

## VIEWPOINT

# CCTA Should Be the New Diagnostic Gateway for Evaluating Intermediate-Risk Stable Angina Patients



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The diagnostic paradigm for patients with stable angina pectoris typically involves: 1) a clinical risk assessment which categorizes patients as low, intermediate, or high risk on the basis of factors such as age, sex, and symptoms; and 2) for those patients who are at intermediate/high risk, further diagnostic testing is needed to determine whether the patient has objective evidence of ischemia, anatomic evidence of coronary artery disease (CAD), or both. Coronary computed tomography angiography (CCTA) has evolved as an accurate, noninvasive alternative to invasive coronary angiography (ICA) for determining the presence and anatomic extent of CAD in intermediate-/high-risk patients. However, the practice of using CCTA as an initial diagnostic approach to diagnose and treat CAD has never been compared directly with ICA in a large, randomized cohort. In this viewpoint, we aim to describe the clinical implications of the DISCHARGE (Diagnostic Imaging Strategies for Patients with Stable Chest Pain and Intermediate Risk of Coronary Artery Disease) study, which directly compares outcomes among intermediate-risk patients receiving either CCTA or ICA for the diagnosis and treatment of CAD.<sup>1</sup>

## KEY FINDINGS FROM THE DISCHARGE STUDY

DISCHARGE was conducted in 26 European centers and randomized nearly 3,600 patients with stable angina referred for ICA and intermediate pretest probability of CAD to undergo either CCTA or ICA with a median 3.5-year follow-up. Patients identified as having obstructive and/or nonobstructive disease were treated according to European Society of Cardiology guidelines pertaining to the management of stable CAD, cardiovascular disease prevention, and revascularization. The primary outcome of major cardiovascular events was a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. Key secondary outcomes included major procedure-related complications associated with either imaging modality or revascularization procedures and patient-reported outcomes including angina in the last 4 weeks of follow-up.

In making the anatomic diagnosis of obstructive CAD, both groups had equal rates of obstructive CAD as assessed by CCTA or ICA—approximately 26% of patients in both groups. In terms of subsequent treatment strategies, revascularization (either percutaneous coronary intervention or coronary artery bypass grafting) was performed in more patients assigned to ICA (17.9% vs 13.0% in the CCTA group), while patients in the ICA group experienced a higher rate of intraprocedural complications (1.9%) than those in the CCTA group (0.5%). Despite these treatment effects (higher revascularization rates in the ICA group; no significant difference in medical treatments among both groups, and a higher rate of procedure-related complications in the ICA group), the primary outcome of death, nonfatal myocardial infarction, and nonfatal stroke was similar in both groups (2.1%

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in the CCTA group and 3.0% in the ICA group,  $P = 0.10$ ), as were patient-reported outcomes including rates of angina and quality-of-life scores.

### WHAT CAN WE LEARN FROM THE DISCHARGE STUDY?

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Although the DISCHARGE trial did not meet the prespecified superiority hypothesis of CCTA over ICA for the primary endpoint, the findings reinforce the strengths of an initial CCTA approach in several ways. First, in patients with stable or atypical angina, CCTA excludes a large proportion of patients without obstructive CAD, obviating the need for invasive angiography. Lower rates of ICA are likely to result in less harm and potentially lower costs of care. Second, the DISCHARGE findings should reassure clinicians who are concerned that CCTA is less accurate in making the anatomic diagnosis of obstructive CAD and that reduced accuracy will translate into inferior patient outcomes. Although a higher percentage of patients undergoing CCTA had nondiagnostic findings (5.7% vs 0.3%), the diagnostic “yield” for obstructive disease with CCTA—the proportion of patients found at ICA to have obstructive disease among those identified with obstructive disease on initial CCTA—in the DISCHARGE study was high (nearly 73%) and remarkably consistent with the yield reported in 2 smaller randomized controlled trials with a similar design.<sup>2,3</sup> Third, DISCHARGE clearly demonstrated that CCTA is a safer diagnostic strategy than ICA, with a relative complication rate that is nearly 4-fold lower.

In addition to its comparative safety, the primary advantage of CCTA over ICA is its ability to detect and quantify the atherosclerotic burden of each patient, regardless of the presence or degree of obstruction.<sup>4</sup> We know that identifying patients with early manifestations of coronary atherosclerosis via CCTA will lead to earlier preventive therapies and improved outcomes.<sup>5</sup>

In the DISCHARGE study, the proportion of patients with any CAD (obstructive or nonobstructive) was higher in the CCTA group (61.9% vs 48.1% in the ICA group), seemingly supporting more favorable outcomes in the ICA group, and yet clinical outcomes among the 2 groups were similar. Could this mean that patients who received CCTA benefited from earlier preventive therapies as well? A thorough analysis of optimal medical therapy in DISCHARGE may yield an answer consistent with what we already learned from the SCOT-HEART (Scottish Computed Tomography of the Heart) trial,

ie, more sensitive detection of atherosclerotic coronary disease is associated with lower risk of myocardial infarction than standard of care with longer follow-up.

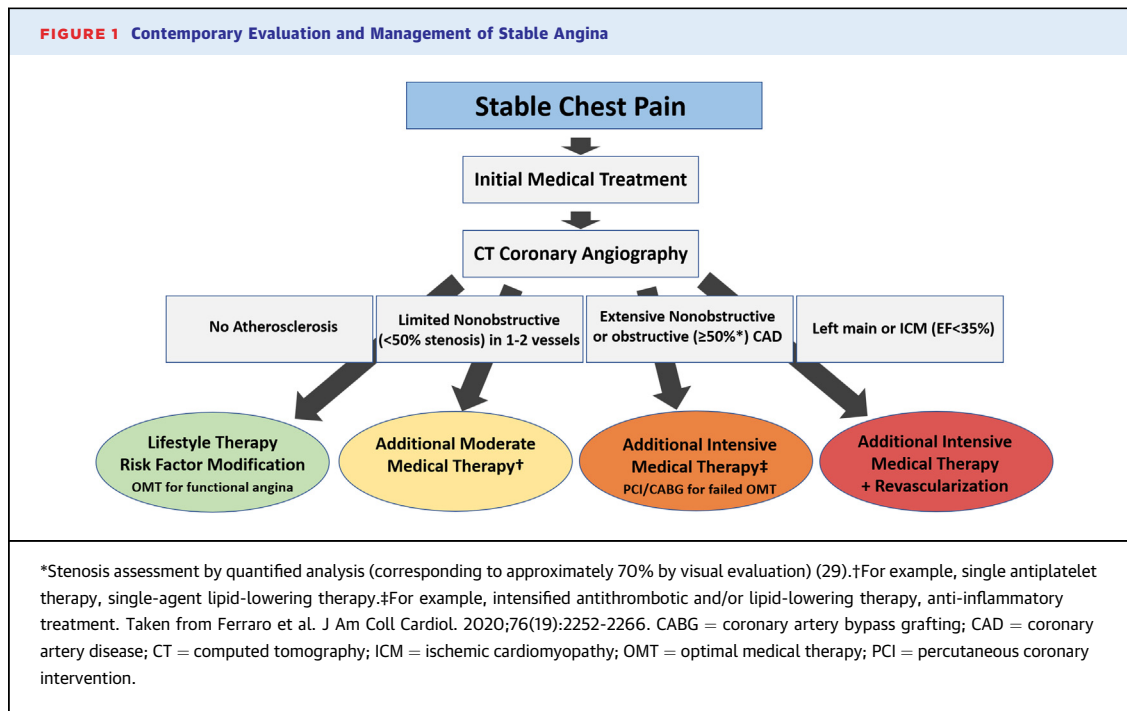
Several prior comparisons of noninvasive imaging in patients with stable chest pain have shown differences in outcomes based on age and sex. A recent substudy of the PROMISE (PROspective Multicenter Imaging Study for Evaluation of Chest Pain) trial, which compared CCTA with noninvasive stress testing, observed that while older (>65 years) patients had a higher prevalence of coronary artery calcium with CCTA than younger patients (<65 years), an elevated coronary artery calcium was only predictive of cardiac events (cardiovascular death or myocardial infarction) in younger patients.<sup>6</sup> In addition, there are important sex differences with respect to the incidence, presentation, pattern, management, and outcomes in patients with CAD.<sup>7</sup> Notably, the DISCHARGE study did not show a clear difference in the primary endpoint or angina alone in prespecified age and sex subgroup analysis (see Supplemental Index Figures S3 and S7 of Maurovich-Horvat et al<sup>1</sup>).

Finally, it is important to note that the DISCHARGE study, as a comparison of diagnostic strategies for CAD and associated clinical outcomes, does not yield additional insight with respect to the optimal treatment strategies in patients identified with either obstructive or nonobstructive CAD by CTA. Due to a lack of well-conducted, prospective, randomized controlled trials, we do not know, for example, what constitutes an optimal medical therapy in patients characterized by CCTA. Building on the results of the DISCHARGE study, CAD management trials based on CCTA are clearly warranted.

### THE CURRENT PARADIGM OF DIAGNOSING STABLE ANGINA PATIENTS WITH INTERMEDIATE RISK USING INVASIVE ANGIOGRAPHY AS AN INITIAL STRATEGY IS NO LONGER THE SOLE EVIDENCE-BASED STRATEGY

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In an accompanying editorial analysis of the DISCHARGE study, Loscalzo<sup>8</sup> describes the current paradigm of treating patients with stable angina, in which patients often undergo ICA as a default strategy with a bias toward performing percutaneous or surgical revascularization for obstructive CAD. This paradigm has been challenged, in part, by the advent of CCTA, which identifies both obstructive and non-obstructive CAD more accurately than noninvasive stress (“functional”) testing. CCTA has been directly



compared with functional stress testing in multiple randomized controlled trials, the largest of which showed no difference in patient outcomes with either strategy.<sup>9</sup>

As the first major randomized comparison of CCTA with ICA, the primary findings in the DISCHARGE study, that patient outcomes are similar regardless of whether CCTA or ICA is used to evaluate stable angina patients, further support the notion that CCTA and ICA are both reasonable and appropriate initial strategies in the evaluation of intermediate-risk patients. The DISCHARGE study findings should empower clinicians to consider CCTA as a prudent, safe, and effective alternative to ICA in their discussions with patients regarding diagnostic options to evaluate stable angina, as suggested in **Figure 1**. The consent process for ICA should include CCTA as an acceptable alternative for patients with stable angina and an intermediate pretest probability for CAD.

**FUTURE CONSIDERATIONS “POST-DISCHARGE”**

As with all trials, the DISCHARGE study leaves many questions unanswered. A cost analysis was not provided which, in times of severe resource constraints, would aid in guiding payers toward appropriate reimbursement decisions—particularly in light of the fact that 38% more patients underwent revascularization with a routine invasive strategy despite a

lack of evidence showing improved patient outcomes. The ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) trial supports an initial conservative strategy even in patients with features formerly considered high-risk (eg, severe inducible ischemia or multivessel CAD), highlighting the importance of an initial “CCTA-first” approach in excluding very high-risk anatomic characteristics, such as left main CAD, to safely facilitate improved diagnostic decision-making.

The diagnostic accuracy of CCTA diminishes in the setting of severe, calcified CAD,<sup>10</sup> and it remains to be seen if CCTA can achieve equipoise with invasive angiography in such high-risk populations. The availability of ultra-high-resolution computed tomography technology now offers similar spatial resolution as invasive angiography with promising early results of high diagnostic accuracy among patients with severe coronary calcification or stents.<sup>11</sup>

**CONCLUSIONS**

For patients with stable angina, the old paradigm of finding obstructive disease and fixing it mechanically via stenting or surgery is no longer evidence-based. We must instead focus on safer means to identify the presence of atherosclerosis, exclude high-risk anatomic groups that might benefit from

revascularization in addition to medical therapy, and initiate proven lifestyle interventions and medical therapies that treat symptoms and reduce cardiovascular events in the great majority of stable CAD patients. DISCHARGE provides another evidence-based study to support CCTA as the preferred noninvasive strategy to evaluate patients with stable chest pain at intermediate pretest probability for CAD and should be viewed as a promising new initial diagnostic gateway to evaluate such patients noninvasively.

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