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EDITORIAL COMMENT

The Shape of Imaging in the Future

Lessons Learned From the CRESCENT II Trial*

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Trials comparing anatomic versus functional testing for coronary artery disease (CAD) are helping us better understand the clinical role of each of these modalities. However, large trials are difficult to conduct, and this calls for novel innovations in study design, strategies of care, and clinical endpoints. One emerging strategy has been tiered testing, in which a simpler, low-cost test is used to trigger subsequent testing, as exemplified by the CRESCENT-I (Comprehensive Cardiac CT versus Exercise Testing in Suspected Coronary Artery Disease) trial (1). In this trial, the investigators devised a computed tomography (CT)-based strategy that used coronary calcium scanning followed by selective coronary CT angiography and compared this strategy with low-cost exercise testing in terms of clinical effectiveness at 1 year of follow-up. Unique features of their first trial were the focus on optimizing low-cost procedures, such as coronary calcium and exercise testing, and the use of broad clinical endpoints reflecting clinical worsening that were tailored for patients with stable chest pain. The CRESCENT-I trial revealed that selective coronary CT angiography was more effective and reduced evaluation costs of care when compared with stress testing (2). In fact, patients in the CT arm of the trial were more often angina-free ($p = 0.012$) and had fewer events ($p = 0.004$) than patients who underwent functional testing. This trial yielded important results that set the standard for selective imaging approaches.

In the issue of *iJACC,* the CRESCENT-II trial investigators Lubbers et al. (1) expand on their earlier evidence by comparing a strategy of index calcium scanning followed by selective coronary CT angiography and, finally, including dynamic CT myocardial perfusion imaging. The CT evaluation strategy limited any follow-up testing to patients with abnormal findings; such that coronary CT was limited to those patients with detectable calcification, and CT myocardial perfusion imaging was limited to those patients with obstructive CAD. In CRESCENT-II, this CT-based strategy was compared with a functional testing strategy (largely including exercise testing)

SEE PAGE 1625

with the primary endpoint being use of invasive coronary angiography in a patient not meeting American College of Cardiology Class I indications for coronary revascularization within 6 months of follow-up. Class I indications included the following: 1) ischemia in the setting of left main or proximal left anterior descending coronary artery stenosis or multivessel CAD with impaired left ventricular function; 2) moderate to severe ischemia encumbering 10% or more of the myocardium; or 3) persistent or worsening anginal symptoms despite optimized medical therapy. By 6 months of follow-up, only 2 of 130 patients randomized to the CT strategy as compared with 10 of 138 patients randomized to the functional testing arm of the trial met the primary endpoint ($p = 0.035$). This is a challenging p value to interpret when <10% ($n = 9$) of those patients randomized to functional testing had abnormal test results, and, as such, most referrals to coronary angiography were likely inappropriate. The lack of guideline-directed care identified in the functional testing arm of the trial is difficult to interpret and may reflect the "real-world" pragmatic nature of the trial. Previous imaging trials failed to guide post-test decisions, as is common among other trials of stable ischemic heart disease (3,4). We believe that there must be some guidance and data collection on nonadherent clinical practices that result in overuse or inappropriate use of coronary angiography. The high rate of nonobstructive CAD

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following stress testing reported in large registries is a compelling argument that physicians need better guidance on whom to refer and when to refer patients undergoing noninvasive testing to invasive coronary angiography (5,6).

By comparison, a total of 19 patients in the CT arm of the trial had ischemia occurring with obstructive CAD. It is striking that so few patients with obstructive CAD had demonstrable ischemia. Our current knowledge of ischemia with and without stenosis is lacking, and these data underscore our paucity of evidence. The CT data are consistent with earlier findings in that nearly 40% had no detectable coronary calcium, and they call into question whether many patients should have undergone a diagnostic imaging evaluation at all (i.e., deferred testing). Our approach to patient selection desperately needs revision and more appropriate tools for identifying at-risk patients. Current pre-test risk scores are challenged and inaccurate in many younger, female, and diverse patient subgroups (7,8). The United Kingdom's guidance document on the evaluation of stable chest pain, which eliminates a formal pre-test risk approach and recommends CT as the index procedure, provides evidence on whether direct imaging may improve patient care (9).

Results from the CRESCENT-II trial revealed a greater need for downstream or induced testing following functional testing (37%), a rate much greater than that of CT (13%; $p < 0.001$). Because most of the patients underwent exercise testing without imaging (95%), follow-up referral to a stress imaging procedure was consistent with a wealth of evidence and is part of guideline-directed testing approaches. Thus, it remains a challenge to criticize what is considered the standard of care for the evaluation of stable ischemic heart disease. Of course, the point of this comparison is to highlight the value and efficiency of CT, and that is noteworthy, but there should be caution in this comparison, given its basis in guideline-directed care.

A final important note for this trial is that there were no differences between the two arms in the rate of clinical events or differences in follow-up angina, including the stability and frequency of symptoms. Recent randomized trials have yielded negative findings when comparing the effectiveness of anatomic with functional imaging strategies (3,4). Currently, we aspire to greater insight into the optimal trial design that fits the risk of an imaging cohort while incorporating aspects of imaging risk markers and their unique contributions to driving optimal clinical management. It is this directed link between an imaging procedure and targeted clinical care that provides the necessary components for improving patients' outcomes. In the CRESCENT-II trial, the CT and functional testing strategies had similar and marked improvements in angina; but without differences in randomization. It would be fascinating to interrogate their data to gather a greater depth of detail regarding who had improved symptoms and what patterns of care resulted in a patient becoming angina-free. We believe that this insight into imaging-guided medical regimens can provide important clues for future trial designs.

So, where do we go from here? It is clear that lack of robust trial evidence is a prominent limitation to wider use of cardiac imaging, and such evidence is needed to optimize imaging in patient care pathways. Conversely, we are not likely to see many large-scale randomized controlled trials in imaging because of the high cost of doing them and the difficulties in controlling nonimaging factors that contribute to outcomes, including downstream use of test information and less than optimum post-test patient care strategies. It is therefore likely that we will see more pragmatic trials with varied clinical endpoints. We have yet to identify trial designs that consistently identify evaluation algorithms of superior or suboptimal effectiveness, safety, or efficiency. It is perhaps time for the imaging community to establish focused discussions on future trial designs, pragmatic yet clinically meaningful trial endpoints, and novel approaches for assessing comparative effectiveness.

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