



Commentary

Preventive cardiology advances in the 2021 AHA/ACC chest pain guideline



A B S T R A C T

A core principle of the 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Chest Pain Guideline is the importance of preventive therapies among patients with nonobstructive or obstructive coronary artery disease (CAD). Accordingly, this editorial provides unique insights that emphasize the role of preventive cardiology throughout the new guideline. For the first time, CAD was defined to also include nonobstructive plaque. This definition was based on the fact that individuals who have nonobstructive plaque are at an increased risk of atherosclerotic events compared with those who do not. Herein, we highlight guideline recommendations related to the diagnosis and management of nonobstructive CAD. We also highlight recommendations which emphasize the importance of preventive therapies. Adoption of these recommendations have the potential to lead to enhanced preventive therapies and improve patient outcomes.

1. Introduction

The recently published 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain has important recommendations for multiple stakeholders in cardiovascular medicine, ranging from primary care and emergency room physicians to cardiologists and cardiac imaging specialists [1]. While there are many new approaches to care highlighted throughout this guideline [2], one particularly important theme underlying many of the recommendations is the importance of preventive care and adherence to guideline-directed medical therapy (GDMT) for the treatment and prevention of coronary artery disease (CAD) events. Herein, we discuss 5 noteworthy points in the 2021 AHA/ACC/Multisociety Chest Pain Guideline that highlight the expanding role of preventive cardiology (Fig. 1).

2. A new emphasis on nonobstructive CAD

In a major step forward, the term *known CAD* in the Guideline now encompasses both obstructive and nonobstructive coronary plaque. Moreover, it also includes patients with coronary artery calcification on a coronary artery calcium (CAC) scan or as an incidental finding on non-gated chest CT. This represents a paradigm shift when compared with prior approaches centered on obstructive or flow-limiting CAD. Indeed, approximately 1 in 3 patients with suspected symptomatic CAD who undergo coronary computed tomography angiography (CCTA) may have nonobstructive CAD, which is notably higher in women [3,4]. These patients have a substantially higher event rate than patients without any CAD [3,5].

Numerous recent studies have reinforced the importance of identifying and treating individuals with nonobstructive CAD. In a registry of over 3,000 patients who underwent a clinically-indicated CCTA, those with nonobstructive CAD (< 50% stenosis) and extensive plaque,

defined as the involvement of > 4 coronary artery segments, had a similar rate of myocardial infarction (MI) or cardiovascular mortality as those with obstructive CAD without extensive plaque [6]. A study of 23,759 symptomatic patients from the Western Denmark Heart Registry found that patients who had a similar burden of calcified coronary plaque had the same risk of severe cardiovascular events over a median follow-up of 4.3 years, independent of whether they had obstructive CAD or not [7].

Nonobstructive plaques are common culprits for acute coronary events. Among nearly 700 patients with acute coronary syndrome in the Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT) registry, all of whom underwent coronary intravascular ultrasonographic imaging, half of recurrent events in 3 years occurred in plaques with a mean angiographic diameter stenosis of 32% [8]. Similarly, in the Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) study, the majority of patients who experienced an adverse event had underlying plaque (in the CCTA arm), but no ischemia (in the functional testing arm), which implicates non-obstructive plaques as the most likely culprits [9].

The 2021 AHA/ACC Multisociety Chest Pain Guideline draws attention to various aspects related to the diagnosis, evaluation, and management of nonobstructive CAD. There is a class 1 recommendation for GDMT in all patients who are found to have nonobstructive CAD, both in the acute and stable chest pain setting, as well as patients with significant ischemia or obstructive CAD (Table 1). In the evaluation of stable patients with known nonobstructive CAD, the guideline provides a class 2a recommendation for use of CCTA (which can be used to assess for progression of disease and for high-risk plaque features), or stress imaging to diagnose myocardial ischemia when there is extensive non-obstructive CAD with stable chest pain symptoms. Notably, the guidelines state that “Irrespective of the test performed, an overarching goal of the evaluation of symptomatic patients with known

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Fig. 1. Preventive cardiology highlights in the 2021 AHA/ACC/Multisociety Chest Pain Guideline.

nonobstructive CAD is to identify those who would benefit from intensification of preventive therapy, as defined by the 2018 AHA/ACC/Multisociety Cholesterol Guideline and the 2019 ACC/AHA Prevention Guideline.”

3. Use of anatomical testing for CAD to enhance prevention among selected patients with stable chest pain

The advantages of identifying coronary plaque in implementing preventive therapies also extend to various recommendations related to the evaluation of patients with chest pain. In those with stable chest pain and no known CAD, there is a class 1 (LOE A) recommendation for CCTA to diagnose CAD, inform risk stratification, and guide treatment decisions (Table 1). Importantly, there is also a class 1 (LOE B-R) recommendation for stress imaging (stress echocardiography, myocardial perfusion imaging with positron emission tomography/single-photon emission computed tomography, or stress cardiac magnetic resonance imaging) in this population. However, the Guideline highlights a particular group that may benefit from CCTA as compared with stress imaging: those who are < 65 years of age and who are not on optimal preventive therapies. In such patients, anatomical testing with CCTA can

diagnose obstructive disease responsible for symptoms and uncover nonobstructive CAD. The diagnosis of CAD, obstructive or not, should lead to the initiation or intensification of preventive therapies, including more aggressive lifestyle improvements, that may improve patient outcomes [10].

In the Scottish Computed Tomography of the Heart (SCOT-HEART) trial, 4,146 patients with stable chest pain were randomized to standard care with or without CCTA. Standard care included stress ECG in 85% of participants [11]. After a median follow-up of 4.8 years, there was a significant reduction in the primary endpoint of coronary heart disease mortality or nonfatal myocardial infarction in the CCTA group (2.3% vs. 3.9%; HR 0.59; 95% CI 0.41-0.84).

Some critics have pointed out that the difference in initiation of preventive therapies between groups (19.4% for CCTA and 14.7% for standard care alone) may be insufficient to explain a 40% relative risk reduction in the primary endpoint. However, it is likely that the targeted allocation of preventive therapies explains the observed reduction in events in the CCTA arm [12]. Within 6 weeks of testing, medical therapy was altered in only 5% of patients in the standard care group and in < 1% of patients with normal CCTA. In contrast, approximately 50% of patients with obstructive or nonobstructive plaque on CCTA who were

Table 1

Key recommendations related to the diagnosis and management of non-obstructive CAD in the 2021 AHA/ACC/Multisociety chest pain guideline.

COR	LOE	Acute chest pain in patients with nonobstructive CAD
1	A	For intermediate-risk patients with acute chest pain who have known CAD and present with new onset or worsening symptoms, GDMT should be optimized before additional cardiac testing is performed.
2a	B-NR	For intermediate-risk patients with acute chest pain and known nonobstructive CAD, CCTA can be useful to determine progression of atherosclerotic plaque and obstructive CAD.
COR	LOE	Stable chest pain in patients with nonobstructive CAD
1	C-EO	For patients with known nonobstructive CAD and stable chest pain, it is recommended to optimize preventive therapies.
2a	B-NR	For symptomatic patients with known nonobstructive CAD who have stable chest pain, CCTA is reasonable for determining atherosclerotic plaque burden and progression to obstructive CAD, and guiding therapeutic decision-making.
2a	C-LD	For patients with known extensive nonobstructive CAD with stable chest pain symptoms, stress imaging (PET/SPECT, CMR, or echocardiography) is reasonable for the diagnosis of myocardial ischemia.
COR	LOE	Identification of plaque with CCTA or add-on CAC testing in patients with stable chest pain
1	A	For intermediate-high risk patients with stable chest pain and no known CAD, CCTA is effective for diagnosis of CAD, for risk stratification, and for guiding treatment decisions.
2a	B-NR	For intermediate-high risk patients with stable chest pain and no known CAD undergoing stress testing, the addition of CAC testing can be useful.
COR	LOE	CAC testing in low-risk symptomatic patients
2a	B-R	For patients with stable chest pain and no known CAD categorized as low risk, CAC testing is reasonable as a first-line test for excluding calcified plaque and identifying patients with a low likelihood of obstructive CAD.

not on antiplatelet or statin therapy at baseline were initiated on these agents within 6 weeks [12].

In contrast, the PROMISE trial found no difference in the primary endpoint of death, myocardial infarction, hospitalization for unstable angina, or major procedural complications between CCTA and stress testing (67% nuclear stress imaging; 23% stress echocardiography; 10% exercise ECG) among 10,003 symptomatic patients randomized to either strategy [13]. However, a prespecified analysis of 1,908 patients with diabetes demonstrated a reduction in the outcome of CAD death or nonfatal myocardial infarction in patients randomized to CCTA as compared with stress testing (1.1% vs. 2.6%; HR 0.38; 95% CI 0.18-0.79) [14]. Both PROMISE and SCOT-HEART demonstrated an increase in the use of preventive therapies in patients who underwent CCTA compared with stress testing alone [11-14].

Importantly, any potential benefit of CCTA mediated by the use of preventive therapies would only apply to patients who actually have CAD. Due to the lower yield of identifying disease in low-risk patients, the 2021 Chest Pain Guideline recommends deferring testing in low-risk patients (e.g., a pretest probability of obstructive CAD <15%) and instead focusing on testing those who have an intermediate-to-high pretest probability.

4. Add coronary artery calcium to stress testing

The 2021 AHA/ACC/Multisociety Chest Pain Guideline includes a new recommendation to add CAC to stress testing in intermediate-high risk patients with stable chest pain and no known CAD (class 2a). When used in this context, the guideline suggests that CAC testing “can improve risk assessment, reduce diagnostic uncertainty, help detect atherosclerotic plaque, and guide preventive management.”

The potential advantage of adding on CAC testing is highlighted in the PROMISE study, where 83% of participants in the CT arm who experienced an MI or cardiovascular death had a CAC score ≥1 Agatston units. By contrast, only 33% of events in the functional testing arm

occurred in participants with abnormal stress tests [9]. In the 2/3 of patients who had myocardial infarction or cardiovascular death with a normal stress test, the presentation with stable chest pain may have represented a missed opportunity to diagnose CAD and intensify preventive therapies. The other potential opportunity (class 2a recommendation) to enhance risk assessment during stress testing is by the use of myocardial blood flow reserve quantification, a technique which is only available with PET or CMR.

CAC provides a quantitative assessment of the atherosclerotic plaque burden, a powerful risk stratification tool for future cardiovascular events, which is significantly more predictive than risk factors alone [15-17]. In patients with normal SPECT imaging, a CAC >400 is associated with a 3 to 4-fold increase in the adjusted annualized rate of cardiovascular events when compared with patients who have a CAC ≤10 [15]. The addition of CAC to stress testing in patients without known CAD prevents a misleading reassurance of “no CAD” in those with negative stress tests. In fact, up to 56% of patients with normal myocardial perfusion imaging results have at least moderate coronary calcifications, with CAC ≥ 100 Agatston units [18].

5. CAC testing for informing need for further testing and identifying low-risk patients

Another new recommendation which may impact cardiovascular disease prevention in the guideline is the option to use CAC testing in low-risk patients with stable chest pain and no known CAD (class 2a). In this context, CAC can be used to identify patients who have a low likelihood of obstructive CAD in whom further testing can be deferred. However, when CAC is present it can identify the need for further testing in persons who continue to have chest pain, while also indicating the need for preventive therapies.

The prevalence of obstructive CAD in all-comers with stable chest pain referred for CCTA who have a CAC of zero has been reported in the range of 1.5 to 6% [9,19,20]. In the PROMISE trial, only 22 of 1,457 (1.5%) symptomatic patients with a CAC of zero had ≥50% stenosis and only 7 (0.5%) had >70% stenosis by CCTA [9]. The negative predictive value of CAC to rule out future events is also excellent, with a cardiovascular event rate of less than 2.0 per 1000 person-years [9,19,21]. Among 7 studies with 3,924 symptomatic patients with a CAC of zero, the pooled incidence of cardiovascular events was 1.8% over a mean follow-up ranging from 17 to 84 months [22]. In a 13-year follow-up of 1,978 symptomatic patients with a CAC of zero, there were no reported coronary deaths [19].

While the guideline recommends that low-risk patients generally do not require further testing, the option to use CAC testing in this group may represent an opportunity to diagnose CAD and optimize guideline-recommended preventive therapies. In fact, between 50% and 65% of patients with stable chest pain have CAC ≥1 [9,23]. The presence of CAC in patients without prior known CAD may lead to escalation of medical therapy for those in whom their current treatment is not adequate [24].

6. Prevention is the ultimate goal

In the last decade, there has been a substantial increase in medical therapy options for prevention of atherosclerotic cardiovascular events. In addition to the critical role of lifestyle interventions, clinicians now may include multiple pharmacotherapy options proven to reduce cardiovascular events in patients with known CAD, such as antiplatelet agents, low-dose anticoagulation, statin and non-statin lipid lowering therapy, and cardiometabolic agents for patients with diabetes, such as GLP-1 receptor agonists and SGLT-2 inhibitors. Therefore, the 2021 AHA/ACC/Multisociety Chest Pain Guideline appropriately recommends adequate guideline-directed preventive medical therapy in all patients with known CAD, regardless of obstructive vs. nonobstructive status. This recommendation is independent of how the diagnosis was made, whether invasively or non-invasively; by functional or anatomic

testing; with CAC testing or non-cardiac CT scans; or in the setting of acute vs. stable chest pain.

Moreover, there is a large subset of symptomatic patients with known CAD who may be treated with medical therapy *only*. The results of the ISCHEMIA trial showed that patients with stable symptoms, obstructive CAD, moderate or severe ischemia, and no left main disease do not have a reduction in ischemic cardiovascular events or all-cause mortality with an initial invasive strategy of angiography and revascularization when compared with an initial approach of medical therapy alone [25]. As a result, the 2021 AHA/ACC/Multisociety Chest Pain Guideline assigned a class 1 recommendation to intensify preventive and anti-anginal therapies in patients with known CAD who present with stable chest pain, with an option to defer further testing. However, in those with documented high-risk anatomy (left main disease, 3-vessel disease, or 2-vessel disease with proximal left anterior descending involvement) or persistent symptoms unacceptable to the patient with known obstructive CAD, an invasive management strategy is recommended. Similarly, in intermediate-risk acute chest pain patients with known CAD who do not have high-risk anatomy or frequent angina, there is an option to defer testing and intensify GDMT (class 1 recommendation).

In summary, the 2021 AHA/ACC/Multisociety Chest Pain Guideline made important advances in cardiovascular prevention by emphasizing the importance of both nonobstructive and obstructive CAD; recommending approaches to identify anatomical evidence of CAD, whether as an initial testing option or added to stress testing; and highlighting the need for preventive therapy in acute and stable patients with known CAD. Future initiatives and research aimed at implementation of these guideline-directed practices are likely to result in significant improvement in patient outcomes.

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