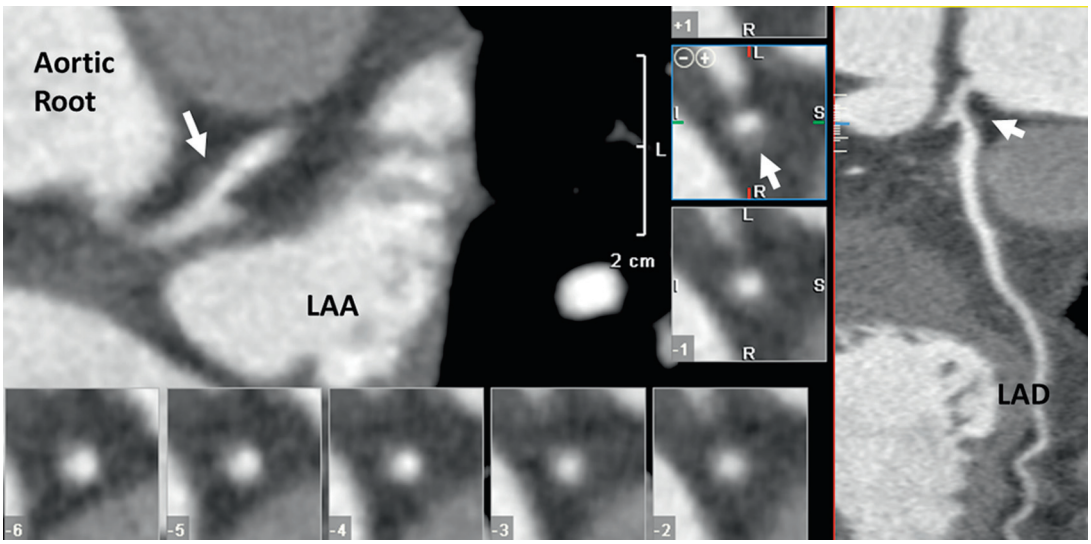
LAD = left anterior descending artery

on the presence of either provocable myocardial ischemia or at least 1 coronary arterial stenosis of 50% or greater (1-3). Such patients are at high risk for adverse cardiac events and are candidates for comprehensive secondary preventive measures (4). Conversely, symptomatic patients without history of myocardial infarction or coronary artery revascularization who have evidence of coronary atherosclerotic disease, but have no provocable ischemia or high-grade stenoses, are presumed to have neither CHD nor clinical atherosclerotic cardiovascular disease (1-5). These patients are considered low risk for death from cardiovascular causes, and the appropriate use of preventive measures (e.g., high-intensity statin therapy) is neither established nor endorsed by practice guidelines (1,4,5). As a result, secondary prevention is less frequently implemented in these patients (6).

Several large clinical datasets, using both conventional and CT coronary angiography, have demonstrated that symptomatic patients with nonobstructive coronary atherosclerotic disease (<50% diameter stenosis) carry risk of myocardial infarction and death, which may be similar to that of patients with single-vessel obstructive disease (7-10). Among more than 11,000 patients undergoing invasive coronary angiography, men and women with diffuse coronary atherosclerotic disease, but without a ≥50% stenosis, had indistinguishable adverse event rates after 7 years compared with patients with single-vessel CHD (**Figure 2**) (10). In a registry of 37,674 Veteran Affairs patients undergoing cardiac catheterization, patients with nonobstructive disease in 3 coronary arteries had an annual risk of myocardial infarction and death exceeding 3% (i.e., consistent with high risk), which was similar to the risk in patients with single-vessel CHD (9). Another large registry demonstrated that the mortality risk gradually increased with the extent of nonobstructive coronary atherosclerotic disease by CT angiography (11). Indeed, these data from more than 80,000 patients consistently demonstrate a risk continuum of adverse events with the extent of atherosclerotic disease without a threshold effect for lumen obstruction or hemodynamically significant CHD (12).

An analysis of chest pain characteristics of 15,888 patients without history of CHD undergoing elective coronary angiography revealed that only 37% had typical angina, whereas most had atypical chest pain or symptoms not ascribed to cardiac disease (13). Yet more than 80% of patients in this cohort had evidence of either obstructive (48%) or nonobstructive (33%) coronary disease by cardiac catheterization. Chest

FIGURE 1 Nonobstructive Coronary Atherosclerotic Disease by Computed Tomography Angiography



A computed tomography angiographic image of coronary atherosclerotic disease in the ostial and proximal left anterior descending artery (LAD) of a 43-year-old woman who presented with atypical chest pain and negative stress test results is shown. The atherosclerotic disease is characterized by a noncalcified plaque that extends from the distal left main coronary artery into the LAD with approximately 40% lumen stenosis. **Arrows** point to the same atherosclerotic plaque displayed in different projections. LAA = left atrial appendage.

pain symptoms in patients with nonobstructive CHD are often attributed to other causes than coronary atherosclerosis because the resultant lumen narrowing is unlikely to reduce coronary flow reserve. However, intermittent myocardial ischemia may yet be elicited via different mechanisms. Vascular endothelial dysfunction is commonly encountered in the presence of coronary atherosclerotic disease, which may lead to vasospasm and/or reduced coronary flow reserve (14). Coronary microvascular dysfunction is an important, frequent cause of myocardial ischemia in women with angina, but without evidence of obstructive CHD (15,16). Last, intermittent myocardial ischemia may occur in the setting of peripheral thrombotic embolization from proximal, nonobstructive coronary atherosclerotic plaques in patients with stable CHD (17,18).

Until recently, patients with nonobstructive CHD were rarely identified because stress tests are insensitive to coronary atherosclerotic disease without advanced lumen narrowing (19); only patients with high suspicion for obstructive CHD undergo cardiac catheterization in which more sensitive tools for detecting atherosclerotic disease are used. With the emergence of noninvasive coronary angiography by CT and, to some extent, cardiac magnetic resonance imaging, even small atherosclerotic plaques are now detectable, but the implications of these findings for patient management remained unclear until recently.

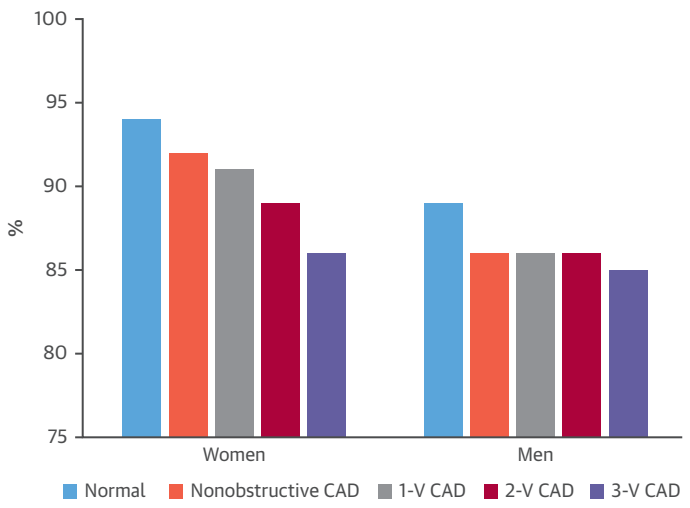
There is strong and consistent evidence from clinical studies that risk from CHD does not abruptly increase with the presence of a stenosis, but reflects the burden of disease on a wide spectrum, rising from very low to very high with the extent of atherosclerotic disease (**Figure 3**) (20). Multivessel CHD is associated with a worse patient outcome than the involvement of only a single artery (21). To appropriately allocate resources, we need to adjust our current approach to CHD and recognize the risk continuum associated with the burden of atherosclerotic disease. Such a view mandates expanding risk assessment in patients from our current simple categorization of presence or absence of obstructive CHD to a wider risk spectrum (i.e., ranging from very low to very high risk).

SCOPE OF THE PROBLEM

The PESA (Progression of Early Subclinical Atherosclerosis) study revealed coronary artery calcification (evidence of coronary atherosclerotic disease) in 18% of an asymptomatic, middle-aged cohort, including many subjects categorized as low risk by traditional risk scores (22). Among 4,184 subjects (mean 45.8 years of age), 63% had evidence of atherosclerotic disease in at least 1 vascular bed (22). Importantly, 39% of subjects in the PESA study had multiterritory disease involvement, indicating the common trait of general manifestation of atherosclerotic disease. In the BIOIMAGE (A Clinical Study of Burden of Atherosclerotic Disease in an At-Risk Population) study, the prevalence of polyatherosclerosis was 58% among 5,808 asymptomatic subjects (mean 69 years of age) with risk factors for CHD (23). Thus, most middle-aged adults in Western industrialized nations have some form of cardiovascular disease.

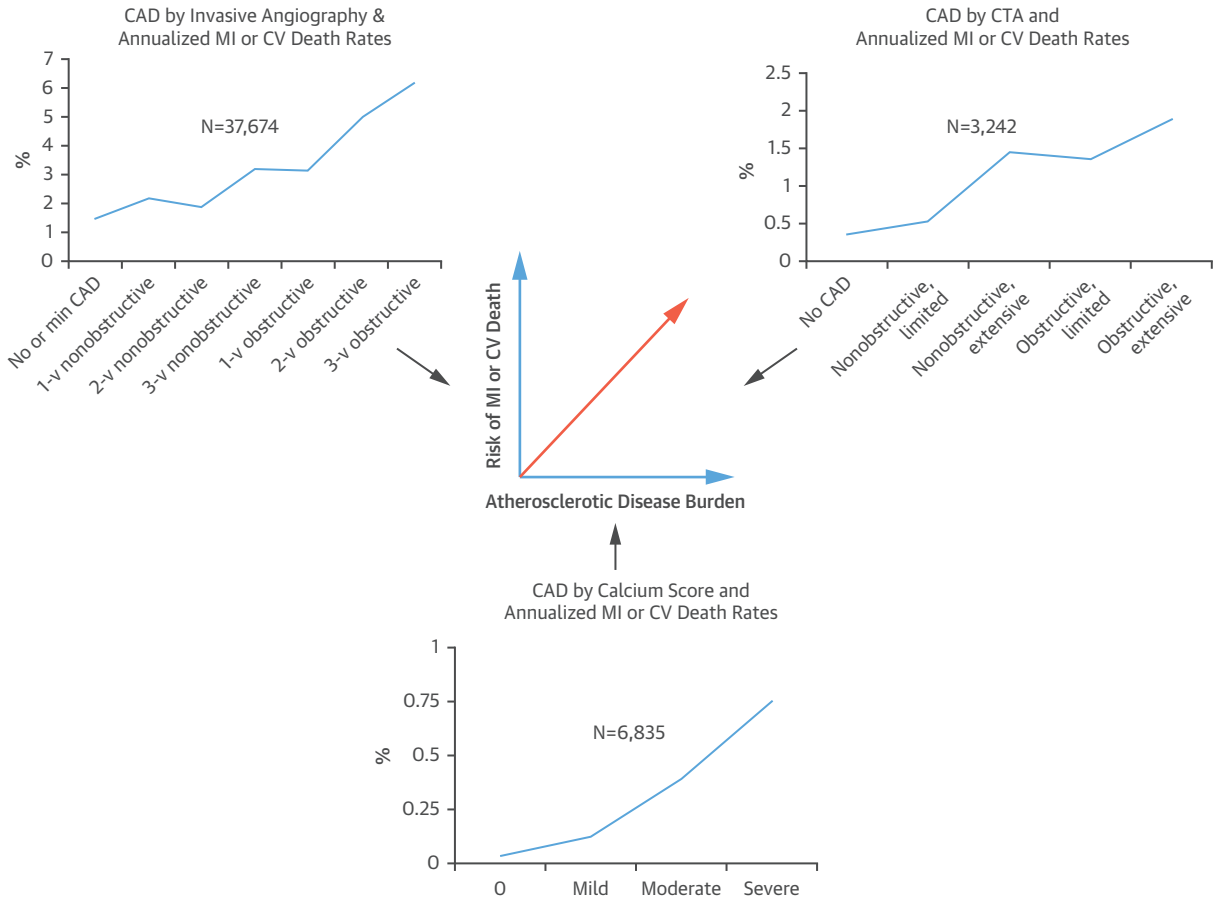
More than 17 million Americans have symptomatic coronary atherosclerotic disease (i.e., CHD), and given the aging of our population, these numbers are expected to rise (24). Among patients presenting with symptoms suspicious for CHD, approximately one-third reveal evidence of nonobstructive coronary atherosclerotic disease, which is associated with a 6-fold increased risk of myocardial infarction or

FIGURE 2 5-Year Event-Free Survival Rates According to the Presence and Extent of CAD



Age-adjusted event-free survival rates for 4,711 women and 6,512 men who underwent invasive coronary angiography for evaluation of stable angina according to the presence and extent of coronary atherosclerotic disease are shown. Obstructive coronary artery disease (CAD) was defined as the presence of at least 1 stenosis of 50% or greater, whereas nonobstructive disease required evidence of coronary atherosclerotic disease with 1% to 49% resultant stenosis in any epicardial coronary artery. Adverse events included cardiovascular death, hospitalization for myocardial infarction, heart failure, and stroke. The data reveal no significant difference in adverse events among women with nonobstructive disease and those with 1-vessel obstructive disease. In men, patients with nonobstructive coronary atherosclerotic disease had the same probability of adverse events as patients with single- or 2-vessel obstructive CAD. Adapted and modified from Jespersen et al. (10). V = vessel.

FIGURE 3 The Risk Continuum of Coronary Atherosclerotic Disease



Continuous risk from coronary atherosclerotic disease according to its disease burden, using 3 clinical studies with different patient risk profiles as examples (8,9,71). For each study, the annualized rate of myocardial infarction (MI) or cardiovascular (CV) death is provided according to the assessment of coronary atherosclerotic disease. Note the near-linear relationship between the extent of coronary artery disease (CAD) and risk, but varying degrees of absolute risk according to patient population risk characteristics. Also, note that patients with extensive nonobstructive coronary atherosclerotic disease and patients with single-vessel CAD have similar risks. Min. = minimal; V = vessel.

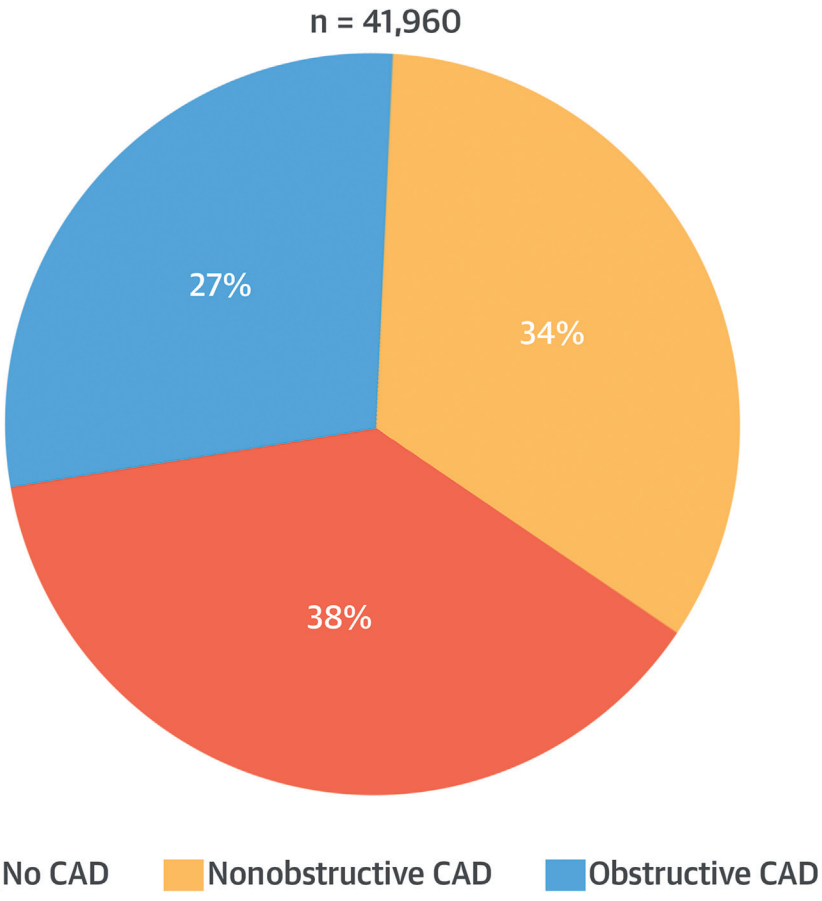
cardiac death over the ensuing 2 years compared with patients without coronary atherosclerosis (**Central Illustration**) (25). Nonobstructive CHD is twice as common among women compared with men undergoing cardiac catheterization for symptoms concerning for CHD (10), representing a major, unaddressed public health problem (15).

Considering that approximately 15 million patients present to health care providers with symptoms concerning for CHD every year in the United States alone (26), several million patients at risk for adverse events are not being identified as having CHD because our current diagnostic criteria do not take into account recent data documenting the considerable risk in patients with nonobstructive CHD (**Figures 2** and **3**). Growing recognition of this issue led to a recent position paper by the European Society of Cardiology on myocardial infarction with nononbstructed coronary arteries (27). However, the magnitude of the problem requires us to go further and include the entity of symptomatic, nonobstructive coronary atherosclerosis in the disease spectrum of CHD.

HISTORICAL PERSPECTIVE

Our understanding of CHD and its associated manifestations has considerably evolved over the past decades. Angina pectoris has been known to arise from reaching a critical threshold of myocardial blood flow reserve. Classic experiments by Gould et al. (28) demonstrated coronary flow reserve to progressively decrease with diameter stenoses exceeding 50% by

CENTRAL ILLUSTRATION **Prevalence of Nonobstructive Coronary Atherosclerotic Disease by Coronary Angiography**

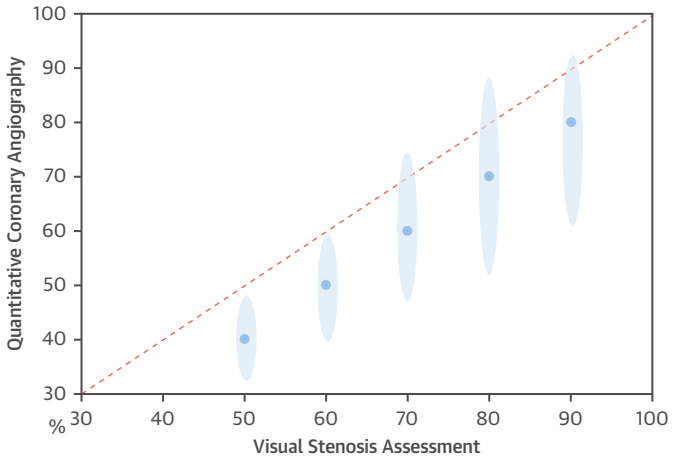


Arbab-Zadeh, A. et al. J Am Coll Cardiol. 2016;68(22):2467–78.

The distribution of coronary angiographic findings among 41,960 patients who underwent computed tomography (CT) angiography for the evaluation of coronary artery disease (CAD) is shown. Adapted and modified from Habib et al. (25).

quantitative assessment in an animal model. These results were later confirmed in humans using myocardial flow reserve assessment (29). Presumably because angina is the most common manifestation of CHD, the diagnosis of CHD was defined by the presence of a coronary artery stenosis of 50% or greater (by quantitative evaluation). Such diagnosis, however, does not consider mechanisms leading to other, more critical, manifestations of CHD (i.e., myocardial infarction and sudden cardiac death). Although the involvement of arterial thrombosis in myocardial infarction had been known for decades, its causative role was not widely accepted until the 1980s (30). Importantly, pathology and clinical studies revealed that culprit lesions triggering occlusive coronary arterial thrombosis and myocardial infarction not infrequently have <50% lumen narrowing (pathology assessment overestimates stenoses compared with angiographic evaluation) (31–33). These findings are consistent with contemporary clinical data aggregates documenting approximately 0.5% to 2% annual rates of myocardial infarction or cardiac death in symptomatic patients with nonobstructive CHD (9–11,25). Because such a degree of disease is common, there is concern that a majority of adverse events from CHD affect patients without high-grade coronary artery stenoses (34). Indeed, a recent analysis of the PROMISE trial revealed that more than 50% of adverse cardiac events occurred in patients with normal stress test findings, that is, without evidence of provocable myocardial ischemia (35).

FIGURE 4 Correlation of Stenoses by Visual and Quantitative Assessment



A comparison of coronary artery stenosis assessment by visual inspection versus quantitative coronary angiography using data synthesized from 3 publications is plotted (52-54). The plot illustrates the large variability of visual stenosis assessment and its systematic overestimation compared with software quantification.

Our understanding of the pathophysiology of acute coronary events also has evolved in the past decades. Acute coronary events are the result of a complex interplay of coronary atherosclerotic characteristics and the organism's response to the stimulus for vascular thrombosis (36). Among the coronary atherosclerotic risk factors, the burden of atherosclerotic disease is most strongly related to the risk of myocardial infarction and death (37). Location, metabolic activity, and characteristics of the atherosclerotic disease in the coronary tree also influence the risk of adverse events (21,38,39).

OBSTRUCTIVE VERSUS HEMODYNAMICALLY SIGNIFICANT CHD

Angiographic coronary artery stenosis assessment correlates only modestly with measurements of blood flow restriction in humans (40). Myocardial perfusion imaging or fractional flow reserve (FFR) assessment is necessary to determine if a coronary stenosis is of clinically meaningful hemodynamic impact unless the coronary anatomy is unequivocal (41). However, mechanisms leading to myocardial infarction and death are not dependent on hemodynamically significant coronary artery stenoses (37). Eliminating FFR-proven blood flow obstruction and/or myocardial ischemia by percutaneous coronary intervention has not been shown to reduce rates of myocardial infarction or death compared with medical therapy in clinical studies (42-44). Numerous investigations documented an escalating risk of myocardial infarction and death in patients with increasing coronary atherosclerotic disease burden, even below hemodynamic thresholds (**Figures 2 to 4**) or in the absence of provocable myocardial ischemia (45-47). The FAME-2 (Fractional Flow Reserve versus Angiography for Multivessel Evaluation-2) study revealed no statistically significant risk differences for myocardial infarction or death at follow-up among patients with FFR-positive lesions versus those without (43). Results from myocardial stress testing failed to predict patient outcomes in large databases, and performed inferiorly compared with an assessment of disease burden in clinical trials (13,35,47). Thus, evaluating the functional significance of CHD is critical for managing angina symptoms, but its use for determining the risk of myocardial infarction and cardiac death independently of coronary anatomic information remains poorly supported (12,37,48). Pending the availability of more conclusive data (e.g., the ISCHEMIA [International Study of Comparative Health Effectiveness with Medical and Invasive Approaches] trial) (49), our focus for defining CHD should continue to rest on proven information for effective risk stratification (i.e., the presence, extent, and location of coronary atherosclerotic disease).

CONTROVERSIES OVER THE NOMENCLATURE AND ANATOMIC THRESHOLD DEFINING CHD

The terms *coronary artery disease*, *coronary heart disease*, and *ischemic heart disease* are often used interchangeably. For example, the European practice guidelines refer to the management of stable *coronary artery disease*, whereas the U.S. guidelines use the term stable *ischemic heart disease* for the entity of symptomatic coronary atherosclerotic disease (1,2). The American College of Cardiology/American Heart Association guideline on the treatment of serum cholesterol to reduce cardiovascular risk in adults addresses *clinical atherosclerotic cardiovascular disease*, which encompasses CHD (5). The issue of defining the entity of coronary atherosclerotic disease is further complicated by the fact that it may be associated with symptoms, even though lumen obstruction is mild (e.g., through vascular dysfunction or by triggering vascular thrombosis), but it also may remain entirely asymptomatic, despite extensive manifestation with severe lumen obstruction (50).

Notwithstanding uncertainty as to whether patients' symptoms are always related to coronary atherosclerotic disease, there is strong evidence of increased adverse event risk in symptomatic versus asymptomatic patients, even when accounting for disease burden (10). The precise mechanisms for this difference remain unclear at this time. Symptomatic patients may be at greater risk than asymptomatic patients because of less well-adapted responses to the presence of coronary atherosclerotic disease (e.g., inadequate vascular function or permission of clinically relevant vascular thrombosis) (36). Accordingly, it is critical to differentiate risk evaluation and management in asymptomatic and symptomatic patients. Our terminology may reflect this differentiation by applying the term *coronary artery disease* to asymptomatic coronary atherosclerotic disease, while reserving *coronary heart disease* for patients with clinical manifestations of coronary artery disease (51). The term *ischemic heart disease* may encompass additional causes of myocardial ischemia (e.g., microvascular dysfunction), and thus refers to a more inclusive view of the disease spectrum.

Currently, we use anatomic criteria (e.g., the presence of at least 1 coronary stenosis) to establish the diagnosis of CHD by coronary angiography. However, the threshold for defining a significant or obstructive stenosis varies in clinic and research. In clinical practice, a 70% or greater diameter stenosis by conventional coronary angiography is typically considered diagnostic, but research studies almost invariably use a 50% stenosis threshold for defining CHD. The reason for these discrepant criteria is founded in the mode of assessment. In clinical practice, coronary artery stenoses are assessed by visual estimate, whereas research studies utilize software tools (quantitative coronary angiography) for semiautomated quantification of stenoses. It has been consistently demonstrated that quantitative tools yield lower stenosis degrees compared with visual evaluation (52–54) (**Figure 4**). Studies generated in the 1990s suggested that a 50% stenosis by quantitative coronary angiography corresponds to an approximately 70% stenosis by visual assessment, which led to using these different thresholds depending on the mode of evaluation (52,53). More recently, a large multicenter evaluation suggested the difference between visual and quantitative evaluation to be smaller, although with large variability of individual estimates (54). Because of inconsistent results with visually interpreting coronary artery stenoses, experts have long been advocating the mandated use of quantitative tools (55,56). Descriptions of mild, moderate, or severe CHD are common in research and clinical reports, but there is considerable variability in interpreting these categories. Because software tools are available for fast and easy stenosis quantification by conventional angiography, intravascular ultrasound, and CT, they indeed should be used routinely for more consistent reporting.

STENOSIS ASSESSMENT VERSUS ATHEROSCLEROTIC BURDEN EVALUATION

The coronary atherosclerotic burden is a strong, consistent predictor of adverse cardiac events in patients with suspected CHD (37). As opposed to evaluating total coronary atherosclerotic burden, clinical trials almost exclusively use percent stenosis assessment and the number of involved coronary arteries to predict patient outcome, as well as to guide management. At this time, it remains unclear if the prognostic information from assessing the severity of CHD by the number of vessels with obstructive coronary artery disease is entirely due its correlation with atherosclerotic disease burden or if there is independent value of stenosis severity assessment over plaque burden evaluation (20). A large observational registry found no difference in risk prediction when using percent stenosis assessment or coronary calcium scanning (a crude surrogate for coronary atherosclerotic disease burden that does not directly account for noncalcified disease) in patients without chest pain (57). Several clinical studies demonstrated similar adverse event rates in patients with extensive nonobstructive CHD and those with single-vessel obstructive disease, which may suggest that the burden of disease is indeed the predominant mechanism of risk prediction (7–10). However, these studies also suggest that extensive nonobstructive disease involving several vessels equates the risk of a *single* vessel with obstructive disease. Because only semiquantitative methods (e.g., number of segments), but no quantitative plaque volume evaluations were used to assess nonobstructive disease, it remains unclear from these investigations if obstructive disease is merely a surrogate for greater disease burden, or if there is indeed an independent predictive role for stenosis severity (20). The former is supported by a good correlation of semiquantitative assessment of coronary disease burden with CHD severity graded by the number of obstructive stenoses (58).

Pathology studies suggest that a certain lesion atherosclerotic plaque volume is required (corresponding to an approximately 30% to 40% diameter stenosis) to be capable of triggering fatal coronary events, but there is no conclusive evidence that

TABLE 1 Proposed Classification of CHD by Coronary Angiography

CHD Stage	Description	Risk of MI or CV Death/Year (%)
Stage 0	No coronary atherosclerotic disease by coronary angiography	<0.1
Stage 1	Mild coronary atherosclerotic disease: <30% lumen stenosis affecting 1 or 2 vessels	0.1–0.9
Stage 2	Moderate coronary atherosclerotic disease: 30%-49% lumen stenosis affecting 1 or 2 vessels or mild disease in 3 vessels	1–1.9
Stage 3	Severe coronary atherosclerotic disease: ≥50% lumen stenosis affecting 1 or 2 vessels or moderate disease in 3 vessels	2–4
Stage 4	Very severe coronary atherosclerotic disease: ≥50% lumen stenosis affecting 3 vessels, or 2 vessels including pLAD, or left main disease	>4

Stenosis values as determined by quantitative assessment.
CHD = coronary heart disease; CV = cardiovascular; MI = myocardial infarction; pLAD = proximal left anterior descending artery.

higher-grade stenoses confer greater risk of myocardial infarction and death (31). The Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT) study merely found an association between individual lesion plaque burden at baseline and subsequent risk of hospitalization for angina, but not for acute myocardial infarctions (36,38).

Assessing total coronary atherosclerotic disease burden continues to be technically challenging for both invasive and noninvasive coronary angiography. Ongoing software improvements show promise for noninvasive, accurate, and fully automated coronary artery contour detection in the near future (59). It remains to be seen if total plaque burden determination offers clinically meaningful advantage over stenosis assessment and vessel involvement. In the meantime, stenosis assessment has not only been shown to approximate plaque burden (58), it has been validated as an effective, practical method for categorizing the severity of CHD and for risk stratifying patients using coronary angiography. The body of supporting published reports, ease of application, and the familiarity of researchers and practitioners support the continued classification of CHD by the severity and location of coronary arterial stenosis, as well as by the number of affected coronary arteries.

EXPANDING THE CRITERIA FOR CHD BY ANGIOGRAPHY

Diagnostic criteria should allow identification of a pathological process and characterize it according to its implications for medical management. Diagnostic criteria should also allow effective risk stratification, identifying patients at low, intermediate, high, and very high risk (**Table 1**). Such risk stratification is critical for appropriately allocating treatment, which ranges from low- to high-intensity medical therapy, to coronary artery revascularization.

Coronary atherosclerotic disease by pathology examination is present in most adult subjects in Western industrialized countries (50). Yet the associated risk of myocardial infarction or cardiovascular death is exceedingly low unless disease is detectable by coronary artery imaging. In a large meta-analysis including mostly symptomatic patients with a wide range of risk characteristics, only 2 patients of 4,460 with no evidence of CHD by CT angiography suffered myocardial infarction or cardiovascular death at a mean of 2 years' follow-up; neither of these 2 events were related to CHD (25). These data are consistent with our understanding of the pathophysiology of acute coronary events, which mandates macroscopic atherosclerotic disease as a prerequisite for increased risk (36).

Based on the foregoing, CHD stage 0 may be defined as the absence of coronary atherosclerotic disease by coronary angiography, despite the possibility of microscopic disease being present. Stage 0 CHD identifies patients who are at exceedingly low risk of adverse cardiac events (<0.1%/year) (25). Only patients without any evidence of coronary atherosclerotic disease are included in stage 0. Notably, the presence of very mild disease (e.g., luminal irregularities) on conventional angiography or CT is associated with increased risk compared with patients with normal coronary arteries, and thus should indicate a more advanced CHD stage (9,25).

Stage I CHD may indicate the presence of mild atherosclerotic disease detected by imaging stenosis severity of <30% (by quantitative assessment) with no more than 2 coronary arteries affected. These patients have greater risk of myocardial infarction and cardiovascular death compared with patients with normal imaging findings, but are overall of low risk (approximately 0.1% to 1.0%/year) (25,60,61). In contrast to patients with stage 0 CHD, the risk of adverse events more strongly depends on the presence of other risk factors.

Stage II may identify patients with moderate atherosclerotic disease with diameter stenoses of 30% to 49% (by quantitative analysis) confined to 2 coronary arteries or <30% stenosis in 3 arteries. The rationale for differentiating Stage I and II by these

criteria stems from data demonstrating a gradual increase in risk from mild to moderate nonobstructive disease (7–11). It is conceivable that these 2 groups require different degrees of preventive measures. Patients with these characteristics generally have moderate annual risk of adverse events, approximately 1% to 2% (7–11,60,62).

Stage III indicates high risk (>2%/year) and involves patients with 50% or greater stenosis (by quantitative assessment) in 1 artery or in 2 arteries without involving the proximal LAD. This stage encompasses most of the traditionally defined CHD patients. An important addition to this group is the inclusion of patients with severe nonobstructive disease (i.e., 30% to 49% stenoses in 3 arteries) on the basis of data from several reports suggesting risk equivalence to patients with single-vessel obstructive disease (7–10).

Stage IV indicates very high risk (>4% year), and includes patients with ≥50% stenoses (by quantitative assessment) in all 3 coronary arteries, 2 arteries with involvement of the proximal LAD, or left main disease (21,63). Patients with stage IV CHD are likely to derive a survival benefit from coronary artery bypass grafting compared with medical therapy alone (21,63).

RISK MODIFIERS

Acute coronary events commonly result from the combination of a stimulus for arterial thrombosis (i.e., coronary atherosclerotic disease) and an inadequate host response, which allows clinically significant vascular thrombosis and resultant myocardial ischemia to occur (36). Accordingly, thrombosis-promoting factors (e.g., diabetes mellitus, inflammatory diseases, hyperlipidemia, among others) increase the risk of acute coronary events in patients with comparable disease burdens (22). The evaluation of CHD risk should therefore consider anatomic risk criteria in the context of the overall patient risk profile. The Framingham risk score or similar scores may serve as convenient metrics to adjust a patient's individual risk assessment for a given CHD stage (22). However, many hypercoagulable conditions are not considered in common risk scores and will require further individualization of risk evaluation (e.g., advanced laboratory or genetic testing) (36).

Compromise of left ventricular systolic function is associated with poorer outcomes compared with patients with normal function (21). Even among patients with depressed left ventricular systolic function, worse ejection fraction is associated with greater risk of mortality (63). Similarly, patients with documentation of myocardial infarction are at greater risk than patients without such history (64). Therefore, imaging evidence of prior myocardial infarction should be strongly considered for risk stratification, in addition to the degree of atherosclerotic disease. It remains unclear to what extent myocardial function assessment modifies patient risk for each CHD stage, and prospective investigations will be needed to further define these risk categories.

In addition to the presence, extent, and severity of CHD, a number of other anatomic features may indicate increased risk of adverse events in patients (e.g., noncalcified atherosclerotic plaques with external remodeling, large lipid pool, speckled calcification, and other vulnerable characteristics) (65,66). None of these features, however, has shown to be predictive of myocardial infarction and death independently of a comprehensive evaluation of coronary atherosclerotic disease burden (37). Furthermore, risk information on these characteristics is still limited, and their assessment is neither standardized nor adequately validated (20). Future studies may define their role in patient risk evaluation in association with standard assessment.

Rapid progression of coronary atherosclerotic disease is a strong predictor of adverse patient outcome (39,66). Markers and tools for assessing coronary artery disease progression are likely to further enhance our ability to risk stratify patients and to adjust treatment intensity. At this time, however, their role is insufficiently defined to be considered in our standard approach to patients with CHD.

IMPLICATIONS FOR MANAGEMENT

Patients with symptomatic coronary atherosclerotic disease benefit from secondary preventive measures (1–4). The intensity of secondary prevention should be adjusted to the patient's risk profile. Patients with stage I or II CHD are likely to require less intense treatment goals than patients with CHD stage III or IV. It remains to be seen if patients in stage I merely require risk factor modification or specific preventive measures. Symptomatic patients assigned to an anatomic strategy in the Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) and Scottish Computed Tomography of the Heart (SCOT-HEART) trials were found to have lower rates of myocardial infarction at follow-up than those randomized to functional testing, which is attributed to greater utilization of secondary preventive measures in response to visualizing (mostly nonobstructive) CHD (67–69). These data support the effectiveness of secondary prevention in patients with nonobstructive CHD, and suggest

that atherosclerosis imaging would be of merit in our approach to patients with suspected CHD (69). The value of atherosclerosis imaging should be addressed in future secondary prevention guidelines. Further research is required to identify the appropriate intensity of preventive measures for each stage of CHD, particularly given our expanding options for lipid-lowering drugs and antiplatelet/anticoagulation agents. Although patients with CHD stage III clearly require comprehensive secondary prevention, coronary artery revascularization may be reserved for addressing angina that is not responding to adequate medical therapy (2). For identifying high-risk patients in need of revascularization, with the intent of improving survival, numerous clinical and imaging characteristics have been proposed (2). However, in prospective clinical studies, only 2 risk features identified patients with stable CHD who derive a survival benefit with coronary artery revascularization (coronary artery bypass surgery): high-risk coronary anatomy (i.e., left main, 3-vessel CHD, or 2-vessel CHD with involvement of the proximal LAD) and severely impaired left ventricular systolic function (21,70). Therefore, these criteria should be considered for selecting patients for coronary artery revascularization with the intention of decreasing mortality.

CONCLUSIONS

Nonobstructive CHD is linked to adverse patient outcomes and may be associated with angina-like symptoms. Given the wide availability of noninvasive coronary angiography capable of detecting nonobstructive coronary atherosclerotic disease, it is time to expand the diagnosis of CHD by coronary angiography for this important entity. A large body of evidence supports the concept of a risk continuum from coronary atherosclerotic disease on the basis of its presence, extent, location, and severity. Data also support the concept of allocating treatment intensity according to the extent of coronary atherosclerotic disease. Provided with more refined criteria for risk stratification, we will be better positioned to identify the most effective management strategies for patients with different stages of stable CHD.

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REFERENCES

1. Task Force Members, Montalescot G, Sechtem U, et al. 2013 ESC guidelines on the management of stable coronary artery disease. Eur Heart J 2013;34:2949–3003.

2. Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol 2012;60:e44–164.

3. Fihn SD, Blankenship JC, Alexander KP, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol 2014;64:1929–49.

4. Smith SC Jr., Benjamin EJ, Bonow RO, et al. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation endorsed by the World Heart Federation and the Preventive Cardiovascular Nurses Association [Published correction appears in J Am Coll Cardiol 2015;65:1495]. J Am Coll Cardiol 2011;58:2432–46.

5. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association task force on practice guidelines [Published corrections appear in J Am Coll Cardiol 2015;66:2812 and J Am Coll Cardiol 2014;63:3024–5]. J Am Coll Cardiol 2014;63:2889–934.

6. Maddox TM, Ho PM, Roe M, et al. Utilization of secondary prevention therapies in patients with nonobstructive coronary artery disease identified during cardiac catheterization: insights from the National Cardiovascular Data Registry Cath-PCI registry. Circ Cardiovasc Qual Outcomes 2010;3:632–41.

7. Mushtaq S, De Araujo Gonçalves P, Garcia-Garcia HM, et al. Long-term prognostic effect of coronary atherosclerotic burden: validation of the computed tomography-Leaman score. Circ Cardiovasc Imaging 2015;8:e002332.

8. Bittencourt MS, Hulten E, Ghoshhajra B, et al. Prognostic value of nonobstructive and obstructive coronary artery disease detected by coronary computed tomography angiography to identify cardiovascular events. Circ Cardiovasc Imaging 2014;7:282–91.

9. Maddox TM, Stanislawski MA, Grunwald GK, et al. Nonobstructive coronary artery disease and risk of myocardial infarction. JAMA 2014;312:1754–63.

10. Jespersen L, Hvelplund A, Abildstrom SZ, et al. Stable angina pectoris with no obstructive coronary artery disease is associated with increased risks of major adverse cardiovascular events. Eur Heart J 2012;33:734–44.

11. Chow BJ, Small G, Yam Y, et al., CONFIRM Investigators. Prognostic and therapeutic implications of statin and aspirin therapy in individuals with nonobstructive coronary artery disease: results from the CONFIRM (COronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter registry) registry. Arterioscler Thromb Vasc Biol 2015;35:981–9.

12. Arbab-Zadeh A. Fractional flow reserve-guided percutaneous coronary intervention is not a valid concept. Circulation 2014;129:1871–8; discussion 1878.

13. Vavalle JP, Shen S, Broderick S, et al. Effect of the presence and type of angina on cardiovascular

events in patients without known coronary artery disease referred for elective coronary angiography. JAMA Cardiol 2016;1:232–4.

14. Gutiérrez E, Flammer AJ, Lerman LO, et al. Endothelial dysfunction over the course of coronary artery disease. Eur Heart J 2013;34:3175–81.

15. Pepine CJ, Ferdinand KC, Shaw LJ, et al., ACC CVD in Women Committee. Emergence of nonobstructive coronary artery disease: a woman's problem and need for change in definition on angiography. J Am Coll Cardiol 2015;66:1918–33.

16. Camici PG, Crea F. Coronary microvascular dysfunction. N Engl J Med 2007;356:830–40.

17. Radico F, Cicchitti V, Zimarino M, et al. Angina pectoris and myocardial ischemia in the absence of obstructive coronary artery disease: practical considerations for diagnostic tests. J Am Coll Cardiol Intv 2014;7:453–63.

18. Heusch G, Kleinbongard P, Böse D, et al. Coronary microembolization: from bedside to bench and back to bedside. Circulation 2009;120:1822–36.

19. Arbab-Zadeh A, Di Carli MF, Cerci R, et al. Accuracy of computed tomographic angiography and single-photon emission computed tomography-acquired myocardial perfusion imaging for the diagnosis of coronary artery disease. Circ Cardiovasc Imaging 2015;8:e003533.

20. Arbab-Zadeh A. What imaging characteristics determine risk of myocardial infarction and cardiac death? Circ Cardiovasc Imaging 2015;8:e003081.

21. Yusuf S, Zucker D, Peduzzi P, et al. Effect of coronary artery bypass graft surgery on survival: overview of 10-year results from randomised trials by the Coronary Artery Bypass Graft Surgery Trialists Collaboration. Lancet 1994;344:563–70.

22. Fernández-Friera L, Peñalvo JL, Fernández-Ortiz A, et al. Prevalence, vascular distribution, and multiterritorial extent of subclinical atherosclerosis in a middle-aged cohort: the PESA (Progression of Early Subclinical Atherosclerosis) study. Circulation 2015;131:2104–13.

23. Baber U, Mehran R, Sartori S, et al. Prevalence, impact, and predictive value of detecting subclinical coronary and carotid atherosclerosis in asymptomatic adults: the BioImage study. J Am Coll Cardiol 2015;65:1065–74.

24. Heidenreich PA, Trogdon JG, Khavjou OA, et al. Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. Circulation 2011;123:933–44.

25. Habib PJ, Green J, Butterfield RC, et al. Association of cardiac events with coronary artery disease detected by 64-slice or greater coronary CT angiography: a systematic review and meta-analysis. Int J Cardiol 2013;169:112–20.

26. Mozaffarian D, Benjamin EJ, Go AS, et al., American Heart Association Statistics Committee; Stroke Statistics Subcommittee. Executive summary: heart disease and stroke statistics—2016 update: a report from the American Heart Association. Circulation 2016;133:447–54.

27. Agewall S, Beltrame JF, Reynolds HR, et al., WG on Cardiovascular Pharmacotherapy. ESC working group position paper on myocardial infarction with non-obstructive coronary arteries. Eur Heart J 2016 Apr 28 [E-pub ahead of print].

28. Gould KL, Lipscomb K, Hamilton GW. Physiologic basis for assessing critical coronary stenosis. Instantaneous flow response and regional distribution during coronary hyperemia as measures of coronary flow reserve. Am J Cardiol 1974;33:87–94.

29. Uren NG, Melin JA, De Bruyne B, et al. Relation between myocardial blood flow and the severity of coronary-artery stenosis. N Engl J Med 1994;330:1782–8.

30. Davies MJ, Fulton WF, Robertson WB. The relation of coronary thrombosis to ischaemic myocardial necrosis. J Pathol 1979;127:99–110.

31. Farb A, Burke AP, Tang AL, et al. Coronary plaque erosion without rupture into a lipid core. A frequent cause of coronary thrombosis in sudden coronary death. Circulation 1996;93:1354–63.

32. Mann JM, Davies MJ. Assessment of the severity of coronary artery disease at postmortem examination. Are the measurements clinically valid? Br Heart J 1995;74:528–30.

33. Ambrose JA, Tannenbaum MA, Alexopoulos D, et al. Angiographic progression of coronary artery disease and the development of myocardial infarction. J Am Coll Cardiol 1988;12:56–62.

34. Fishbein MC, Siegel RJ. How big are coronary atherosclerotic plaques that rupture? Circulation 1996;94:2662–6.

35. Hoffmann U, Ferencik M, Udelson JE, et al. Abstract 18503: Prognostic value of anatomic versus functional diagnostic testing strategies in symptomatic patients with suspected CAD: the PROMISE Trial (PROspective Multicenter Imaging Study for Evaluation of Chest Pain). Circulation 2015;132:A18053 (abstr).

36. Arbab-Zadeh A, Nakano M, Virmani R, et al. Acute coronary events. Circulation 2012;125:1147–56.

37. Arbab-Zadeh A, Fuster V. The myth of the "vulnerable plaque" - transitioning from a focus on individual lesions to atherosclerotic disease burden for coronary artery disease risk assessment. J Am Coll Cardiol 2015;65:846–55.

38. Stone GW, Maehara A, Lansky AJ, et al., PROSPECT Investigators. A prospective natural-history study of coronary atherosclerosis. N Engl J Med 2011;364:226–35.

39. Budoff MJ, Hokanson JE, Nasir K, et al. Progression of coronary artery calcium predicts all-cause mortality. J Am Coll Cardiol Img 2010;3:1229–36.

40. Meijboom WB, Van Mieghem CA, van Pelt N, et al. Comprehensive assessment of coronary artery stenoses: computed tomography coronary angiography versus conventional coronary angiography and correlation with fractional flow reserve in patients with stable angina. J Am Coll Cardiol 2008;52:636–43.

41. Tonino PA, De Bruyne B, Pijls NH, et al., FAME Study Investigators. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med 2009;360:213–24.

42. Stergiopoulos K, Boden WE, Hartigan P, et al. Percutaneous coronary intervention outcomes in patients with stable obstructive coronary artery disease and myocardial ischemia: a collaborative meta-analysis of contemporary randomized clinical trials. JAMA Intern Med 2014;174:232–40.

43. De Bruyne B, Pijls NH, Kalesan B, et al., FAME 2 Trial Investigators. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease [Published correction appears in N Engl J Med 2012;367:1768]. N Engl J Med 2012;367:991–1001.

44. Bangalore S, Maron DJ, Hochman JS. Evidence-based management of stable ischemic heart disease: challenges and confusion. JAMA 2015;314:1917–8.

45. Chang SM, Nabi F, Xu J, et al. The coronary artery calcium score and stress myocardial perfusion imaging provide independent and complementary prediction of cardiac risk. J Am Coll Cardiol 2009;54:1872–82.

46. Blumenthal RS, Becker DM, Moy TF, et al. Exercise thallium tomography predicts future clinically manifest coronary heart disease in a high-risk asymptomatic population. Circulation 1996;93:915–23.

47. Mancini GBJ, Hartigan PM, Shaw LJ, et al. Predicting outcome in the COURAGE trial (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation): coronary anatomy versus ischemia. J Am Coll Cardiol Intv 2014;7:195–201.

48. Reynolds HR, Picard MH, Hochman JS. Does ischemia burden in stable coronary artery disease effectively identify revascularization candidates? Ischemia burden in stable coronary artery disease does not effectively identify revascularization candidates. Circ Cardiovasc Imaging 2015;8:e000362.

49. Stone GW, Hochman JS, Williams DO, et al. Medical therapy with versus without revascularization in stable patients with moderate and severe ischemia: the case for community equipoise. J Am Coll Cardiol 2016;67:81–99.

50. Nemetz PN, Roger VL, Ransom JE, et al. Recent trends in the prevalence of coronary disease: a population-based autopsy study of nonnatural deaths. Arch Intern Med 2008;168:264–70.

51. Grundy SM. Coronary calcium as a risk factor: role in global risk assessment. J Am Coll Cardiol 2001;37:1512–5.

52. Gottsauner-Wolf M, Sochor H, Moertl D, et al. Assessing coronary stenosis. Quantitative coronary angiography versus visual estimation from cine-film or pharmacological stress perfusion images. Eur Heart J 1996;17:1167–74.

53. Stadius ML, Alderman EL. Coronary artery revascularization. Critical need for, and consequences of, objective angiographic assessment of lesion severity. Circulation 1990;82:2231–4.

54. Nallamothu BK, Spertus JA, Lansky AJ, et al. Comparison of clinical interpretation with visual assessment and quantitative coronary angiography in patients undergoing percutaneous coronary intervention in contemporary practice: the Assessing Angiography (A2) project. Circulation 2013;127:1793–800.

55. White CW, Wright CB, Doty DB, et al. Does visual interpretation of the coronary arteriogram predict the physiologic importance of a coronary stenosis? N Engl J Med 1984;310:819–24.

56. Marcus ML, Skorton DJ, Johnson MR, et al. Visual estimates of percent diameter coronary stenosis: "a battered gold standard". J Am Coll Cardiol 1988;11:882–5.

57. Cho I, Chang HJ, Sung JM, et al. Coronary computed tomographic angiography and risk of all-cause mortality and nonfatal myocardial infarction in subjects without chest pain syndrome from the CONFIRM registry (coronary CT angiography evaluation for clinical outcomes: an international multicenter registry). Circulation 2012;126:304–13.

58. Nakagomi A, Celermajer DS, Lumley T, et al. Angiographic severity of coronary narrowing is a surrogate marker for the extent of coronary atherosclerosis. Am J Cardiol 1996;78:516–9.

59. Kishi S, Magalhães TA, Cerci RJ, et al. Total coronary atherosclerotic plaque burden assessment by CT angiography for detecting obstructive coronary artery disease associated with myocardial perfusion abnormalities. J Cardiovasc Comput Tomogr 2016;10:121–7.

60. Detrano R, Guerci AD, Carr JJ, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. N Engl J Med 2008;358:1336–45.

61. Papanicolaou MN, Califf RM, Hlatky MA, et al. Prognostic implications of angiographically normal and insignificantly narrowed coronary arteries. Am J Cardiol 1986;58:1181–7.

62. Budoff MJ, Shaw LJ, Liu ST, et al. Long-term prognosis associated with coronary calcification: observations from a registry of 25,253 patients. J Am Coll Cardiol 2007;49:1860–70.

63. Velazquez EJ, Lee KL, Deja MA, et al., STICH Investigators. Coronary-artery bypass surgery in patients with left ventricular dysfunction. N Engl J Med 2011;364:1607–16.

64. Armstrong PW, Fu Y, Chang WC, et al. Acute coronary syndromes in the GUSTO-IIb trial: prognostic insights and impact of recurrent ischemia. Circulation 1998;98:1860–8.

65. Fleg JL, Stone GW, Fayad ZA, et al. Detection of high-risk atherosclerotic plaque: report of the NHLBI Working Group on current status and future directions. J Am Coll Cardiol Img 2012;5:941–55.

66. Motoyama S, Ito H, Sarai M, et al. Plaque characterization by coronary computed tomography angiography and the likelihood of acute coronary events in mid-term follow-up. J Am Coll Cardiol 2015;66:337–46.

67. Douglas PS, Hoffmann U, Patel MR, et al., PROMISE Investigators. Outcomes of anatomical versus functional testing for coronary artery disease. N Engl J Med 2015;372:1291–300.

68. SCOT-HEART investigators. CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open-label, parallel-group, multicentre trial. Lancet 2015;385:2383–91.

69. Fordyce CB, Newby DE, Douglas PS. Diagnostic strategies for the evaluation of chest pain: clinical implications from SCOT-HEART and PROMISE. J Am Coll Cardiol 2016;67:843–52.

70. Velazquez EJ, Lee KL, Jones RH, et al., STICHES Investigators. Coronary-artery bypass surgery in patients with ischemic cardiomyopathy. N Engl J Med 2016;374:1511–20.

71. LaMonte MJ, FitzGerald SJ, Church TS, et al. Coronary artery calcium score and coronary heart disease events in a large cohort of asymptomatic men and women. Am J Epidemiol 2005;162:421–9.

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