

The ISCHEMIA trial: Implications for non-invasive imaging

 Amina Rakisheva^{1,2},  Mohamed Marwan¹,  Stephan Achenbach¹

¹Department of Cardiology, Friedrich Alexander University Erlangen-Nürnberg (FAU); Erlangen-Germany

²Department of Cardiology, Scientific Institution of Cardiology and Internal Diseases; Almaty-Kazakhstan

ABSTRACT

Coronary artery disease (CAD) is highly prevalent and constitutes the single most common cause of death worldwide. However, the diagnosis of CAD remains challenging. There are two ways to approach the diagnosis of CAD, namely (1) by a functional non-invasive stress test to detect ischemia (stress echocardiography, stress cardiovascular magnetic resonance, single-photon emission computed tomography, positron emission tomography) or (2) by imaging for stenosis visualization (coronary computed tomography angiography or invasive coronary angiography). There are also two approaches for treatment: medical treatment and revascularization. The International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial investigated the outcome differences of patients who had moderate to severe ischemia on stress testing and who, after CT angiography, had ruled out left main stenosis and demonstrated at least 1 coronary artery stenosis exceeding 50%. The patients were randomized to an initially conservative treatment versus immediate revascularization. No difference in hard outcomes was found, but angina relief was more effective in the revascularization group. In this article, we explore the implications of the ISCHEMIA trial for non-invasive testing in suspected CAD. (*Anatol J Cardiol* 2020; 24: 2-6)

Keywords: coronary computed tomography angiography, coronary stenosis, ischemia, non-invasive stress test, revascularization

Introduction

There are 2 possible clinical manifestations of coronary artery disease (CAD). The first is chronic coronary syndromes, which are often also referred to as chronic stable coronary artery disease or stable angina. The second is the development of acute coronary syndromes. This explains the 2 major goals of treatment for CAD: reducing the symptoms and related restrictions of daily activities and prevention of acute coronary events, particularly myocardial infarction (MI), with the associated risks of death and heart failure (1). To achieve these goals, available treatment options include optimal medical therapy (OMT) and revascularization. OMT comprises anti-ischemic drugs to relieve symptoms and medication such as antithrombotic agents and statins which mitigate disease progression and reduce the risk of acute coronary events and death. Revascularization can be performed by percutaneous coronary intervention and bypass surgery. According to current guidelines, demonstration of coronary stenoses as well as inducible ischemia is required in order to revascularize patients with stable symptoms using either technique (1).

Consequently, diagnostic approaches to patients with suspected CAD can follow two initial strategies: detection of ischemia or anatomical visualization of the coronary arteries. Different imaging modalities are applied for this purpose (see Figs. 1 and 2). Coronary anatomy can be visualized either noninvasively, by coronary computed tomographic angiography (coronary CTA), or through invasive coronary angiography. Ischemia can be detected by stress echocardiography, stress single photon emission computed tomography, positron emission tomography, and cardiac magnetic resonance. A positive ischemia test often serves as the basis for subsequent coronary angiography. To a large extent, the strong role ischemia testing plays in current guidelines for the management of CAD is based on data demonstrating that when the amount of ischemic myocardium in stress testing exceeds 10% of the left ventricle, patients would benefit from revascularization as opposed to medical therapy alone (2). Notably, this is registry data and not the result of a randomized clinical trial.

In spite of the tremendous clinical importance of CAD and associated management strategies, conclusive evidence as to the benefit of revascularization in patients with CAD and non-

Address for correspondence: Amina Rakisheva, MD, Department of Cardiology, Friedrich Alexander University Erlangen-Nürnberg (FAU); Erlangen-Germany
Phone: +77017446557 E-mail: amina.grakisheva@gmail.com

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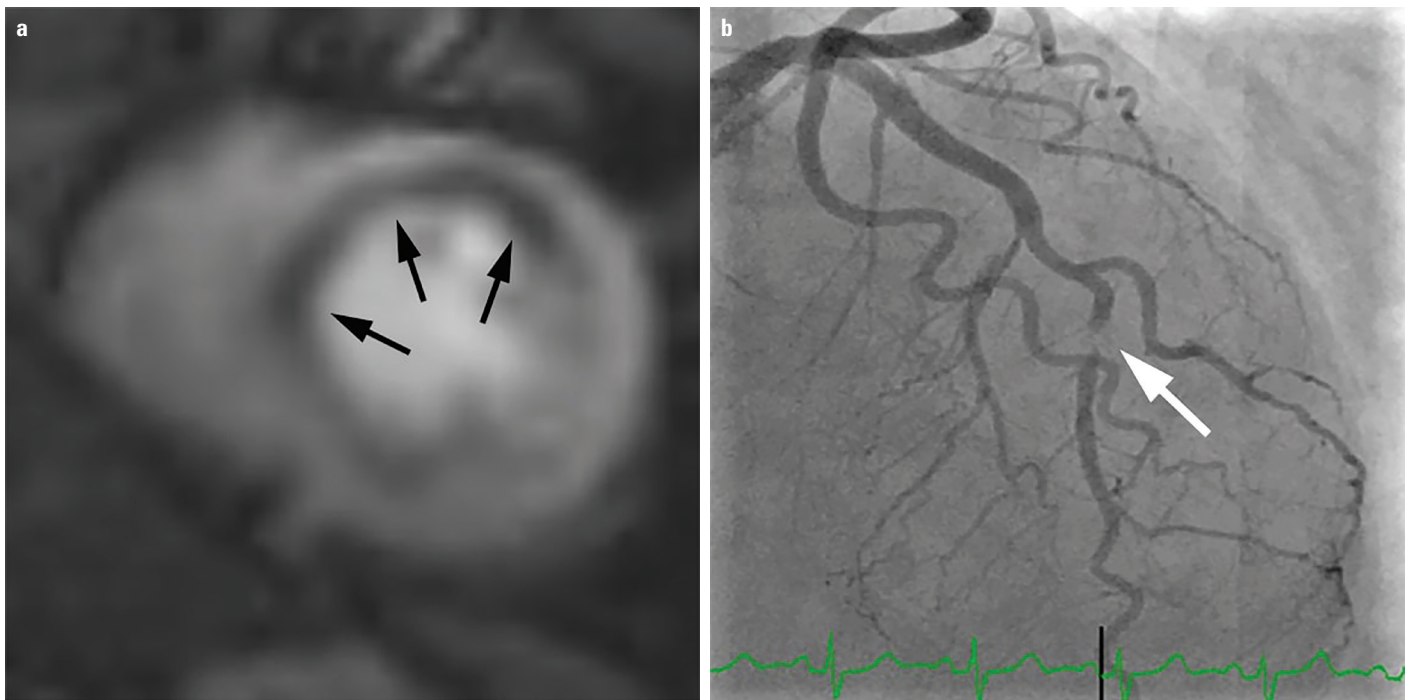


Figure 1. Short-axis view of stress perfusion magnetic resonance (a) showing a perfusion defect in the anterior and anteroseptal segments (arrows). The corresponding invasive coronary angiogram demonstrates a subtotal stenosis of the left anterior descending artery territory (b, arrow)

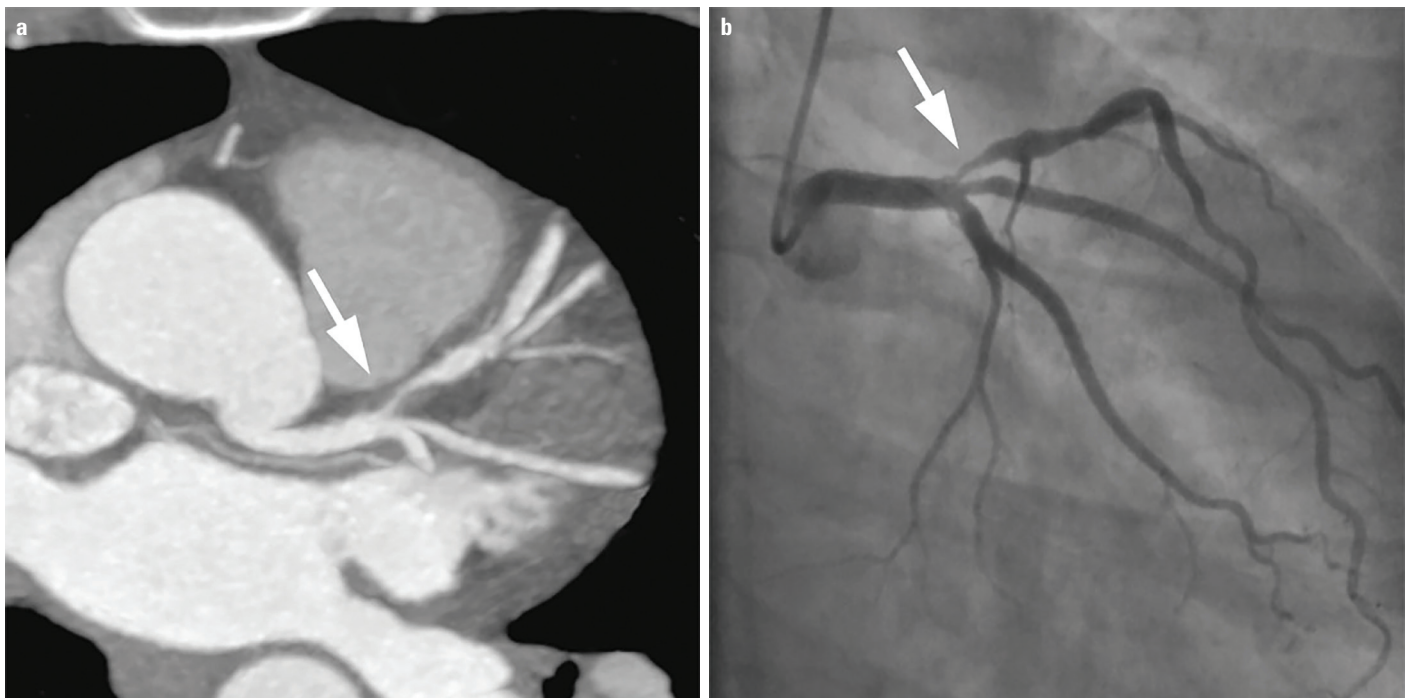


Figure 2. Contrast-enhanced coronary computed tomography angiography (a) showing an obstructive stenosis of the ostial left anterior descending coronary artery (arrow). This corresponds with invasive coronary angiography (b, arrow)

invasive proof of ischemia has been lacking. This prompted the large and complex International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial in patients with moderate-to-severe cardiovascular risk, which aimed to determine whether a routine invasive strategy in addition to OMT would significantly reduce adverse events

compared with an initially conservative strategy of OMT alone, whereby catheterization and revascularization are reserved for cases of medical therapy failure (3). The eligibility criteria for the study included stable CAD, either medically controlled or silent, with moderate-to-severe ischemia confirmed on stress imaging or severe ischemia on non-imaging exercise tolerance testing.

Thereafter, in most qualified participants with an estimated glomerular filtration rate of at least 60 mL/min/1.73 m², coronary CTA was performed for two reasons (3). First, to confirm the presence of at least one stenosis of 50% narrowing or more in a major coronary artery and, secondly, to rule out left main stenosis because randomization of patients with critical left main lesions would have been considered unethical. From a total of 8518 enrolled participants, 3339 were excluded, including 434 because of unprotected left main disease ($\geq 50\%$) and 1218 because of

lack of obstructive CAD. The protocol relied on left main disease being well visualized by coronary CTA, although this can be challenging (see Figs. 3 and 4), whereas “balanced ischemia” can cause difficulties in identifying left main stenoses with non-invasive stress testing, such as nuclear imaging (single photon emission computed tomography) (4).

In the ISCHEMIA trial, 5179 patients were randomized over a period of 6 years, with 2588 patients randomized to the invasive group and 2591 to the conservative group. Overall, 35% of the par-

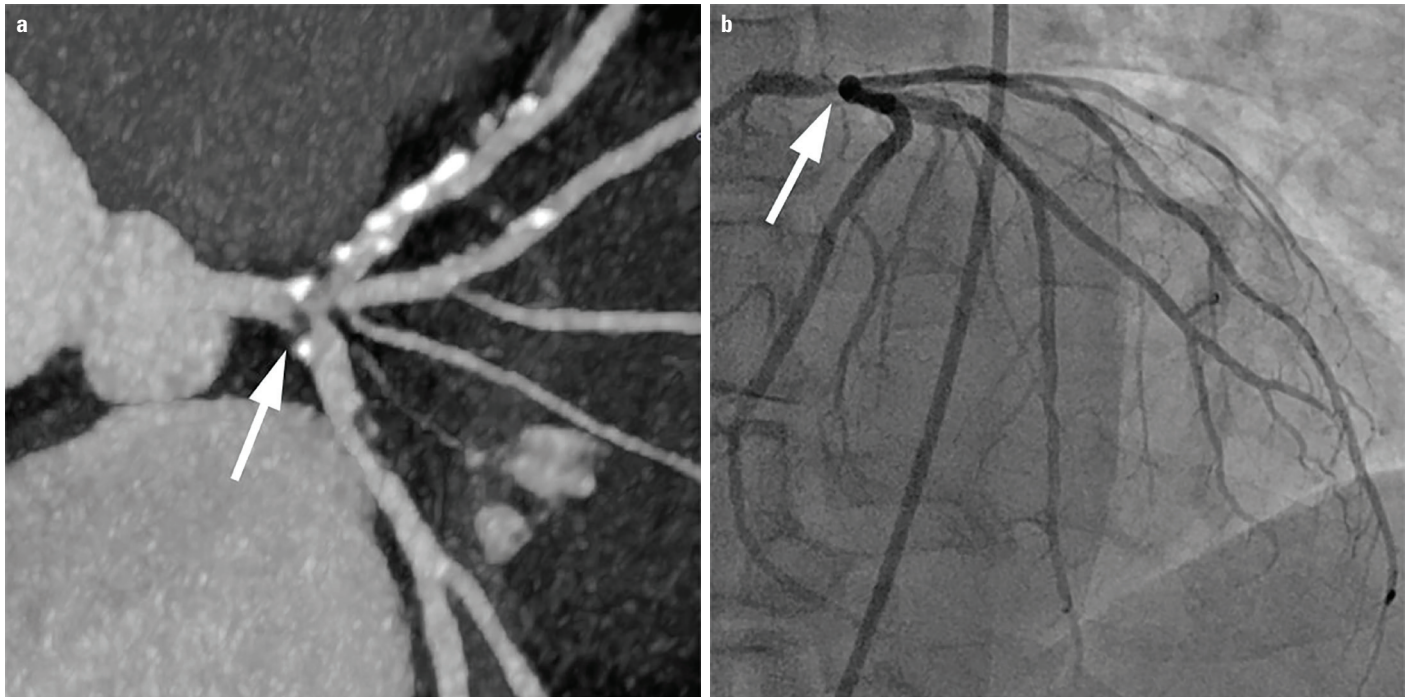


Figure 3. Coronary computed tomography angiography and invasive coronary angiography of a 70-year-old man with a high-grade left main coronary artery stenosis. (a) Coronary computed tomography angiography with maximum intensity projection of the left coronary system (5 mm slab thickness) showing a distal left main stenosis (arrow). (b) Invasive coronary angiography confirming the stenosis (arrow)

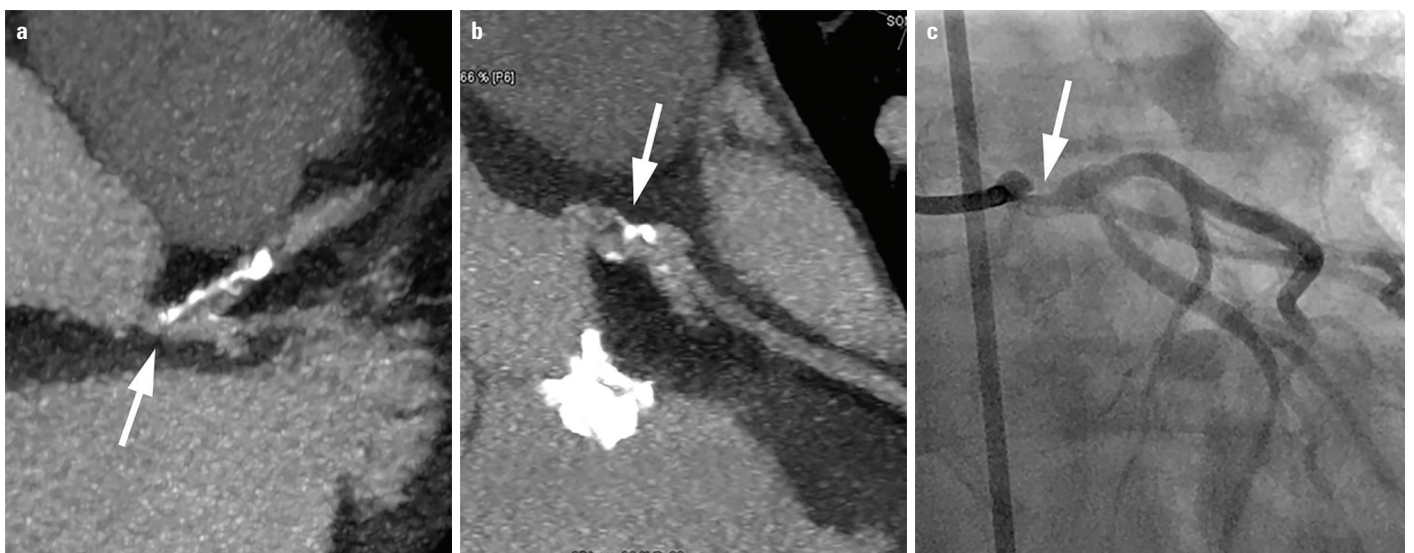


Figure 4. Assessment of left main stenosis can be difficult in coronary computed tomography angiography. Contrast-enhanced coronary CTA (a and b) showing a partially calcified obstructive stenosis of the left main artery (arrow). It is confirmed by invasive coronary angiography (c, arrow)

ticipants had no angina, 44% had angina one to three times per month, and only 20% had daily or weekly angina. Moreover, the Seattle Angina Questionnaire score was 73.4 ± 19.1 in the invasive group and 74.8 ± 18.8 in the conservative group. This indicates that the majority of participants in both arms were asymptomatic or only mildly symptomatic at baseline (5). Predictably, the number of patients who underwent revascularization in the invasive arm was high at 79% (74% percutaneous coronary intervention and 26% bypass surgery), whereas in the conservative arm, revascularization was performed in only 21% of patients (6). Over a median follow-up duration of 3.2 years, the invasive strategy was not superior to the initially conservative strategy in the composite of primary outcome, including death from cardiovascular causes, MI, or hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest (318 and 352 patients, respectively). Interestingly, during the first 6 months, the estimated cumulative event rate was 5.3% in the invasive strategy group and 3.4% in the conservative strategy group [difference, 1.9%; 95% confidence interval (CI), 0.8-3.0]. At 5 years, however, the cumulative event rate was 16.4% in the invasive strategy group and 18.2% in the conservative strategy group (difference, -1.8%; 95% CI, -4.7-1.0). A similar result was observed for the secondary outcome measure of the composite of death from cardiovascular causes or MI and angina-related quality of life with a cumulative event rate of 14.2% in the invasive strategy group and 16.5% in the conservative strategy group (difference, -2.3%; 95% CI, -5.0-0.4). The secondary analysis showed greater improvement in health status scores among patients who underwent the initially invasive strategy. The mean Seattle Angina Questionnaire summary scores for the invasive arm versus the conservative arm were 84.7 ± 16 versus 81.8 ± 17 at 3 months, 87.2 ± 15 versus 84.2 ± 16 at 12 months, and 88.6 ± 14 versus 86.3 ± 16 at 36 months, respectively, which was statistically significant. This difference was mainly due to participants who had experienced angina within 4 weeks before randomization (5).

Interestingly, patients with advanced chronic kidney disease in addition to the other conditions ($n=777$) were included in a separate trial (ISCHEMIA-CKD) with the same inclusion criteria for ischemia. In contrast with the ISCHEMIA trial, however, there was not a recommended coronary CTA or core laboratory review of stress tests (7). Similar to the main trial, there was no evidence of different treatment effects on the primary and secondary outcome in either arm. Over a median follow-up period of 2.2 years, events occurred in 123 patients in the invasive strategy group and in 129 patients in the conservative strategy group (adjusted hazard ratio, 1.01; 95% CI, 0.79-1.29; $p=0.95$). Results for the key secondary outcome were similar (38.5% vs. 39.7%; hazard ratio, 1.01; 95% CI, 0.79-1.29). In addition, the invasive arm was associated with a higher incidence of stroke than the conservative arm (hazard ratio, 3.76; 95% CI, 1.52-9.32; $p=0.004$), as well as a higher combined incidence of death or dialysis onset (hazard ratio, 1.48; 95% CI, 1.04-2.11; $p=0.03$). Mortality from any cause occurred in 94 patients in the invasive arm versus 98 in the conservative arm (24.2 vs. 25.2%; hazard ratio, 1.02; 95% CI, 0.76-1.35) (7).

Regarding the use of non-invasive testing for the diagnostic workup of CAD, the results of the ISCHEMIA trial may seem disappointing. After all, according to clinical practice, a prognostic benefit of revascularization has thus far been assumed in patients with a positive ischemia testing result. The ISCHEMIA trial failed to provide that evidence. Nevertheless, the trial provides several interesting findings in terms of non-invasive imaging. In fact, the trial design underscores how difficult it is to establish the diagnosis of CAD. The complex patient enrollment protocol required both moderate-to-severe ischemia confirmed by functional tests and coronary stenoses in coronary CTA, whereas left main stenosis needed to be excluded. Of note, even in patients with moderate-to-severe ischemia according to non-invasive testing, computed tomography ruled out the presence of any coronary obstruction 50% or greater in approximately 20% of cases, which confirms previous meta-analyses that demonstrated a superior diagnostic performance of coronary CTA to identify coronary stenoses that stress testing, which evaluates myocardial perfusion (8-10). As a major advantage in the design of both the ISCHEMIA and ISCHEMIA-CKD trials compared with previous trials, randomization was carried out before coronary angiography was performed, thereby reducing the likelihood of bias (11).

From a clinical prospective, these findings are the basis for several conclusions. The protocol and results of the ISCHEMIA trial nicely confirm what has already found in the most recent European Society of Cardiology Clinical Practice Guidelines for the Diagnosis and Management of Chronic Coronary Syndromes. It may be a very reasonable approach to perform coronary CTA first (1). If not all patients with positive ischemia tests benefit from revascularization, then it may make a lot of sense to perform another, more definitive test first; coronary CTA in this case. This makes sense particularly in patients with relatively low pre-test likelihood, again as suggested by the current guidelines (1).

As outlined above, ischemia testing may have resulted in false-positive findings in a number of cases. CTA eliminated some of these patients. But even then, a 50% stenosis threshold to label a computed tomography scan as positive may have been too low, as many stenoses of 50% are not associated with ischemia (12, 13).

The ISCHEMIA trial also highlights the importance and effectiveness of current OMT. Strict risk modification in both arms may explain part of the discrepancies when compared with the results of Hachamovitch et al. (2), as well as the lack of demonstrable benefit of revascularization on events. In that context, the ability of computed tomography to identify non-stenotic atherosclerosis (see Fig. 5) and in this way to identify patients who may benefit from prognosis-modifying therapy may be of particular interest (2, 10, 14).

Summary

Despite some uncertainties, the ISCHEMIA trial provides several important findings regarding the contemporary manage-

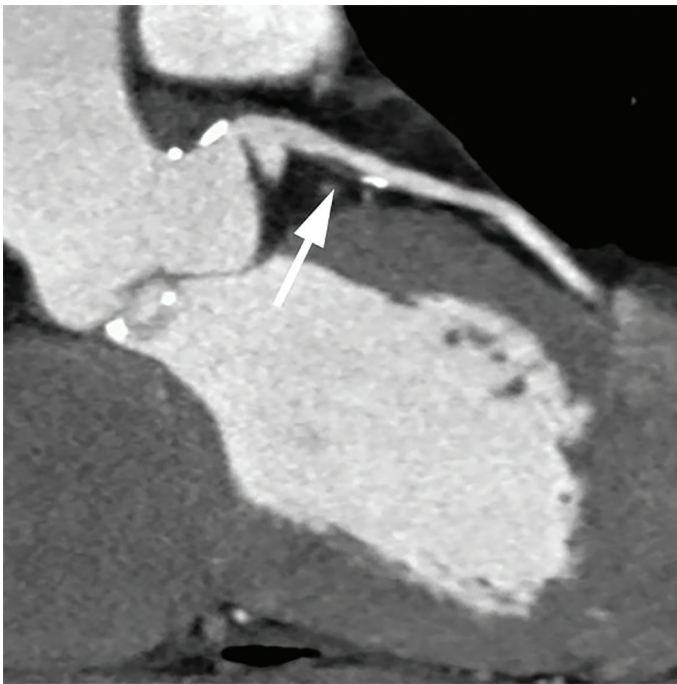


Figure 5. Contrast-enhanced coronary computed tomography angiography showing partially calcified non-obstructive coronary atherosclerotic plaque in the proximal left anterior descending artery (arrow)

ment of CAD. Both strategies, conservative and invasive, remain valuable for the management of patients with CAD. The use of OMT in asymptomatic or mildly symptomatic patients, who fit the ISCHEMIA profile, can be an initial strategy with favorable prognosis. In symptomatic patients with frequent anginal episodes, an invasive strategy would be a reasonable complementary approach to OMT for effective symptom relief.

The ISCHEMIA trial design does not allow for assessing the value of ischemia testing (because there was no control group without ischemia testing or with a negative stress test), but it does highlight the increasing importance and relevance of coronary CTA relative to ischemia tests and it strongly lends credibility to a strategy of coronary CTA first, particularly in low-risk patients if they are suitable candidates for coronary CT angiography.

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