A new algorithm for the management of stable coronary artery disease incorporating CT coronary angiography and fractional flow reserve: how we can improve outcomes and reduce costs

Victor Kalff, Stephen J Duffy and Andrew J Taylor

To the Editor: Harper and Ko recently suggested radically changing the way we investigate patients with stable coronary artery disease (CAD), stating that they should initially undergo computed tomography coronary angiography (CTCA), with subsequent stress testing if CTCA shows atherosclerosis.[1] To save costs, they recommend excluding stress nuclear myocardial perfusion imaging (MPI) because it has similar accuracy to stress echocardiography and involves ionising radiation.

To suggest that the available evidence supports CTCA as the first-line investigation of stable CAD is premature, and likely to cause more therapeutic confusion than it resolves. Of particular concern is the assertion that all patients with any detectable atherosclerosis on CTCA should undergo intensive medical therapy for CAD. The clinical significance of mild atherosclerosis detected on CTCA in patients with chest pain that is unlikely to be of cardiac origin is uncertain, with no clinical studies demonstrating a benefit of medical management for CAD based on CTCA findings. Conversely, were such patients investigated first with a stress test, those with a negative test could be reassured that their chest pain is not cardiac and their intermediate-term prognosis is excellent. Importantly, the directive for unproven lifelong medical therapy for CAD is averted.

It is also incorrect to imply that different stress-testing modalities may be seen as equivalent because they have comparable diagnostic accuracies, because their strengths and weaknesses remain complementary. This allows referring physicians to choose the modality that most suits the individual patient. For example, stress echocardiography is more operator-dependent, with known limitations in patients with obesity, airways disease, arrhythmias, poorly controlled hypertension, and contraindications for β-blocker cessation. It also cannot be fused with CTCA images, as myocardial perfusion images can.[2]

While we agree that measurement of fractional flow reserve (FFR) is an extremely important advance in interventional cardiology, it has the limitation of underestimating ischaemia in patients with small-vessel disease (eg, patients with diabetes).[3] We agree that demonstrating ischaemia is the critical component in the decision to perform either percutaneous coronary intervention or coronary artery bypass graft surgery — and until now the largest body of evidence has been accumulated with MPI.[4] Moreover, demonstration of regional ischaemia on MPI associated with an angiographic stenosis obviates the need for FFR. Electrocardiographic stress testing alone cannot provide these localising data.

The advent of CTCA promises to reshape how we assess and manage CAD in the future, but today we should be guided by the clinical evidence, and be mindful not to put the cart before the horse.

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1 Harper RW, Ko BS. A new algorithm for the management of stable coronary artery disease incorporating CT coronary angiography and fractional flow reserve: how we can improve outcomes and reduce costs. *Med J Aust* 2011; 194: 186-189.
2 Gaemperli O, Schepis T, Valenta I, et al. Cardiac image fusion from stand-alone SPECT and CT: clinical experience. *J Nucl Med* 2007; 48: 696-703.
3 Beller GA, Ragosta M. Decision making in multivessel coronary disease: the need for physiological lesion assessment. *JACC Cardiovasc Interv* 2010; 3: 315-317.
4 Hachamovitch R, Rozanski A, Shaw LJ, et al. Impact of ischaemia and scar on the therapeutic benefit derived from myocardial revascularization vs. medical therapy among patients undergoing stress-rest myocardial perfusion scintigraphy. *Eur Heart J* 2011; Jan 21. [Epub ahead of print.] ❑

William J van Gaal and Kevin Allman

To the Editor: Harper and Ko have ignored significant facts regarding myocardial perfusion scintigraphy and made unsubstantiated conclusions regarding computed tomography coronary angiography (CTCA) and fractional flow reserve (FFR).[1]

Their investigation algorithm for suspected and known stable coronary artery disease (CAD) is flawed. By definition, stable CAD patients cannot be categorised into a "suspected CAD" subgroup. CTCA is not an appropriate first-line investigation for patients presenting with atypical chest pain or equivalent syndromes. Being purely anatomical, CTCA cannot determine the functional significance of CAD, rendering it ineffective in intermediate disease. Furthermore, CTCA often overestimates stenoses due to partial voluming and blooming. Guidelines from the United Kingdom National Institute for Health and Clinical Excellence (NICE) state that "questions remain about the ability of multislice CT coronary angiography to accurately identify stenoses of functional significance … in people with stable chest pain".[2] Harper and Ko's algorithm will lead to more investigation, provide no differentiation over and above Step 2 (functional imaging), and increase radiation dose, contrast burden and delays between presentation and definitive treatment.

The real potential of CTCA lies in its ability to non-invasively assess plaque burden and therefore help rationalise long-term pharmacotherapy in high-risk, asymptomatic patients. However, because there is a lack of evidence for this approach, it has been largely ignored and instead the CTCA community has been "sidetracked" into comparing CTCA with functional imaging.

Harper and Ko claim that additional costs from the inevitable increase in CTCA scans would be "minor in comparison to the savings". This is unproven, and not supported by NICE.[2] For atypical symptoms, Harper and Ko recommend "the less expensive ECG [electrocardiogram] exercise test" to risk-stratify patients; however, stress ECG testing is poor at predicting the degree of myocardium at risk, a key factor in risk-stratifying patients. The exercise ECG lacks specificity, leading to unnecessary invasive testing, and many patients are unable to comply. NICE has abandoned exercise ECG testing completely.[2]

The authors state that a "wealth of data has validated the accuracy of FFR". The original papers demonstrating a significant FFR of 0.75 were based on perfusion imaging.[3,4] The review cited quotes a lower sensitivity and specificity of FFR compared with perfusion scintigraphy, and lists scintigraphy as the "clinical gold standard of ischemia".[5] This is because scintigraphy is the most sensitive technique for identifying functionally significant CAD, as it detects the first abnormality in the ischaemic cascade (reduced myocardial perfusion). Furthermore, the exact level of FFR significance (0.75 v 0.80) is debated. In practice, there is a large degree of operator "discretion" in deciding to revascularise, irrespective of the FFR value, which is often "intermediate" in itself. Harper and Ko question the cost of scintigraphy; however, it is more than $300 cheaper than FFR measurement. They overstate the cost of a standard guidewire by threefold.[1]

In just one study of over 5000 patients (three times the population of a recent FFR meta-analysis[6]), increasingly abnormal perfusion scans predicted death and myocardial infarction. There was a reduction in death following revascularisation according to defect severity.[7] The nuclear substudy of the COURAGE trial confirmed this.[8] No study of CTCA or FFR has been able to predict survival with revascularisation, as the technology is unable to define area at risk. Despite this, Harper and Ko conclude that the Medicare rebate for nuclear testing should be abolished. The authors state that "instituting these changes would undoubtedly result in improved outcomes and substantial savings". This comment is opinionated, inflammatory and not based on current evidence. The only reasonable conclusion is that before a rebate for CTCA is even proposed, it should be proven diagnostically and prognostically equivalent to myocardial perfusion scintigraphy in predicting ischaemia.

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1 Harper RW, Ko BS. A new algorithm for the management of stable coronary artery disease incorporating CT coronary angiography and fractional flow reserve: how we can improve outcomes and reduce costs. *Med J Aust* 2011; 194: 186-189.
2 Cooper A, Calvert N, Skinner J, et al. Chest pain of recent onset: assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin. London: National Clinical Guideline Centre for Acute and Chronic Conditions, 2010.
3 Miller DD, Donohue TJ, Younis LT, et al. Correlation of pharmacological 99mTc-sestamibi myocardial perfusion imaging with poststenotic coronary flow reserve in patients with angiographically intermediate coronary artery stenoses. *Circulation* 1994; 89: 2150-2160.
4 Heller LI, Cates C, Popma J, et al. Intracoronary Doppler assessment of moderate coronary artery disease: comparison with 201Tl imaging and coronary angiography. FACTS Study Group. *Circulation* 1997; 96: 484-490.
5 Kern MJ, Samady H. Current concepts of integrated coronary physiology in the catheterization laboratory. *J Am Coll Cardiol* 2010; 55: 173-185.
6 Christou MA, Siontis GC, Katritsis DG, Ioannidis JP. Meta-analysis of fractional flow reserve versus quantitative coronary angiography and noninvasive

imaging for evaluation of myocardial ischemia. *Am J Cardiol* 2007; 99: 450-456.
7 Hachamovitch R, Berman DS, Shaw LJ, et al. Incremental prognostic value of myocardial perfusion single photon emission computed tomography for the prediction of cardiac death: differential stratification for risk of cardiac death and myocardial infarction. *Circulation* 1998; 97: 535-543.
8 Shaw LJ, Berman DS, Maron DJ, et al. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial nuclear substudy. *Circulation* 2008; 117: 1283-1291. ❑

Peter Karamoskos

To the Editor: Although Harper and Ko's effort at proposing an algorithm[1] to reduce unnecessary cardiac catheterisation and stenting is laudable, it is concerning that they advocate investigating patients with stable coronary artery disease (CAD) using computed tomography coronary angiography (CTCA), with an algorithm, furthermore, that has not been validated in terms of patient outcomes.

The COURAGE trial demonstrated that percutaneous coronary intervention (PCI) provided no survival advantage or reduction in myocardial infarction over 5 years of follow-up compared with optimal medical management in patients with chronic stable angina.[2] PCI provided a relative symptomatic benefit only within the first 3 years. Therefore, it is debatable whether imaging most of these stable patients — much less catheterising them — provides any enduring favourable patient outcomes.

For those who do require intervention, fractional flow reserve (FFR) measurement does obviate unnecessary stenting during a cardiac catheterisation. But why perform CTCA — which cannot diagnose ischaemia — in the first place, only to then perform an expensive invasive catheterisation to compensate for it? Why not diagnose ischaemia with an initial non-invasive stress test (nuclear or echocardiography) and only proceed to catheterisation if revascularisation is warranted, thus also lessening the radiation dose? Modern gamma cameras allow nuclear stress studies with radiation doses as low as 2–3 mSv. Yes, CTCA *can* (as opposed to *does*) achieve comparable doses with prospective gating, but without the left-ventricular function analysis that nuclear or echocardiography studies provide. Advocating the elimination of the rebate for nuclear stress studies is thus premature, if not ill informed.

Harper and Ko's algorithm relies on the assumption that medical therapy is appropriate in asymptomatic patients for *any* degree of coronary atherosclerosis, hence justifying the use of CTCA for its detection. However, there is considerable uncertainty about the benefits of medical therapy for primary prevention in low-risk patients.[3] Furthermore, the use of CTCA has not been validated as a determinant of appropriate medical management leading to favourable patient outcomes. This contention remains speculative.

Indeed, contrary to the claims of CTCA supporters, the United States Centers for Medicare and Medicaid Services has declared that

> there is uncertainty regarding any potential health benefits or patient management alterations from including coronary CTA [computed tomography angiography] in the diagnostic workup of patients who may have CAD. No adequately powered study has established that improved health outcomes can be causally attributed to coronary CTA … the body of evidence is of overall limited quality and limited applicability … in community practice.[4]

Consequently, the technology also poses significant potential to unnecessarily increase the population radiation burden.[5]

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1 Harper RW, Ko BS. A new algorithm for the management of stable coronary artery disease incorporating CT coronary angiography and fractional flow reserve: how we can improve outcomes and reduce costs. *Med J Aust* 2011; 194: 186-189.
2 Boden WE, O'Rourke RA, Teo KK, et al; COURAGE Trial Research Group. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med* 2007; 356: 1503-1516.
3 Taylor F, Ward K, Moore THM, et al. Statins for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev* 2011; (1): CD004816. http://www2.cochrane.org/reviews/en/ab004816.html (accessed Mar 2011).
4 Phurrough SE, Salive ME, Baldwin J, Chin J. Decision memo for computed tomographic angiography (CAG-00385N). Baltimore: Centers for Medicare & Medicaid Services, 2008. http://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=206&ver=17&NcaName=Computed+Tomographic+Angiography&DocID=CAG-00385N (accessed Mar 2011).
5 Redberg RF, Walsh J. Pay now, benefits may follow — the case of cardiac computed tomographic angiography. *N Engl J Med* 2008; 359: 2309-2311. ❑

Nathan Better, Myles B Webb, David L Prior, Steven A Unger and George Larcos

To the Editor: Harper and Ko stress the importance of differentiating the presence of atherosclerosis from ischaemia,[1] a concept that has been well understood for years. We agree that identifying myocardial ischaemia is important in the management of atherosclerosis; there are a variety of well validated non-invasive tools for this, including exercise electrocardiography, stress echocardiography, and nuclear myocardial perfusion imaging (MPI).

However, we have concerns about some of the sweeping changes suggested by the authors — in particular, replacing nuclear MPI with stress echocardiography. While published studies report similar accuracy for these modalities, it is clear that each has strengths and weaknesses. Stress echocardiography is an excellent tool that will often suffice but it is operator-dependent, while MPI is more accurate for single-vessel ischaemia. It is well known that a diagnostic stress echocardiogram cannot be achieved in some patients, so an alternative modality may be required. This is particularly problematic in Australia, where there is no mechanism in place to fund the use of ultrasound contrast imaging.

MPI remains a widely accepted technique globally, with a substantial evidence base to support its diagnostic and prognostic impact. For instance, a negative MPI study is generally associated with a cardiac event rate of < 1% in the following year.[2] Further, its role in directing the mode of treatment on the basis of extent of ischaemia and its cost-effectiveness as the "gatekeeper" to cardiac catheterisation have been amply demonstrated.[3]

The use of radiation in medical procedures is always subject to the ALARA (as low as reasonably achievable) principle, and prescribed doses in Australia are typically lower than those quoted in the American literature cited by Harper and Ko. Recent advances in hardware and software with MPI have achieved additional gains in reducing radiation exposure.[4] The cost of MPI is greater than stress echocardiography, but remains less than angiography and fractional flow reserve (FFR) measurement. Further, Harper and Ko's proposed cost savings will not be realised with their call for an increased use of computed tomography coronary angiography and FFR measurement.

The job of a good clinician is to choose the right test for the patient; in some cases this is a stress echocardiogram but it is often an MPI study, as supported by international guidelines.[5] Thus, readers should be mindful that Harper and Ko's views about replacing nuclear stress tests with stress echocardiography and abolishing the Medicare item number for nuclear stress tests are personal and may be contrary to sound evidence.

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1 Harper RW, Ko BS. A new algorithm for the management of stable coronary artery disease incorporating CT coronary angiography and fractional flow reserve: how we can improve outcomes and reduce costs. *Med J Aust* 2011; 194: 186-189.
2 Hachamovitch R, Hayes S, Friedman JD, et al. Determinants of risk and its temporal variation in patients with normal stress myocardial perfusion scans: what is the warranty period of a normal scan? *J Am Coll Cardiol* 2003; 41: 1329-1340.
3 Freeman MR. Growing evidence that radionuclide imaging identifies management strategies that improve outcome. *J Nucl Cardiol* 2009; 16: 844-845.
4 Cerqueira MD, Allman KC, Ficaro EP, et al. Recommendations for reducing radiation exposure in myocardial perfusion imaging. *J Nucl Cardiol* 2010; 17: 709-718.
5 Brindis RG, Douglas PS, Hendel RC, et al. ACCF/ASNC appropriateness criteria for single-photon emission computed tomography myocardial perfusion imaging (SPECT MPI): a report of the American College of Cardiology Foundation Quality Strategic Directions Committee Appropriateness Criteria Working Group and the American Society of Nuclear Cardiology endorsed by the American Heart Association. *J Am Coll Cardiol* 2005; 46: 1587-1605. ❑

Richard W Harper and Brian S Ko

In reply: We thank the authors of these letters for their comments on our article.

In response to Kalff and colleagues, we firmly believe stress testing should be reserved for the *diagnosis of ischaemia* in patients with known coronary artery disease (CAD), and computed tomography coronary angiography (CTCA) is the investigation of choice for *anatomical diagnosis of CAD* in patients with suspected CAD. In this, we are supported by recent guidelines from the American Heart Association and others.[1] Most heart attacks occur as a result of plaque rupture in coronary lesions of insufficient severity to cause ischaemia on stress testing, but that would be detected on CTCA.[2] In view of the undoubted benefits of medical therapy in both primary[3] and secondary prevention of CAD events, do Kalff et al seriously suggest that coronary atherosclerosis detected on CTCA should not be treated with proven anti-atherosclerotic therapy?

Regarding comments made by van Gaal and Allman, and Karamoskos, we believe the upfront use of CTCA in our proposed algorithm would substantially decrease downstream referrals for both stress testing and invasive angiography in patients with suspected CAD. The current practice of referrals for invasive angiography based on clinical assessment and functional tests results in a low yield of obstructive disease.[4] Furthermore, we believe the responsible use of CTCA can be promoted by restricting its use to the anatomical diagnosis of CAD as a once-only investigation. Once the diagnosis is established, further functional testing can be pursued if clinically indicated. Multicentre studies designed to determine the optimal role of CTCA are underway and will provide important insights regarding our viewpoint.[5]

Van Gaal and Allman place considerable emphasis on the 5000-patient study of myocardial perfusion imaging.[6] We point out, however, that this was an observational study. In contrast, the FAME study on which we base our views of fractional flow reserve (FFR) was a randomised study.[7] In addition, we are bemused by their statement that "The review cited quotes a lower sensitivity and specificity of FFR compared with perfusion scintigraphy, and lists scintigraphy as the 'clinical gold standard of ischaemia'". To quote directly from the review article:

> … scintigraphy, although considered the clinical gold standard of ischemia, has limitations in identifying the hemodynamic significance of individual lesions in patients with multivessel CAD.[8]

Regarding comments made by Better and colleagues, we believe both stress echocardiography and nuclear stress testing are overused in clinical practice. In most circumstances, a standard electrocardiographic stress test is sufficient to exclude significant ischaemia and thus to determine who should undergo invasive angiography. In circumstances requiring stress imaging, our preference is to perform stress echocardiography, as its accuracy is comparable to nuclear stress testing, with no additional radiation. Notably, in multilesion CAD, none of the stress testing modalities are sufficiently accurate to determine which lesions require intervention.[9,10] Only FFR, a proven cost-effective investigation, can decide this.[9,10]

Rather than putting the cart before the horse, as suggested by Kalff et al, our algorithm provides a horse with the potential to win the Melbourne Cup.

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1 Taylor AJ, Cerqueira M, Hodgson J, et al. ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR 2010 appropriate use criteria for cardiac computed tomography: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the Society of Cardiovascular Computed Tomography, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the American Society of Nuclear Cardiology, the North American Society for Cardiovascular Imaging, the Society for Cardiovascular Angiography and Interventions, and the Society for Cardiovascular Magnetic Resonance. *J Am Coll Cardiol* 2010; 56: 1864-1894.
2 Stone GW, Maehara A, Lansky AJ, et al. A prospective natural-history study of coronary atherosclerosis. *N Engl J Med* 2011; 364: 226-235.
3 Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 2008; 359: 2195-2207.
4 Patel MR, Peterson ED, Dai D, et al. Low diagnostic yield of elective coronary angiography. *N Engl J Med* 2010; 362: 886-895.
5 Min JK, Dunning A, Lin FY, et al. Rationale and design of the CONFIRM (COronary CT angiography EvaluatioN For Clinical outcomes: An InteRnational Multicenter) Registry. *J Cardiovasc Comput Tomogr* 2011. In press.
6 Hachamovitch R, Berman DS, Shaw LJ, et al. Incremental prognostic value of myocardial perfusion single photon emission computed tomography for the prediction of cardiac death: differential stratification for risk of cardiac death and myocardial infarction. *Circulation* 1998; 97: 535-543.
7 Tonino PA, De Bruyne B, Pijls NH, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med* 2009; 360: 213-224.
8 Kern MJ, Samady H. Current concepts of integrated coronary physiology in the catheterization laboratory. *J Am Coll Cardiol* 2010; 55: 173-185.
9 Melikian N, De Bondt P, Tonino P, et al. Fractional flow reserve and myocardial perfusion imaging in patients with angiographic multivessel coronary artery disease. *JACC Cardiovasc Interv* 2010; 3: 307-314.
10 Rieber J, Jung P, Erhard I, et al. Comparison of pressure measurement, dobutamine contrast stress echocardiography and SPECT for the evaluation of intermediate coronary stenoses. The COMPRESS trial. *Int J Cardiovasc Intervent* 2004; 3: 142-147. ❑