

Computed Tomography or Functional Stress Testing for the Prediction of Risk

Can I have my cake and eat it?

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The clinician now has an overwhelming array of investigations at their disposal for patients with suspected coronary heart disease. These tests are used to diagnose or to risk stratify patients, and thereby enable the clinician to treat their symptoms and to reduce their future risk. Ultimately, these investigations assess either risk factors (such as lipid, glucose and c-reactive protein concentrations) and proxies for disease (such as carotid intima-media thickness and coronary artery calcium score), or they are looking to provide circumstantial downstream evidence of disease (such as markers of ischemia and infarction: Q waves on an electrocardiogram, fibrosis on magnetic resonance imaging or functional stress testing). In this issue of *Circulation*, Budoff and colleagues¹ compare two of the most widely used approaches, coronary artery calcium scoring and functional stress testing, within the framework of the PROspective Multicenter Imaging Study for Evaluation of chest pain (PROMISE) trial.

Coronary artery calcification is considered pathognomic of atherosclerosis and has been a marker of coronary artery disease for millennia.² Its presence is however a proxy of disease because it is induced in response to atherosclerosis, and, apart from rare calcific nodules, calcification does not directly cause ischemic heart disease events. Indeed, calcification appears to be an adaptive healing response to the necrotic atheromatous plaque whereby the body attempts to limit and contain the disease, much like the calcification of a caseating granuloma from mycobacterium tuberculosis infection. However, calcification does not directly relate to the degree of luminal or functional stenosis of the coronary artery, nor does it necessarily reflect the current status of the plaque since the calcification may be inactive, ongoing or incomplete. Indeed, large areas of inert macrocalcification are associated with plaque

stability whereas spotty calcifications or microcalcifications are associated with high-risk plaques probably because of incomplete calcification.³⁻⁵ Consequently, the presence of coronary artery calcification is a surrogate for the extent of coronary atheromatous plaque, and by inference, the risk of future adverse cardiovascular events. Its major strength is its sensitivity and high negative predictive value with the absence of coronary artery calcification taken to exclude coronary heart disease, the so called 'power of zero'.

Functional stress testing has been at the heart of diagnosing ischemic heart disease for many decades. It has been the investigation of choice for many centers worldwide because not only does it greatly assist in the diagnosis of ischemia as the cause of chest pain, but it can also provide prognostic information and guide coronary revascularisation strategies. Of course, functional stress tests principally diagnose the presence of ischemia due to flow-limiting obstructive coronary artery disease. As such, these tests describe the functional consequences of the disease rather than the disease itself. In this regard, it is important to remember that myocardial ischemia is not necessarily specific for coronary artery disease since it can occur in the absence of epicardial coronary obstruction, such as with microvascular angina or marked left ventricular hypertrophy. Nevertheless, the major strength of functional testing lies in its specificity for severe coronary artery disease. The more territories and the greater the extent of the ischemia, the more severe the underlying obstructive coronary artery disease and the greater the future risk will be. The shortcomings of perfusion imaging relate to the prediction of acute thrombotic cardiovascular events, especially in patients with milder disease. This reflects the fact that most acute coronary events occur on non-obstructive coronary plaques that cannot be detected by myocardial



perfusion imaging. Furthermore, reversible ischemia does not play a pathogenic role in the causation of thrombotic coronary artery occlusion and type 1 myocardial infarction. In contrast, it may have a role in type 2 myocardial infarction where there is an imbalance between myocardial blood supply and demand that drives ischaemic tissue infarction. However, this area is under researched, and we currently do not know how best to identify and to manage the causes of type 2 myocardial infarction.

The contrasting strengths and weaknesses of coronary artery calcification and functional stress testing are nicely drawn out by this current analysis of the PROMISE trial. Budoff and colleagues clearly describe the reassuring prognostic benefits of a zero calcium score with an event rate of ~1%. However, zero calcium scores cannot be relied upon in symptomatic individuals as non-calcific obstructive plaque may be the underlying cause. These non-calcified plaques tend to occur in younger patients with new onset symptoms and relatively dynamic plaques.⁶ As such, they are an important potential high-risk sub-group to identify and this is one of the areas where the supremacy of coronary computed tomography angiography is demonstrated. The current analysis also confirmed the poor specificity of coronary artery calcium scoring. Calcification is not synonymous with flow obstruction and increased calcification does not necessarily equate with current disease activity. Indeed, progression of coronary calcification occurs following initiation of statin therapy^{7,8} and, if representative of plaque stabilisation and healing, increasing calcification of an individual plaque may be protective.³ The greater use of statins in those with increased coronary artery calcification may also have influenced the predictive power of the calcium score and this may have led to some underestimation of reported risk.¹

The functional testing strategy reaffirmed its strength in identifying patients with the highest risk. The 365 patients with a severely abnormal functional test result had the highest cardiovascular death and myocardial infarction rates of all the sub-groups, underlining the superior specificity of this approach to identify those at greatest risk. However, the overall hazard ratios were similar to those observed across the entire range of abnormal coronary artery calcium scores. Moreover, functional testing lacked sensitivity for the risk of cardiovascular death and myocardial infarction, with most events occurring in those with a normal test. The inclusion of unstable angina did appear to improve performance of the functional testing strategy, but in the modern era of high-sensitivity troponin assays, unstable angina is becoming rarer and often reflects ischemia from stable obstructive disease (more suited to functional stress testing) rather than true plaque rupture events. Finally, functional stress testing did provide additive discrimination to the Framingham risk score, something that only coronary artery calcium score has previously achieved. In contrast, many other biomarkers, including carotid intimal media thickness and c-reactive protein, have been disappointing with no or negligible added value.⁹

How should we use these findings by Budoff and colleagues? Their analysis highlights the differing strengths of these two approaches and will help make the selection of investigations clearer. If the primary purpose of the investigation is to identify low-risk individuals and exclude coronary artery disease to avoid unnecessary treatment and further investigation, then coronary calcium score would seem more appropriate. If the purpose is to identify the highest risk individuals perhaps to guide the risk of non-cardiac surgery or more intensive and advanced therapies, then a functional test would seem more appropriate.

For many, it is the reliable identification of the right patient for the right treatment, and both coronary artery calcium score and functional testing strategies are unable to achieve this for all patients in all circumstances. The PROMISE group have recently demonstrated the superiority of coronary computed tomography angiography over functional testing for the prediction of future cardiovascular events.¹⁰ Here some of the shortcomings of coronary calcium scoring are overcome, and this begs the question, should we abandon coronary artery calcium scoring for coronary computed tomography angiography? With modern volume scanners, imaging protocols have improved and, in many centers across the world, the radiation dose for coronary computed tomography angiography is comparable or even lower than that for coronary artery calcium scoring.¹¹ The use of intravenous contrast and the modestly higher costs should not be an impediment for the vast majority of patients undergoing scanning in accredited centers. It will be interesting to see what role coronary artery calcium scoring will have for symptomatic patients in the modern area of coronary computed tomography angiography.



One size does not fit all. Whilst we wish to avoid unnecessary testing and reduce redundancy, we should play to the mutual strengths of sensitivity for computed tomography and specificity for functional testing. Indeed, combining a simple low-cost functional test, such as exercise treadmill electrocardiogram, with a coronary computed tomography angiogram perhaps provides the best of both worlds. Indeed, the addition of coronary computed tomography angiography to an exercise treadmill electrocardiogram markedly increases discrimination (c-statistic rises from 0.79 to 0.91).¹² Furthermore, this strategy appears to have been successful in reducing

cardiovascular events in the Scottish COmputed Tomography of the HEART (SCOT-HEART) trial,^{13,14} although the 5-year clinical outcomes of this trial are awaited and will be reported next year. We also need to consider a ‘no testing’ option. The recent update to the National Institute for health and Care Excellence (NICE) guidelines for the investigation of chest pain has recommended that no testing is required in patients with non-anginal symptoms and a normal electrocardiogram.¹⁵ This excludes more than a third of individuals presenting for the evaluation of stable chest pain and, in those selected for testing, appears to confer the greatest benefit from testing and improvements in outcomes.¹⁶

This latest analysis by Budoff and colleagues highlights the complementary and contrasting strengths of both computed tomography and functional stress testing for patients with symptoms suggestive of coronary artery disease. For me, I would like to have both approaches available before deciding how to manage my patient with typical or atypical chest pain symptoms. Yes, I want to have my cake and eat it.



Disclosures

DEN was the Chief Investigator of the SCOT-HEART trial.



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