

Computed Tomography or Functional Stress Testing for the Prediction of Risk

Can I Have My Cake and Eat It?

Article, see p 1993

David E. Newby, DM, PhD

The clinician now has an overwhelming array of investigations at his or her disposal for patients with suspected coronary heart disease. These tests are used to diagnose or risk-stratify patients and thereby enable the clinician to treat their symptoms and reduce their future risk. Ultimately, these investigations either assess risk factors (eg, lipid, glucose, and C-reactive protein concentrations) and proxies for disease (eg, carotid intima-media thickness and coronary artery calcium score) or are looking to provide circumstantial downstream evidence of disease (eg, markers of ischemia and infarction: Q waves on an ECG, fibrosis on magnetic resonance imaging or functional stress testing). In this issue of *Circulation*, Budoff and colleagues¹ compare 2 of the most widely used approaches, coronary artery calcium scoring and functional stress testing, within the framework of the PROMISE trial (Prospective Multicenter Imaging Study for Evaluation of Chest Pain).

Coronary artery calcification is considered pathognomonic 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 because 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 it not only greatly assists in the diagnosis of ischemia as the cause of chest pain but also can provide prognostic information and guide coronary revascularization strategies. Of course, functional stress tests principally diagnose the presence of ischemia resulting from flow-limiting obstructive coronary artery disease. Therefore, 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

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

Correspondence to: David E. Newby, DM, PhD, British Heart Foundation Centre for Cardiovascular Science, Room SU314, Chancellor's Bldg, 49 Little France Crescent, Edinburgh, Scotland EH16 4SA. E-mail d.e.newby@ed.ac.uk

Key Words: Editorials
■ tomography, x-ray, computed

© 2017 American Heart Association, Inc.

because 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 is 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 nonobstructive 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 in which there is an imbalance between myocardial blood supply and demand that drives ischemic tissue infarction. However, this area is underresearched, and we currently do not know how best to identify and 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 the present analysis of the PROMISE trial. Budoff and colleagues¹ clearly describe the reassuring prognostic benefits of a zero calcium score with an event rate of $\approx 1\%$. However, zero calcium scores cannot be relied on in symptomatic individuals because noncalcific obstructive plaque may be the underlying cause. These noncalcified plaques tend to occur in younger patients with new-onset symptoms and relatively dynamic plaques.⁶ Therefore, they are an important potential high-risk subgroup to identify, and this is one of the areas in which the supremacy of coronary computed tomography angiography is demonstrated. The present 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 after the initiation of statin therapy,^{7,8} and if representative of plaque stabilization and healing, increasing calcification of an individual plaque may be protective.³ The greater use of statins in those with increased coronary artery calcification also may 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 subgroups, 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 appeared to improve the 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 provided additive discrimination to the Framingham risk score, something that only the coronary artery calcium score has previously achieved. In contrast, many other biomarkers, including carotid intima-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?¹ Their analysis highlights the differing strengths of these 2 approaches and will help make the selection of investigations clearer. If the primary purpose of the investigation is to identify low-risk individuals and to 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 noncardiac 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 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 to 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 era of coronary computed tomography angiography.

One size does not fit all. Although 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 ECG 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 ECG 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 SCOT-HEART trial (Scottish Computed Tomography of the Heart),^{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 guidelines for the investigation of chest pain recommends that no testing is required in patients with nonanginal symptoms and a normal ECG.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 colleagues¹ highlights the complementary and contrasting strengths of both computed tomography and functional stress testing for patients with symptoms suggestive of coronary artery disease. 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

Dr Newby was the chief investigator of the SCOT-HEART trial.

AFFILIATION

British Heart Foundation Centre for Cardiovascular Science, University of Edinburgh, UK.

FOOTNOTES

Circulation is available at <http://circ.ahajournals.org>.

REFERENCES

- Budoff MJ, Mayrhofer T, Ferencik M, Bittner D, Lee KL, Lu MT, Coles A, Jang J, Krishnam M, Douglas PS, Hoffmann U; on behalf of the PROMISE Investigators. Prognostic value of coronary artery calcium in the PROMISE Study (Prospective Multicenter Imaging Study for Evaluation of Chest Pain). *Circulation*. 2017;136:1993–2005. doi: 10.1161/CIRCULATIONAHA.117.030578.
- Thompson RC, Allam AH, Lombardi GP, Wann LS, Sutherland ML, Sutherland JD, Soliman MA, Frohlich B, Mininberg DT, Monge JM, Vallodolid CM, Cox SL, Abd el-Maksoud G, Badr I, Miyamoto MI, el-Halim Nur el-Din A, Narula J, Finch CE, Thomas GS. Atherosclerosis across 4000 years of human history: the Horus study of four ancient populations. *Lancet*. 2013;381:1211–1222. doi: 10.1016/S0140-6736(13)60598-X.
- Motoyama S, Kondo T, Sarai M, Sugiura A, Harigaya H, Sato T, Inoue K, Okumura M, Ishii J, Anno H, Virmani R, Ozaki Y, Hishida H, Narula J. Mul-

tilislice computed tomographic characteristics of coronary lesions in acute coronary syndromes. *J Am Coll Cardiol*. 2007;50:319–326. doi: 10.1016/j.jacc.2007.03.044.

- Joshi NV, Vesey AT, Williams MC, Shah AS, Calvert PA, Craighead FH, Yeoh SE, Wallace W, Salter D, Fletcher AM, van Beek EJ, Flapan AD, Uren NG, Behan MW, Cruden NL, Mills NL, Fox KA, Rudd JH, Dweck MR, Newby DE. ¹⁸F-fluoride positron emission tomography for identification of ruptured and high-risk coronary atherosclerotic plaques: a prospective clinical trial. *Lancet*. 2014;383:705–713. doi: 10.1016/S0140-6736(13)61754-7.
- Irkle A, Vesey AT, Lewis DY, Skepper JN, Bird JL, Dweck MR, Joshi FR, Gallagher FA, Warburton EA, Bennett MR, Brindle KM, Newby DE, Rudd JH, Davenport AP. Identifying active vascular microcalcification by (18)F-sodium fluoride positron emission tomography. *Nat Commun*. 2015;6:7495. doi: 10.1038/ncomms8495.
- Marwan M, Ropers D, Pflederer T, Daniel WG, Achenbach S. Clinical characteristics of patients with obstructive coronary lesions in the absence of coronary calcification: an evaluation by coronary CT angiography. *Heart*. 2009;95:1056–1060. doi: 10.1136/hrt.2008.153353.
- Houslay ES, Cowell SJ, Prescott RJ, Reid J, Burton J, Northridge DB, Boon NA, Newby DE; Scottish Aortic Stenosis and Lipid Lowering Therapy, Impact on Regression trial Investigators. Progressive coronary calcification despite intensive lipid-lowering treatment: a randomised controlled trial. *Heart*. 2006;92:1207–1212. doi: 10.1136/hrt.2005.080929.
- Raggi P, Davidson M, Callister TQ, Welty FK, Bachmann GA, Hecht H, Rumberger JA. Aggressive versus moderate lipid-lowering therapy in hypercholesterolemic postmenopausal women: Beyond Endorsed Lipid Lowering with EB T Scanning (BELLES). *Circulation*. 2005;112:563–571. doi: 10.1161/CIRCULATIONAHA.104.512681.
- Kavousi M, Elias-Smale S, Rutten JH, Leening MJ, Vliegenthart R, Verwoert GC, Krestin GP, Oudkerk M, de Maat MP, Leebeek FW, Mattace-Raso FU, Lindemans J, Hofman A, Steyerberg EW, van der Lugt A, van den Meiracker AH, Witteman JC. Evaluation of newer risk markers for coronary heart disease risk classification: a cohort study. *Ann Intern Med*. 2012;156:438–444. doi: 10.7326/0003-4819-156-6-201203200-00006.
- Hoffmann U, Ferencik M, Udelson JE, Picard MH, Truong QA, Patel MR, Huang M, Pencina M, Mark DB, Heitner JF, Fordyce CB, Pellikka PA, Tardif J-C, Budoff M, Nahhas G, Chow B, Kosinski AS, Lee KL, Douglas PS; PROMISE Investigators. Prognostic value of noninvasive cardiovascular testing in patients with stable chest pain: insights from the PROMISE trial (Prospective Multicenter Imaging Study for Evaluation of Chest Pain). *Circulation*. 2017;135:2320–2332. doi: 10.1161/CIRCULATIONAHA.116.024360.
- André F, Fortner P, Vembar M, Mueller D, Stiller W, Buss SJ, Kauczor HU, Katus HA, Korosoglou G. Improved image quality with simultaneously reduced radiation exposure: knowledge-based iterative model reconstruction algorithms for coronary CT angiography in a clinical setting. *J Cardiovasc Comput Tomogr*. 2017;11:213–220. doi: 10.1016/j.jcct.2017.02.007.
- Versteylen MO, Joosen IA, Winkens MH, Laufer EM, Snijder RJ, Wildberger JE, Crijns HJ, Narula J, Hofstra L. Combined use of exercise electrocardiography, coronary calcium score and cardiac CT angiography for the prediction of major cardiovascular events in patients presenting with stable chest pain. *Int J Cardiol*. 2013;167:121–125. doi: 10.1016/j.ijcard.2011.12.016.
- Scottish Computed Tomography of the HEART (SCOT-HEART) Trial Investigators. Computed tomography coronary angiography in patients with suspected angina due to coronary heart disease. *Lancet*. 2015;385:2383–2391.
- Williams MC, Hunter A, Shah AS, Assi V, Lewis S, Smith J, Berry C, Boon NA, Clark E, Flather M, Forbes J, McLean S, Roditi G, van Beek EJ, Timmis AD, Newby DE; SCOT-HEART Investigators. Use of coronary computed tomographic angiography to guide management of patients with coronary disease. *J Am Coll Cardiol*. 2016;67:1759–1768. doi: 10.1016/j.jacc.2016.02.026.
- National Institute for Health and Care Excellence. *Chest Pain of Recent Onset: Assessment and Diagnosis of Recent Onset Chest Pain or Discomfort of Suspected Cardiac Origin (Update)*. London, UK: NICE; 2016. Clinical Guideline 95.
- Adamson PD, Amanda Hunter A, Williams MC, Shah ASV, McAllister D, Pawade TA, Dweck MR, Mills NL, Berry C, Boon NA, Clark E, Flather M, Forbes J, Scott McLean S, Roditi G, van Beek EJ, Timmis AD, Newby DE. Diagnostic and prognostic benefits of computed tomography coronary angiography using the 2016 NICE guidance within a randomised trial [published online ahead of print August 27, 2017]. *Heart*. doi: 10.1136/heartjnl-2017-311508. <http://heart.bmj.com/content/early/2017/08/16/heartjnl-2017-311508.long>.

Computed Tomography or Functional Stress Testing for the Prediction of Risk: Can I Have My Cake and Eat It?

David E. Newby

Circulation. 2017;136:2006-2008; originally published online August 28, 2017;

doi: 10.1161/CIRCULATIONAHA.117.031178

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Copyright © 2017 American Heart Association, Inc. All rights reserved.

Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://circ.ahajournals.org/content/136/21/2006>

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the [Permissions and Rights Question and Answer](#) document.

Reprints: Information about reprints can be found online at:
<http://www.lww.com/reprints>

Subscriptions: Information about subscribing to *Circulation* is online at:
<http://circ.ahajournals.org/subscriptions/>