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EDITORIAL

Why We Might Not Need to Stress About Ruling Out Inducible Myocardial Ischemia

In patients with symptoms of stable angina, cardiac stress testing and angiography have been recommended to evaluate for inducible myocardial ischemia and obstructive coronary artery disease (CAD). Walter and colleagues (1) investigated whether high-sensitivity cardiac troponin (hs-cTn) tests could be introduced in this diagnostic pathway. Because of the tests' high sensitivity for detecting myocardial injury, negative results are used to rule out acute coronary syndrome in patients presenting with acute chest pain, allowing safe discharge home from the emergency department (the tests' clinical utility for ruling in myocardial infarction is more uncertain [2]). Walter and colleagues (1) hypothesized that hs-cTn tests could be used in a similar way in patients with stable angina, such that a negative result would safely rule out inducible myocardial ischemia without the need for further tests.

They tested this hypothesis in a well-conducted diagnostic accuracy study of 1896 consecutive patients who had been referred to a single treatment center for stress testing using myocardial perfusion imaging with single-photon emission computed tomography or computed tomography. The investigators used 3 different assays to measure hs-cTn in blood samples that had been taken before stress testing and processed by personnel blinded to clinical data. Adjudication of inducible myocardial ischemia was based on expert interpretation of imaging for all 1896 cases, combined with information obtained from invasive coronary angiography and fractional flow reserve measurements in the 405 cases where this information was available. The authors found that the diagnostic accuracy of hs-cTn to identify inducible myocardial ischemia was low, and no cutoff level provided the predefined minimum negative predictive value and sensitivity of at least 90% (defined on the basis of acceptable risk for false-negative results as a safety threshold [3]). Patients with low pretest probability (for example, those with <20% risk as judged by the treating clinician, women without hypertension, and women without previous myocardial infarction) came close to meeting these specified criteria for ruling out disease without further testing, but they tended to represent only a small proportion of the study population (7%, <1%, and 8%, respectively).

Under the current diagnostic pathway, patients with a positive result on a stress test are referred for invasive coronary angiography, and a decision is made whether revascularization may be beneficial—particularly if the patient is already receiving maximal antiangina medical therapy. However, approximately half of patients with angina and an abnormal result on a stress test do not have obstructive CAD on angiography, and women are more likely than men to have negative findings on an angiogram (4). The cause of symptoms in these patients may be coronary microvascular dysfunction, conduit arterial vessel stiffness, or diffuse atherosclerosis of both the macro- and microvasculature. Optimizing risk factor management through lifestyle change and medical therapy is the mainstay of treatment of nonobstructive CAD (4, 5).

Recent evidence from randomized trials questions whether revascularization via percutaneous coronary intervention is beneficial, even for patients with obstructive CAD, including those who have moderate or severe ischemia on stress testing (6). Randomized controlled trials in patients with stable obstructive CAD who are receiving optimal medical therapy have found no evidence that percutaneous coronary intervention reduces risk for an ischemic event (6, 7) or that it reduces symptoms more than a sham procedure (8). This raises the question of whether symptoms of stable CAD have been wrongly attributed to obstructive CAD found on tests, when the nonobstructive CAD causes just outlined may be the true culprits (5). The evidence for benefit from detection of obstructive CAD and subsequent revascularization is clear in patients with acute coronary syndrome and in those with severe stenosis of the left main coronary artery. Evidence also suggests that in selected patients with stable CAD receiving optimal medical therapy, revascularization via coronary artery bypass grafting reduces risk for myocardial infarction—perhaps reflecting treatment of atherosclerotic plaques throughout the diseased vessel rather than just a discrete lesion (5).

So how do we interpret the findings of the current study on hs-cTn in light of the limited clinical utility of identifying inducible myocardial ischemia and obstructive CAD? In the setting of imperfect reference standards, the concept of the "fair umpire" may help us work out when a new test may be better than the existing test (9). The clinical consequences of the new test can be understood by applying a fair umpire test to cases where the old and new tests disagree—that is, to patients with a positive hs-cTn result and negative findings on a stress test or angiogram, or those with a negative hs-cTn result and positive findings on a stress test or angiogram. The study presents data on an umpire test that we can use to assess the implications of the discordant test results in these patients: prognosis or risk for adverse clinical outcomes. In both patients with and those without inducible myocardial ischemia, higher hs-cTn concentrations were associated with a higher cumulative incidence of cardiovascular death, all-cause death, and nonfatal acute myocardial infarction. From the Kaplan–Meier curves presented, a positive result for inducible ischemia seemed to add to the prediction of revascularization beyond hs-cTn level, likely reflecting the influence of this result on the decision for revascularization (operators were not blinded

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to results for inducible ischemia). For cardiovascular death and all-cause death, the curves show larger differences across hs-cTn quartiles than between inducible and noninducible ischemia test results, suggesting that hs-cTn may in fact be a better prognostic test in patients with stable CAD than the existing reference standard of stress test and angiography. This prognostic ability is supported by the findings of a recently published study that included more than 240 000 patients without acute coronary syndrome and found strong associations between troponin levels and mortality (10).

If identifying coronary artery stenoses for revascularization does not benefit patients with stable CAD but may cause them harm (through complications of percutaneous coronary intervention), is it a diagnosis we actually want to make? Walter and colleagues (1) conclude that hs-cTn concentrations cannot safely exclude inducible myocardial ischemia, and by implication stable obstructive CAD, but the bigger question is whether it needs to be excluded in the first place. Rather, should the focus of testing in patients with stable CAD be on safely ruling out significant pathology, such as left main artery disease (revascularization likely to have net benefit), while preventing unnecessary invasive tests and interventions (likely to have net harm) in most patients? Whether hs-cTn has a role in such a triage process remains unclear.

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