Editorial

The Essence of STRATEGY Is Choosing What Not to Do

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The essence of strategy is choosing what not to do.
—Michael Porter, Harvard Economist

Clinicians must evaluate on a daily basis patients with symptoms of possible coronary artery disease (CAD). Decades of progress in various technologies used for cardiovascular imaging have produced a wide array of choices, and consequently selecting the best test for a given patient has become increasingly complex. Anatomic techniques to evaluate for CAD include invasive coronary angiography (ICA) or coronary computed tomographic angiography (CTA). However, functional approaches evaluate the myocardial response to exercise or pharmacological stress, often together with imaging. When considering the available functional imaging tests, stress echocardiography and nuclear myocardial perfusion imaging are commonly available and well-established techniques. However, there are now emerging data that stress cardiac magnetic resonance imaging (CMR) may offer comparable, or in some cases superior, diagnostic accuracy.[1] More recently, the CE-MARC 2 trial (Clinical Evaluation of Magnetic Resonance Imaging in Coronary Heart Disease 2) suggested that CMR and nuclear myocardial perfusion imaging may decrease the rate of unnecessary ICA (defined as invasive angiography that results in nonobstructive or nonflow limiting disease) when compared with clinical evaluation using the NICE guideline (National Institute for Health and Care Excellence).[2] Importantly, among patients randomized to the NICE guideline group, ≈35% underwent immediate ICA as directed by the guidelines. CE-MARC 2 also demonstrated a strategy of CMR was safe, as the event rate observed in this trial was extremely low and did not differ between the groups compared. These findings, together with others,[3,4] suggest that in stable patients who do not have prior known CAD, noninvasive testing should be performed before invasive angiography.

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Aside from increasing the yield of detecting obstructive CAD on invasive angiography, there are many other important ways in which noninvasive testing can affect patient management and outcomes. For instance, in some clinical settings, negative tests can provide immense reassurance. When abnormal, anatomic tests can provide prognostically important data on the presence and severity of CAD, whereas functional tests can inform clinicians about the severity of myocardial ischemia, data that can be essential for deciding on the potential benefit of coronary revascularization.

When considering all the various objectives of cardiac testing, instead of a 1-test fits all approach, clinicians should select the right test for the right patient. Choosing among the different testing options is no simple task, and the scientific evidence on which to inform our decision remains more limited than we would want. Thus, clinicians and imagers must consider both technical factors that influence the diagnostic accuracy of different techniques and clinical information that influences how the test might affect patient management. Examples of some of the variables that may influence this decision include age, sex, body composition, ability to exercise, contraindications to medications, renal function pretest probability of obstructive CAD, or the presence of prior known CAD. Moreover, clinicians should also consider local availability and expertise as well as economic factors. Although the medical literature does have increasing, albeit sometimes insufficient, evidence comparing various testing strategies among patients with possible CAD symptoms, there is far less evidence about how different tests compare in patients who have CAD and previous coronary revascularization.

In this issue of *Circulation: Cardiovascular Imaging*, Pontone et al[5] report the results of the STRATEGY study (Stress Cardiac Magnetic Resonance Versus Computed Tomographic Coronary Angiography for the Management of Symptomatic Revascularized Patients). In this study, 600 patients with chest pain and previous coronary revascularization were enrolled in a prospective registry. The registry includes 300 patients evaluated by CTA and 300 patients evaluated by stress CMR. The results demonstrated that either test option was feasible, but a diagnostic strategy involving stress CMR versus CTA reduced downstream noninvasive tests (17% versus 28%, $P<0.05$), ICA (20% versus 31%, $P<0.05$), and coronary revascularization (16% versus 24%, $P<0.05$). Those evaluated by stress CMR also received a lower estimated effective radiation, incurred lower cost, and had a reduction in combined cardiovascular events (5% versus 10%, $P<0.01$). These results must be interpreted with caution because this was not a randomized trial, and thus it is possible that various confounders may have been present. For instance, patients who were clinically referred to CTA may have had other characteristics that would influence the decision to proceed with further ICA or revascularization.

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Do the results make intuitive sense? We know from numerous studies of CTA[6–8] that, when compared with physiological testing, anatomic evaluation may lead to increased ICA and coronary revascularization. Presumably, this is because anatomic imaging identifies angiographically obstructive lesions that do not cause functional ischemia but present enticing targets for revascularization. This phenomenon of the oculostenotic reflex has been described for decades and remains a clinical dilemma.[9] Indeed, CTA has a high sensitivity but a low specificity for detecting coronary ischemia,[1] test parameters that may be ideally suited for low to intermediate pretest probability patients[10] who do not have known CAD. However, patients with previous coronary artery bypass graft surgery (CABG) or percutaneous coronary intervention (PCI) are far more likely to have extensive coronary calcifications, which could limit the ability of CTA to detect stenosis (in native coronary vessels) or lead to overestimation of the severity of obstructive disease. With a higher prevalence of inconclusive or anatomically significant CAD, CTA can lead to increased ICA, and coronary revascularization, and subsequently increase cost.[6,7]

The high sensitivity and improved specificity of physiological testing such as stress CMR[1] should be favorable for patient subgroups with known CAD. In such settings, the prevailing clinical questions are (1) are the patient's symptoms related to their underlying CAD? (ie, is there myocardial ischemia?) and (2) would the patient benefit from additional coronary revascularization? (ie, what is the extent and severity of myocardial ischemia?). One of the potential clinical benefits by which CTA could improve outcomes[8] is through intensification of medical therapy for those without known previous CAD,[11] but patients with previous coronary revascularization should already be on aspirin and high potency statin therapy. Thus, a variety of factors explain why functional evaluation by stress CMR may be preferable for most patients with previous PCI or CABG.

Nevertheless, there are possible exceptions when CTA may be more useful than stress CMR. For example, CTA may be useful in clinical scenarios when it is particularly important to evaluate for graft failure, such as when data on native anatomy is already known or if there are other data on the presence or severity of ischemia. In such cases, evaluation for focal graft stenosis by CTA can be performed with a high diagnostic accuracy,[12] owing to the fact that bypass grafts are usually large, rarely calcify, and relatively immobile. CTA also has a high diagnostic accuracy for evaluating in-stent restenosis in large, proximal stents. Accordingly, the appropriateness criteria for CTA rate evaluation of symptomatic or asymptomatic patients with left main stent >3 mm as appropriate and symptomatic patients >2 years post-PCI with other stents >3 mm as uncertain appropriateness, whereas all other stents are classified as rarely appropriate.[13] In the STRATEGY study,[5] there was an average of 2.5 stents per patient, and most of stents evaluated by CTA were large (85% >3.0 mm), although 66% were reportedly overlapping, which may be more challenging to evaluate by CTA. However, this reflects real-world evaluation of stents and not solitary, proximal large stents as enrolled in some accuracy studies.

Stress CMR may be less preferable than the rapid scan acquisition of CTA for patients with claustrophobia or for patients who are unable to tolerate lying flat for the entire examination (≈60 minutes). Finally, patients with cardiac implantable electronic devices, such as pacemaker and debrillator, are generally less preferable to evaluate by stress CMR. Such scans can be safely performed for select devices but require device interrogation pre- and post scan, have a rare chance of device or lead damage, and can result in artifacts that impair image quality.[14] Patients with cardiac implantable electronic device generally should not be referred to CMR, but rather to CTA or alternative physiological testing, such as stress nuclear myocardial perfusion imaging.

However, there may be other compelling indications to perform CMR when other clinical questions may be addressed simultaneously. For example, in patients who have had a previous myocardial infarction (MI) or who have left ventricular systolic dysfunction, CMR—by virtue of visualizing late gadolinium enhancement—can be extremely useful to assess myocardial viability, which cannot be performed on routine CTA.

The results of the study by Pontone et al[5] are informative for several reasons. First, as mentioned above, there is a paucity of published data for selecting between anatomic versus functional imaging for symptomatic patients with previous coronary revascularization. Second, we also lack well-designed comparative cost-effectiveness studies of CTA versus stress CMR. Third, most medical societies have identified a continuously growing public health problem of increasing medical radiation exposure, and all physicians have an obligation to choose practices that can minimize radiation.[15,16] Thus, accurate and cost-effective tests with no ionizing radiation, including stress CMR, to evaluate possible coronary ischemia bear universal appeal, despite the fact that stress CMR is not widely performed.

In addition to concerns about radiation exposure, an additional safety concern for CTA versus stress CMR, is that CT contrast agents, while generally well tolerated by most patients, do have a small risk of anaphylaxis and renal injury. Gadolinium-containing magnetic resonance imaging contrast agents have been associated with nephrogenic systemic fibrosis when given to patients with end-stage renal disease (glomerular filtration rate <30 mL/min per 1.73 m^2) but are otherwise safe.[17,18] Recently, gadolinium deposits have been identified long after contrast magnetic resonance imaging in trace residuum within brain tissue and in other organs, and whether this has any clinical impact warrants further study.[19]

One finding that will require further verification is the reduction in death/MI reported in the STRATEGY study.[5] Interestingly, this difference was not detected in the CE-MARC 2 randomized trial,[2] possibly because of differences in population and trial design. In STRATEGY, there were 31 death/MI (1 death and 30 MI) in the CTA group (n=300) versus 15 (1 death and 14 MI) in the CMR group (n=300), which was significant (P=0.014). Although it may be anticipated that the higher event rate in patients undergoing CTA could be because of events related to revascularization, this study reported that only 5 of the MI in the CTA group and 2 of the events in the CMR group were periprocedural. As readers of the study we remain puzzled as to the exact mechanism that could have accounted for the lower event rate observed in patients undergoing CMR, particularly given the low number of periprocedural events and the fact that the CMR group and the CTA group were reported to be well matched. It seems plausible that the observed difference in event rates in this trial could

have been because of delayed complications of PCI or CABG that were not reported as periprocedural events, or the possibility of residual confounding inherent in this nonrandomized cohort study. Another, albeit less likely, explanation would be if despite undergoing significantly more coronary revascularization, that patients undergoing CTA were less likely to have revascularization of high-risk lesions that caused ischemia if these were somehow missed on coronary computed tomography angiography and only identified on stress CMR.

As with any registry study, one must interpret the results within the context of important limitations. First, and most importantly, the patients were not randomized, and thus randomized trials are needed to further inform us about the optimal diagnosis and management of symptomatic patients with previous coronary revascularization. Next, emerging CTA software postprocessing techniques such as plaque quantification or fractional flow reserve estimated by computed tomography could improve the specificity of a routine CTA.[4] None of these software techniques could be evaluated in this study; however, they all remain in their infancy with regard to clinical experience and they will likely further raise cost of a CTA, so the cost-effectiveness of these techniques will require further evaluation as well. In addition, as the authors noted, the CTA were performed with 64-multidetector scanners. Although these represent the most commonly available CTA technology, newer generation scanners now have the potential to reduce the effective radiation dose of CTA even further. Nonetheless, despite these advances, to effectively evaluate patients with previous CAD, it will be important for future cardiac CT technologies to improve image quality and better mitigate artifacts related to calcium blooming or beam hardening.

The STRATEGY study[5] offers useful results that stress CMR is potentially cost-effective, and in some instances a preferable, option for evaluating patients with previous revascularization. In addition, the results add to previous data that anatomic-based diagnostic strategies are associated with increased downstream ICA and coronary revascularization. In summary, the STRATEGY cohort study demonstrated that for patients with previous PCI or CABG, stress CMR compared with CTA could potentially reduce downstream noninvasive testing, ICA, coronary revascularization, radiation, cost, and adverse clinical outcomes. Although these findings are not from randomized data, they are important and support the use of stress CMR for symptomatic patients with previous PCI or CABG.

Disclosures

None.

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