

The difference in clinical outcome between the FAME study groups was not driven by small periprocedural infarctions (creatinine kinase MB fraction, 3 to 5 times the normal value). The rates of periprocedural infarction were 3.2% and 2.4% in the angiography and FFR groups, respectively, and did not significantly affect the statistical difference in outcome between the two groups.

In response to the question posed by Garg et al.: we believe that it makes little sense to compare the randomized FAME study with the ARTS II registry, which excluded vessels smaller than 2.5 mm and patients with previous PCI.<sup>1</sup> It seems more appropriate to compare FAME with the only other large, randomized, controlled trial of drug-eluting stents for the treatment of multivessel disease — that is, the recently published Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) study.<sup>2</sup> In the SYNTAX study, PCI was guided by angiography alone. Not surprisingly, the clinical outcome was similar to that in the angiography group in the

FAME study. In contrast, the clinical outcome in the FFR group in the FAME study was similar to that in the group of patients in SYNTAX who underwent coronary-artery bypass grafting (Table 1).

Taken together, the results of the FAME study show how to perform PCI in patients with multivessel disease with a better clinical outcome and at lower cost.

Nico H.J. Pijls, M.D., Ph.D.

Pim A.L. Tonino, M.D.

William F. Fearon, M.D.

Catharina Hospital  
5623 EJ Eindhoven, the Netherlands  
nico.pijls@inter.nl.net

for the FAME Investigators

1. Serruys PW, Ong ATL, Morice MC, et al. Arterial Revascularisation Therapies Study part II — sirolimus-eluting stents for the treatment of patients with multivessel de novo coronary artery lesions. *Eurointervention* 2005;1:147-56.
2. Serruys PW, Morice MC, Kappetein AP et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med* 2009;360:961-72.

## Coronary Angiography by 64-Row CT

**TO THE EDITOR:** In their article on the Coronary Artery Evaluation Using 64-Row Multidetector Computed Tomography Angiography (CORE 64) trial (Nov. 27 issue),<sup>1</sup> Miller et al. rather miss the point of contemporary computed tomographic (CT) angiography, as do Redberg and Walsh in their accompanying Perspective article.<sup>2</sup> CT angiography will never replace catheter angiography in the same manner that CT pulmonary angiography has usurped its invasive counterpart as the standard. Even the use of CT scanners with a steadily rising number of detectors is unlikely to fully overcome the limits on spatial resolution imposed by cardiac motion.

With this in mind, the sensitivity and specificity of CT angiography and its negative predictive value of 83% compare more than favorably with other noninvasive approaches. The role and key benefits of CT angiography — not in the future but now — lie in the avoidance of invasive angiography and its inherent risk of major cardiovascular complications in patients with a low-to-moderate risk of requiring revascularization. Arguing against the use of CT angiography on the basis of cost is illogical. If CT angiography is used judiciously with follow-up catheter angiog-

raphy as needed, it should reduce rather than increase costs in part by removing the medical and legal costs of the complications associated with catheter angiography.

Andrew C. McCulloch, M.B., Ch.B.

Stirling Royal Infirmary  
Stirling FK8 2AU, United Kingdom  
andrew.mcculloch@nhs.net

1. Miller JM, Rochitte CE, Dewey M, et al. Diagnostic performance of coronary angiography by 64-row CT. *N Engl J Med* 2008; 359:2324-36.
2. Redberg RF, Walsh J. Pay now, benefits may follow — the case of cardiac computed tomographic angiography. *N Engl J Med* 2008;359:2309-11.

**TO THE EDITOR:** The comparative evaluation of 64-row CT with selective contrast angiography has a severe shortcoming in that it uses a two-dimensional measurement of vessel diameter, expressed as percent narrowing, which is known to have a very low degree of precision. In addition, such a measure cannot account for the wide variation in local vascular changes that determine the degree of obstruction of flow.<sup>1,2</sup> Unfortunately, Miller et al. are not the first investigators to be misled by “our preoccupation with coronary lumenology,” in the words of some leading cardi-

ologists.<sup>3</sup> The authors used an arbitrary stenosis threshold of 50% as an indicator of obstruction and did not account for the clinical outcome of such a cutoff. They completely disregarded the ability of contrast angiography to identify a delay in regional flow and the existence of relevant collaterals in relation to myocardial injury.<sup>4</sup> Although I agree with the conclusion that multidetector CT angiography cannot replace conventional coronary angiography at present, this conclusion is based on multiple considerations that were not covered in this study.

Sven Paulin, M.D., Ph.D.

Beth Israel Deaconess Medical Center  
Boston, MA 02215

1. Robbins SL, Bentov J. The kinetics of viscous flow in a model vessel: effect of stenoses of varying size, shape, and length. *Lab Invest* 1967;16:864-74.
2. Paulin S. Assessing the severity of coronary lesions with angiography. *N Engl J Med* 1987;316:1405-7.
3. Topol EJ, Nissen SE. Our preoccupation with coronary lumens: the dissociation between clinical and angiographic findings in ischemic heart disease. *Circulation* 1995;92:2333-42.
4. Paulin S. Functional alterations in the coronary circulation as mirrored in the angiogram. *Cardiovasc Intervent Radiol* 1982;5:177-85.

**TO THE EDITOR:** Miller et al. have compared the accuracy of 64-slice CT angiography with conventional angiography for the identification of coronary artery disease. Of the 405 patients who underwent screening, 89 (22%) were excluded from the study because they had a coronary calcium score of more than 600. An additional, undisclosed proportion of patients were excluded because they had a serum creatinine level of more than 1.5 mg per deciliter, a creatinine clearance of less than 60 ml per minute, a history of previous cardiac surgery or recent intervention, atrial fibrillation, heart failure, or a body-mass index (the weight in kilograms divided by the square of the height in meters) of more than 40, among other criteria. These criteria characterize an additional nontrivial proportion of patients with chest pain who could be evaluated for possible coronary disease. In contrast, none of these criteria are necessarily exclusionary for other noninvasive approaches (e.g., myocardial perfusion scintigraphy) for the assessment of hemodynamically significant coronary obstruction. The potentially large proportion of patients who were deemed to be ineligible for coronary assessment on CT angiography prompts the question posed in the Discussion section of the article: What is the role of this test in

the diagnostic algorithm for patients with suspected coronary artery disease?

Stephen K. Gerard, M.D., Ph.D.

Seton Medical Center  
Daly City, CA 94015

**TO THE EDITOR:** Miller et al. conclude that in symptomatic patients with suspected coronary artery disease, CT angiography does not have a sufficient positive or negative predictive value to replace conventional angiography. Two issues merit highlighting in this context. First, whatever its accuracy, CT angiography is unlikely to replace conventional angiography for patients at intermediate or high risk for coronary artery disease because the prospective use of CT angiography in this population would expose a large proportion of patients to the cumulative risks, radiation, and costs associated with undergoing both procedures. Furthermore, previous studies have suggested that CT angiography has the best diagnostic performance in low-risk patients, as evidenced by high positive likelihood ratios and low negative likelihood ratios.<sup>1</sup> Second, as noted by the authors, positive and negative predictive values depend on the prevalence of disease, and it may therefore be more appropriate to present likelihood ratios to describe diagnostic-test performance (positive likelihood ratio, 8.5; negative likelihood ratio, 0.2).

Ganesan Karthikeyan, M.D., D.M.

McMaster University  
Hamilton, ON L8L 2X2, Canada  
karthik2010@gmail.com

1. Meijboom WB, van Mieghem CA, Mollet NR, et al. 64-Slice computed tomography coronary angiography in patients with high, intermediate, or low pretest probability of significant coronary artery disease. *J Am Coll Cardiol* 2007;50:1469-75.

**TO THE EDITOR:** Redberg and Walsh make several unsubstantiated and misleading claims in their Perspective article. CT angiography is a diagnostic test, not a therapeutic intervention, and thus cannot have a direct effect on clinical outcomes, as drugs or devices can.

I fully support clinical trials examining the potential benefit that CT angiography may have for patients. Luckily for Redberg and Walsh, such studies have been performed, and more are in the pipeline. These trials have so far shown that the use of CT angiography has a prognostic value,<sup>1</sup> reduces costs,<sup>2-4</sup> and reduces the length of stay in overcrowded emergency rooms.<sup>3</sup> As for

Redberg and Walsh's statement that CT angiography "bombards patients with radiation," it should be noted that the dose of radiation with prospective gating is now at half the level of that with diagnostic angiography.<sup>5</sup> In addition, newer CT scanning techniques have been devised that maintain full chest angiography at less than 1 mSv of total radiation dose.

It undoubtedly makes sense to scrutinize new technologies and drugs carefully with the public's interest at heart. But it is impractical and inappropriate to assume a lack of benefit for all diagnostic techniques unless large, randomized, outcome-based studies demonstrate direct improvement in outcomes for patients from the outset.

Gabriel Vorobiof, M.D.

Yale University School of Medicine  
New Haven, CT 06520

1. Min JK, Shaw LJ, Devereux RB, et al. Prognostic value of multidetector coronary computed tomographic angiography for prediction of all-cause mortality. *J Am Coll Cardiol* 2007;50:1161-70.
2. Min JK, Shaw LJ, Berman DS, Gilmore A, Kang N. Costs and clinical outcomes in individuals without known coronary artery disease undergoing coronary computed tomographic angiography from an analysis of Medicare category III transaction codes. *Am J Cardiol* 2008;102:672-8.
3. Ladapo JA, Hoffman U, Bamberg F, et al. Cost-effectiveness of coronary MDCT in the triage of patients with acute chest pain. *AJR Am J Roentgenol* 2008;191:455-63.
4. Goldstein JA, Gallagher MJ, O'Neill WW, Ross MA, O'Neil BJ, Raff GL. A randomized controlled trial of multi-slice coronary computed tomography for evaluation of acute chest pain. *J Am Coll Cardiol* 2007;49:863-71.
5. Earls JP, Schrack EC. Prospectively gated low-dose CCTA: 24 months experience in more than 2,000 clinical cases. *Int J Cardiovasc Imaging* 2008 November 25 (Epub ahead of print).

**TO THE EDITOR:** Redberg and Walsh have written one of the most important articles of the year. They clearly point out the need for evaluation of new technology if we are to have the resources to revamp our broken health care system and to cover the many people who are uninsured. I would add that this evaluation should be paid for by the government and performed by researchers who are not beholden to the manufacturers of the technology in question. I would also suggest that the same restrictions apply to drugs that should be tested against current therapies and not a placebo. Only technologies and drugs that are clearly superior and cost-effective should be approved for use and insurance coverage. We, as physicians and citizens, should demand nothing less than evidence-based and cost-effective procedures and treatments for our patients.

William M. Fogarty, Jr., M.D.

Saint Louis University School of Medicine  
St. Louis, MO 63119  
wmfogartyjr@sbcglobal.net

**DRS. LIMA AND MILLER REPLY:** We agree with McCulloch that 64-row CT angiography is an excellent option for selected symptomatic patients with suspected coronary artery disease.<sup>1</sup> Our study was not designed to test multidetector CT angiography as a replacement for conventional angiography but, rather, to compare its diagnostic accuracy with that of conventional angiography, the standard by which noninvasive tests have been established. The test's patient-based area under the curve (AUC) (0.93; 95% confidence interval [CI], 0.90 to 0.96) supports the clinical use of CT angiography in selected symptomatic patients and suggests that such use could reduce unnecessary procedures with their associated risks and costs. Our conclusions aimed to clarify that although CT angiography and the conventional method both use angiography, the role of conventional angiography extends beyond strict diagnosis by guiding revascularization procedures.

Paulin challenges the use of stenosis as measured on conventional angiography as the reference standard for defining obstructive coronary artery disease. We agree on the shortcomings of measurement of vessel diameter by both conventional and CT angiography, given that anatomical measures are inherently limited in assessing the physiological severity of coronary stenosis. Conversely, conventional angiography continues to be the clinical standard for assessing lesions and determining approaches to revascularization. Although there are increasing data supporting adjunctive physiological measurements,<sup>2</sup> conventional angiography that is used in isolation remains the most widely available diagnostic test and the standard against which noninvasive tests are compared.

We agree with Gerard that the exclusion criteria we used in our study reduced the population of patients eligible for CT angiography. This fact does not limit the value of CT angiography to the much larger group of patients who do meet the inclusion criteria. Indeed, all approaches that are used for the noninvasive assessment of coronary artery disease have important benefits and limitations, and alternative diagnostic approaches offer an opportunity to select the best test for

each patient. Moreover, the evolution of CT angiography continues at such a rapid pace that the broadening of the population eligible to undergo such testing appears to be practically inevitable.

Karthikeyan notes the dependence of predictive values on disease prevalence. This highlights our choice of the AUC as the most appropriate index of the performance of CT angiography.<sup>3</sup> Previous studies have not assessed the severity of stenosis on continuous scales and thus have allowed only dichotomous thresholds to be validly applied (predictive values and likelihood ratios). By contrast, we obtained continuous measurements and showed that the robust performance of CT angiography was actually independent of cutoffs above the 50% threshold for stenosis, as shown in Figure 2 of the article. Moreover, in the identification of patients with at least one stenosis of 50% or more, CT angiography had a positive likelihood ratio of 8.4 (95% CI, 5.0 to 14.1) and a negative likelihood ratio of 0.16 (95% CI, 0.10 to 0.28), which reflects its accuracy. Finally, the prevalence of 56% for coronary artery disease among patients in our study extends diagnostic performance to patients who are at intermediate risk for disease.

In summary, we believe that the value of 64-row CT angiography lies in providing the clinician with enough certainty to assist in medical decisions by classifying patients on the basis of whether they may or may not need further invasive procedures.

João A.C. Lima, M.D.

Julie M. Miller, M.D.

Johns Hopkins Hospital  
Baltimore, MD 21287  
jlma@jhmi.edu

for the CORE 64 Investigators

1. Meijboom WB, Meijns MFL, Schuijf JD, et al. Diagnostic accuracy of 64-slice computed tomography coronary angiography: a prospective, multicenter, multivendor study. *J Am Coll Cardiol* 2008;52:2135-44.
2. Tonino PA, De Bruyne B, Pijls NH, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med* 2009;360:213-24.
3. Pepe MS. *The statistical evaluation of medical tests for classification and prediction*. Oxford, England: Oxford University Press, 2003.

**DRS. WALSH AND REDBERG REPLY:** Vorobiof states that because CT angiography is a diagnostic test, it cannot have a direct effect on clinical outcomes. Diagnostic tests are valuable only if their use

leads to a treatment that results in improved clinical outcomes. To date, CT angiography has not been shown to lead to improved clinical outcomes. Vorobiof goes on to state that four trials have shown a potential benefit of CT angiography. However, of these trials, only one was a clinical trial; two were observational studies, and one was a microsimulation model to evaluate cost-effectiveness.

In the sole clinical trial cited by Vorobiof, Goldstein and colleagues compared CT angiography with nuclear stress testing for the evaluation of acute chest pain in 197 patients who presented to the emergency department. Although CT angiography either ruled out or identified coronary artery disease in 75% of the patients, the remaining 25% required stress testing to evaluate lesions of intermediate severity or nondiagnostic scans, which the authors acknowledge as an important limitation of the technology.<sup>1</sup>

One of the two observational studies cited by Vorobiof showed that CT angiography, not surprisingly, predicted an increased risk of death among patients with chest pain.<sup>2</sup> In the second study, a retrospective analysis of a claims database showed that expenditures were lower for patients who underwent CT angiography than for those who underwent single-photon-emission computed tomography, with no difference in adverse cardiovascular outcomes.<sup>3</sup> Although these results are interesting, they do not show that CT angiography improves clinical outcomes.

The goal of the microsimulation study was to evaluate the cost-effectiveness of CT angiography.<sup>4</sup> However, in order to determine cost-effectiveness, actual effectiveness must be known. Since CT angiography has not been shown to be effective in improving outcomes for patients, cost-effectiveness is difficult to determine.

Finally, although prospectively gated, low-dose CT angiography may reduce the dose of radiation, even a lower radiation risk may not be acceptable if the technology does not have a proven benefit.

We agree with McCulloch that the test characteristics of CT angiography compare favorably with those of other technologies and that “arguing against the use of CT angiography on the basis of cost” does not make sense. The concern with CT angiography is not whether the cost is warranted but, rather, whether a technology with-

out a proven benefit and with a potential risk from radiation and possible complications from the pursuit of incidental findings should be covered by insurance, regardless of how much it costs.

Finally, Fogarty emphasizes the importance of having unbiased researchers perform critical evaluations of new technologies and the importance of comparing new technologies with the standard of care. We agree with him entirely.

Judith Walsh, M.D., M.P.H.

Rita F. Redberg, M.D.

University of California, San Francisco  
San Francisco, CA 94143

1. Goldstein JA, Gallagher MJ, O'Neill WW, Ross MA, O'Neil BJ, Raff GL. A randomized controlled trial of multi-slice coronary computed tomography for evaluation of acute chest pain. *J Am Coll Cardiol* 2007;49:863-71.
2. Min JK, Shaw LJ, Devereux RB, et al. Prognostic value of multidetector coronary computed tomographic angiography for prediction of all-cause mortality. *J Am Coll Cardiol* 2007;50:1161-70.
3. Min JK, Shaw LJ, Berman DS, Gilmore A, Kang N. Costs and clinical outcomes in individuals without known coronary artery disease undergoing coronary computed tomographic angiography from an analysis of Medicare category III transaction codes. *Am J Cardiol* 2008;102:672-8.
4. Ladapo JA, Hoffmann U, Bamberg F, et al. Cost-effectiveness of coronary MDCT in the triage of patients with acute chest pain. *AJR Am J Roentgenol* 2008;191:455-63.

## Glucose Control and Vascular Complications in Type 2 Diabetes

**TO THE EDITOR:** Reporting on the results of the Veterans Affairs Diabetes Trial (VADT), Duckworth et al. (Jan. 8 issue)<sup>1</sup> conclude that intensive glucose control in patients with poorly controlled type 2 diabetes had no significant effect on the rates of major cardiovascular events in their study.

In their discussion, the authors do not acknowledge that the assumptions of the prespecified analysis were not met. The observed event rate in the standard-therapy group was 33.5%, much lower than the predicted rate of 40.0%. Also, the observed dropout rate of 14% was much higher than the predicted rate of 5%. Given these event and dropout rates, can the authors provide the actual power of the study to detect the 21% relative difference in the rate of the composite cardiovascular outcome that was initially planned?

It would also be of great interest to know the power of the study to detect a difference of 15% between the groups; this is arguably a clinically meaningful difference and along the lines of the difference that was found in the long-term follow-up of the United Kingdom Prospective Diabetes Study (UKPDS).<sup>2</sup>

A negative finding in an underpowered study should not change the way we think about the importance of glucose control in the prevention of diabetes-related complications.

Salomon Banarer, M.D.

Dallas Diabetes and Endocrine Center  
Dallas, TX 75230  
salomonbanarer@dallasdiabetes.com

1. Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med* 2009;360:129-39.
2. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HAW. 10-Year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008;359:1577-89.

**TO THE EDITOR:** Duckworth et al. report a lack of effect of intensive glucose control on the rates of major cardiovascular events among patients with poorly controlled type 2 diabetes. Their findings echo the findings of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial.<sup>1</sup> However, patients from the two groups received different doses of rosiglitazone (maximal doses vs. half the maximal doses). Two of the major adverse effects of thiazolidinediones in general, and rosiglitazone in particular, are fluid retention and the exacerbation of congestive heart failure; these effects could be dose-dependent.<sup>2</sup> The use of rosiglitazone has been associated with an increased risk of myocardial infarction and death from cardiovascular causes.<sup>3,4</sup> In a patient population such as that in the VADT, with a high prevalence of cardiovascular events at baseline, the potential negative effect of rosiglitazone should not be discounted. The fact that dyspnea, the most common specified serious adverse event, was more frequent in the intensive-therapy group than in the standard-therapy group (11.0% vs. 7.2%,  $P=0.006$ ), raises at least the suspicion of such possible confounding effects. This issue needs to