Errare humanum est, perseverare autem diabolicum

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Abstract
The initial evaluation of patients with suspected chronic angina is supported by the use of noninvasive tests and risk stratification models, which aim to identify obstructive coronary artery disease (CAD). Therefore, comparative effectiveness trials, testing the ability of a noninvasive strategy to increase the diagnostic yield for obstructive CAD have drawn increasing interest. However, after an initial increase in the diagnostic yield, there remains a significant discrepancy in results from noninvasive tests and those from coronary angiography, the latter being considered the gold standard technique for diagnosing CAD. These findings are in line with the new paradigm for ischemic heart disease, with obstructive CAD considered only one among many other determinants. With that in mind and given also the low, but persistent, risk for adverse events and the increasing costs associated with invasive management, is it appropriate to continue investing major research efforts on the development of a strategy that identifies and removes obstructive CAD? ■ *Heart Metab*. 2017;72:44-46

Keywords: comparative effectiveness of noninvasive diagnostic strategies; coronary artery disease; ischemic heart disease; percutaneous coronary intervention

The traditional understanding of stable coronary artery disease (CAD) is that this disease causes exercise- and/or stress-related chest symptoms that are caused by a 50% or greater narrowing of the left main coronary artery and/or a 70% or greater narrowing of one or several of the major coronary arteries.[1] Therefore, identification and removal of obstructive CAD is a main therapeutic target.

At initial presentation, the diagnosis of angina pectoris is supported by the use of noninvasive tests and risk stratification models.[1,2] Thus, comparative effectiveness trials that test the ability of a noninvasive strategy to improve the rate of diagnosis of obstructive CAD at subsequent angiography have gained increasing interest.[3] The CE-MARC 2 study (Clinical Evaluation of Magnetic Resonance Imaging in Coronary Heart Disease 2), recently published in the *Journal of the American Medical Association*, tested the hypothesis that cardiac magnetic resonance (CMR)-guided care is superior to UK national guidelines (National Institute for Health and Care Excellence [NICE]-guidelines)-directed care and myocardial perfusion scintigraphy (MPS)-guided care in reducing the occurrence of unnecessary invasive angiography in patients with suspected ischemic heart disease (IHD).[4] Patients randomized to the NICE-guidelines–directed care were scheduled for cardiac computed tomography if the pretest likelihood for CAD was low (10%

Abbreviations

CAD: coronary artery disease; **CE-MARC 2:** Clinical Evaluation of Magnetic Resonance Imaging in Coronary Heart Disease 2; **CMR:** cardiac magnetic resonance; **IHD:** ischemic heart disease; **MPS:** myocardial perfusion scintigraphy; **NICE:** National Institute for Health and Care Excellence

to 29%), underwent MPS if the pretest likelihood for obstructed CAD was intermediate (30% to 60%), or were directly sent to coronary angiography if the likelihood for obstructed CAD was high (61% to 90%). Patients randomized to the CMR-directed–care and MPS-directed–care groups underwent initial evaluation with CMR and MPS, respectively, and those with positive results were directed to coronary angiography. The primary end point was unnecessary coronary angiography, defined as a normal fractional flow reserve value (or computed angiographic assessment) for all vessels of 2.5 mm or more in diameter. At 12 months from inclusion, 42.5% of patients receiving NICE-guidelines–directed care underwent coronary angiography (34% because of a pretest likelihood of >61%, and the remaining because of a positive test result or physician judgment). The initial test result was deemed positive in 12.4% of patients in the CMR group and 18.2% of patients in the MPS group; respectively, 17.7% and 16.2% of them underwent coronary angiography. An unnecessary angiography was performed in 28.8% of patients included in the NICE-guidelines-directed–care group, 7.5% of patients in the CMR-directed–care group, and 7.1% of patients in the MPS-directed–care group. There was no significant difference in revascularization rates or major cardiovascular events between the three groups. Authors concluded that investigation by CMR and MPS resulted in a lower probability of unnecessary angiography as compared with NICE-guidelines–directed care.

The use of CMR and MPS significantly lowered the rate of negative coronary angiograms in the CE-MARC 2 study; however, when considering only the patients undergoing coronary angiography, the results are not that gratifying. Indeed, the rate of unnecessary angiography was 67.6% (69 of the 102 patients undergoing coronary angiography) in the guidelines-directed group, 42.3% (36 of the 85 patients) in the CMR group, and 43.5% in the MPS group (34 of the 78 patients).

CE-MARC 2 is only the last of a long series of studies investigating the role of noninvasive strategies in diagnosing IHD.[5] Noninvasive tests are used for detection and/or assessment of the functional significance of epicardial stenosis. Similarly, the clinical pretest probability cited in major guidelines unconditionally refers to the probability of detecting CAD by coronary angiography.[6,7] In line with previous studies,[3] these findings confirm that, despite the adoption of progressively sophisticated tests and clinical prediction tools, there remains a significant divergence between the results from noninvasive strategies and those from invasive coronary angiography. Additionally, other studies have documented a high grade of variability among different noninvasive strategies.[8,9] These findings are in line with the new paradigm for IHD, which considers obstructive CAD to be only one among many other determinants. Therefore, excluding or confirming obstructive CAD should not be the sole focus when evaluating a patient with suspected heart disease. In line with these considerations, there are two main issues with this approach. Firstly, only a minority of patients with chest pain will have obstructive CAD detected at coronary angiography,[3,10-13] with as many as 55% to 75% of men and 75% to 90% of women with typical angina displaying no or mild CAD.[14] Additionally, stable coronary plaques can be completely clinically silent.[9,15,16] Secondly, contrary to expectations, revascularization by means of percutaneous coronary intervention performed in chronic IHD patients has a limited, if any, impact on prognosis.[17-19] Indeed, whereas the risk of major cardiovascular events is known to increase with increasing CAD burden, this risk does not appear to be reduced by percutaneous coronary intervention.[15,20]

Therefore, with the current attitude, we might be neglecting the patient subset with angina and no obstructive CAD and are probably overtreating those with obstructive CAD. Given also the low, but persistent, risk for adverse events and the increasing costs associated with invasive management, is it appropriate to continue investing major research efforts in developing the best strategy to identify and remove obstructive CAD? Instead of repeatedly praising the modest results of a single strategy, shouldn't we take advantage of these tools and look carefully at the determinant factors behind the discordant results. This could be a first step toward a better understanding and treatment of patients with suspected chronic IHD. ■

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