

EDITORIAL COMMENT

Coronary Computed Tomography Angiography

Our Time Has Come, But There Are Miles to Go Before We Sleep*

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In this issue of the *Journal*, Budoff et al. (1) publish results from the ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial comparing non-invasive coronary computed tomography angiography (CCTA) with invasive quantitative coronary angiography (QCA) for definition of atherosclerotic luminal narrowing at the 50% and/or 70% stenosis levels. At first glance my reaction was, "Oh, no, not another 64-slice CT scan 'validation' report looking at sensitivity (Se)/specificity (Sp) for finding obstructive coronary disease! Didn't I just read a similar report in *JACC*, *JAMA*, *Circulation*, etc.!" However, this was and is not the case.

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In fact, the current report is a verification of what those of us in the field have known privately, but were not prepared to admit in public; however, allow me to comment further, citing some unique attributes:

- **A multicenter investigation.** The ACCURACY trial is the combination of CCTA studies conducted in 16 different performance sites, some of which were situated in academia, but most of which were high-quality computed tomography (CT) laboratories in the private sector. Prior published investigations of CCTA were almost universally performed in singular, tertiary referral/academic sites where strict attention to detail is expected and time is measured in resident and fellow hours. Not uncommonly, busy private practices may not have adequate staff and ideal patients to optimally perform some imaging studies; this may result in inferior clinical performance. However, the current investigation provided

straightforward (in fact, a generally "routine") CCTA application and image reconstruction protocols that can be achieved regardless of performance site. This is very important because duplication of similar methods at a site using current state-of-the-art 64-slice CT scanners (regardless of the manufacturer) is to be highly anticipated.

- **Low to intermediate obstructive disease prevalence.** The data reported per patient by the ACCURACY investigators shows that an Se and Sp for any obstructive narrowing (using a definition of $\geq 70\%$ focal coronary stenosis, which is more clinically relevant for ischemic potential than the commonly applied 50% stenosis) for CCTA was 83% and 83%, respectively. These results rival the best statistics for noninvasive stress imaging and, although the positive predictive value (PPV) was only 48%, the negative predictive value (NPV) was 99%! Interestingly, these statistics are similar to those reported by other single-site academic centers reporting their CCTA findings, and that fact alone is of note. However, more importantly, the current study did not include patients with known coronary disease, and the final tally shows the prevalence of any $\geq 70\%$ narrowing by QCA to be found in only 32 (14%) of the 230 patients included in the investigation. Although these study subjects were all recruited from individuals clinically scheduled for diagnostic angiography (of which at least 64% had abnormal prior stress test results), the actual prevalence of obstructive disease ranged from low to intermediate. Prior single-site and multi-site CCTA studies (although some were performed using 16-slice CT) were universally performed in individuals with known coronary artery disease or those with very high pre-test likelihood. This underscores 2 important points: 1) CCTA is a superb test (99% NPV) for ruling out obstructive disease in symptomatic but intermediate pre-test likelihood individuals; and 2) the accuracy of CCTA in defining obstructive disease is relatively independent of prevalence in the population under investigation. This latter point requires comment because it is well known that general noninvasive cardiac test accuracy (essentially stress testing with or without imaging) is dependent on population disease prevalence. However, CCTA, which is direct visualization of the arteries rather than a surrogate based on potential compromise in perfusion, compares very favorably with direct visualization with angiography. To emphasize the point, all patients who were subsequently found to have a $\geq 70\%$ stenosis by QCA were identified in ACCURACY to have at least a $\geq 50\%$ visual narrowing by CCTA. In other words a report indicating no stenosis $> 50\%$ in the CCTA was 100% predictive of the absence of a $\geq 70\%$ by QCA!
- **Interpretation.** The studies were interpreted independently and separately by 3 well-known experts in CCTA. The interpreters were free to use all variety of 2- and

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3-dimensional tools commonly available on all advanced computer workstations and were not constrained to using pre-processing algorithms that are often touted by workstation vendors to save time. The use of any or all interactive processing algorithms available has been shown to be superior in CCTA interpretation to more convenient pre-processing algorithms (2). The protocol required agreement between ≥ 2 interpreters on a per-patient and per-artery basis, and in only 3 cases (1.3% of the total) was there no agreement. Standards for level II and III CCTA competency for interpretation were put forward by the American College of Cardiology Foundation (3) in 2005 and are strictly enforced by the Society of Cardiovascular CT on all sanctioned CCTA training programs in the U.S. Furthermore, a certification board examination is now established for cardiac CT by the Certification Board of Cardiovascular Computed Tomography (first examination, September 2008). Thus duplication of these results is to be expected by current and future level II- and III-qualified CCTA interpreters.

- **No patient exclusions.** Prior published investigations regarding the validity of CCTA often excluded unevaluable coronary segments, vessels of < 2 mm in diameter, segments with dense coronary calcification, patients with heart rates > 65 beats/min, and because image noise is a concern, some obese subjects. The ACCURACY investigators determined that all study patients with or without obesity (the mean body mass index for the study was 31.4 kg/m^2), whether optimal heart rate control (< 65 beats/min) was achieved, and whether or not there was a high coronary calcium score (> 400 or > 600 using the Agatston criteria) were to be included in the final analysis. The ACCURACY investigators also evaluated the diagnostic accuracy of CCTA in individuals with calcium scores above and below 400 and found no clear reduction in Se, although the Sp clearly was moderately compromised. The clinical implications for application of CCTA in symptomatic intermediate risk subjects regardless of whether they are optimal candidates are to be underscored.

The Rest of the Story

The above comments suggest that the time for CCTA to rule out obstructive coronary disease in symptomatic patients (regardless of performance site and disease prevalence) has arrived, and I would whole-heartedly (pun intended) agree (consistent 99% NPV).

However what about ruling in obstructive disease; is CCTA actually a noninvasive coronary arteriogram? Does it really have the diagnostic capability at the present time to define focal obstructive coronary disease, as we have come to expect of conventional diagnostic angiography? The PPV was only around 50%. I would say, a qualified maybe. The spatial resolution of a conventional angiogram is roughly 0.1 mm, and the spatial resolution of 64-slice (and for that

matter 256- and 320-slice CCTA) is currently, at best, 0.3 to 0.4 mm. The ever-present cardiac motion and the presence of focal calcification (not at issue with invasive angiography) will continue to compromise the determination of advanced luminal narrowing by CCTA and will remain until there are serious improvements in CT detector technology.

But, "who wants to be a silly old angiogram, anyway?" The true power of CCTA lies not in its value as a coronary artery stenosis definer, but in its clear and unique noninvasive ability as a coronary artery plaque definer. Although the ACCURACY study is confined to reporting the accuracy of obstructive stenosis definition, the interpretation by the readers required evaluation of lesion characteristics, which would have included eccentricity or concentricity of calcified and noncalcified plaque, the length of the presumed narrowing, the estimated minimal luminal diameter/area, and subtle changes in contrast opacification before and after the lesion. Furthermore, it is becoming increasingly apparent that prognostication using CCTA may be the real long-term value of the test, especially in the low to intermediate risk individual. It has already been noted that the CT calcium score alone provides incremental prognostic information to angiography stenosis severity (4), and that the complexity of the plaques identified by CCTA imparts significant information on culprit lesion morphology (5). The yes-or-no answer to whether or not a symptomatic patient has obstructive disease remains very clinically relevant; however, the severity and extent of atherosclerotic plaque is perhaps the ultimate definer of prognosis. The initial investigations of Falk (6) from autopsy studies ("...the less obstructive plaques gave risk to more occlusions than did the severely obstructed plaques because of their much greater number...") and Kern (7) using intravascular ultrasound ("Because the aggregate risk of rupture associated with many nonsignificant lesions exceeds that of the fewer significant lesions, a myocardial infarction will more likely originate from a nonsignificant lesion") in defining the vulnerable patient underscore the prognostic importance of defining plaque severity in at-risk individuals, over and above that of defining stenosis.

Leber et al. (8) have suggested that using 64-slice CCTA, they may be able to define up to 80% of the total atherosclerotic burden, but this still remains the Holy Grail of atherosclerosis imaging. All current CT workstation vendors offer a means to define noncalcified plaque. but the truth is that the CT densities of fibrous versus lipid-laden plaque using CCTA are too variable and overlapping at present to be consistent between subjects (9). Thus, in my opinion, we still have "miles to go before we sleep" in this regard. Improvements in temporal and spatial resolution are still required to elevate CCTA to this lofty goal. But in the meantime, we can currently define a surrogate to plaque burden using the established and easily quantified coronary calcium score in all cardiac CT studies, and we must continue to define, although visually estimated and not

quantitative, the presence of noncalcified, ulcerated, complex/mixed, and other plaque characteristics on *ALL* CCTA reports, because the CCTA promise and ultimate goal is not just diagnostics for stenotic lesions but also prognostics in terms of plaque severity and plaque characteristics.

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Key Words: CT angiography ■ diagnosis ■ coronary angiography ■ MDCT ■ coronary CTA.