The OPT-CHF (Oxypurinol Therapy for Congestive Heart Failure) Trial
A Question of Dose

We read the OPT-CHF (Oxypurinol Therapy for Congestive Heart Failure) study results with interest (1). We agree with the authors’ comments regarding the possible reasons oxypurinol did not lead to clinical benefits. However, the issue of dose needs to be emphasized further, as the urate fall from baseline with 600 mg oxypurinol in the OPT-CHF study was ≈26% (2.1 mg/dl [0.12 mmol/l]). Our group has previously demonstrated that with allopurinol 300 mg, a urate fall of 44% (3.0 mg/dl [0.18 mmol/l]) can be achieved; with allopurinol 600 mg, we achieved a mean urate fall of 61% from baseline (4.2 mg/dl [0.25 mmol/l]) (2). Crucially, in this head-to-head comparison, there was a steep dose-response curve between the dose of allopurinol and its beneficial vascular effects (2). This dose-response was also seen in an observational study of heart failure patients, looking at 100 mg versus 300 mg allopurinol (3).

These observations and the degree of urate lowering seen in the OPT-CHF study suggest that the dose of oxypurinol used was well below the optimum dose. In fact, at the Arthritis Advisory Committee Meeting of the Food and Drug Administration (FDA) in June 2004, data from the bioequivalence AAI-US-175 study showed that 600 mg oxypurinol had a relative bioavailability equivalent to 81 mg allopurinol (4). That is less than the usual starting dose of 100 mg and ≈10% of the maximal FDA-allowed dose of 800 mg.

In addition, clinical outcomes in a 6-month trial may be more determined by changes in volume status rather than by improvements in mechanoenergetic uncoupling, left ventricular remodeling, and endothelial function, which would require a longer duration of treatment to change clinical end points, especially in an outcome trial with only 400 patients. Despite these limitations, oxypurinol did appear to benefit high-risk patients with raised urate levels, a finding that underscores the need for larger studies using larger doses.

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Coronary Angiography: Catheter Based or Computed Tomography Based

I read with interest the paper by Meijboom et al. (1) relating to diagnostic accuracy of 64-slice computed tomographic coronary angiography (CTA) and the editorial comment on the limitations of CTA by Nissen (2).

Bluemke et al. (3), in a scientific statement on noninvasive coronary artery imaging, remind us that CTA gives one no option for immediate intervention, does not serve as the only basis for coronary artery bypass grafting (CABG), has no outcome analyses, has angiographic comparisons with small groups pre-selected to undergo both procedures, and has lower spatial resolution compared to catheter-based coronary angiography (CBA); in addition, motion and other artifacts may result in false-negative and false-positive results with CTA, and continuous visualization of the coronaries with CTA is not possible at present on patients with atrial fibrillation or frequent ectopy.

Further limitations as outlined by Nissen (2) are as follows: when CTA is used to visualize the coronary arteries, calcification of the coronaries can cause false-negative and false-positive results, stents make visualization of the coronary lumen difficult, and the predominant risk of CTA is radiation exposure. However, I am told by CTA advocates that radiation reduction strategies such as tube modulation or prospectively ECG-triggered acquisitions are on the horizon (4).

I have no doubt that CTA will become a useful, but limited, diagnostic imaging device for coronary artery assessment. However, I would like to point out some of the positive values of CBA since it has been and remains the standard of reference for coronary noninvasive imaging techniques. CBCA provides assessment about stenosis percent narrowing, location, morphology, and condition of the distal vessel, stenosis

number in the same vessel, number of vessels containing stenoses, Thrombolysis In Myocardial Infarction (TIMI) flow grade, and TIMI myocardial perfusion grade. It also provides access for intracoronary ultrasound, optical coherence tomography (vascular wall evaluation), coronary flow reserve (microcirculation evaluation), and fractional flow reserve (epicardial stenosis evaluation).

CBCA also can detect minimal irregularities (such as plaque prone to rupture). Collateral flow is easily detected with this method as are coronary artery anomalies as well as evaluation of microcirculation by assessment of myocardial blush and collateral blood flow. With the catheters in place, one can obtain information about regional and global ventricular function, valves can be assessed, and pressures measured.

CBCA is useful for the detection of myocardial bridges and coronary artery spasm, physiologic investigation of the coronary circulation, detection of coronary artery dissections, and their therapy. Coronary artery calcium seen at fluoroscopy does not interfere with the detection of coronary stenoses an angiography. Coronary angiography also provides information about regional myocardial viability by the assessment of TIMI flow grade, TIMI myocardial blush grade, and left ventricular regional wall motion on ventriculography.

With catheters in the heart, the coronary venous circulation may also be assessed, either by runoff from the coronary arteries or by direct catheterization of the coronary sinus with retrograde coronary venous perfusion possibly useful in biventricular pace implantation.

I would add to this that oftentimes when pictures of CTA are compared to pictures of CBCA, only a single view and single frame of the catheter-based angiogram is shown. This is not the real world of coronary angiography. No one looks at a single frame, and no one looks in one single projection to assess coronary pathology.

Finally, all things considered, properly done cardiac catheterization with contrast angiography can be a 1-stop shop for diagnostic imaging and therapy of the cardiovascular system, and the radiation dose is acceptable.

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doi:10.1016/j.jacc.2009.02.060

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Reply

As a practicing coronary angiographer and interventionalist for many years, I appreciate, respect, and agree with the comments of Dr. Conti regarding our recent paper (1). The virtues of catheter-based coronary angiography, so well presented in his letter to the editor, are many, and the majority of the opportunities of invasive coronary angiography cannot be replaced by a noninvasive imaging technique such as computed tomography (CT) coronary angiography. But I do not entirely agree with the notion that CT coronary angiography will become a useful but “limited” imaging device for coronary assessment. At the current stage of CT technology, it definitely falls short of invasive coronary angiography, but new detector technology has improved the spatial resolution to reduce the gap between the diagnostic accuracy of invasive coronary angiography and CT coronary angiography. Obviously, the dynamic nature of Thrombolysis In Myocardial Infarction flow grade, myocardial blush, and assessment of collaterals, as well as pressure measurements will remain in the domain of invasive coronary angiography, whereas invasive coronary angiography is an indispensable roadmap for intracoronary diagnostic devices and invasive catheter-based coronary obstruction treatment.

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doi:10.1016/j.jacc.2009.03.034

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