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EDITORIAL COMMENT

Cardiac Computed Tomographic Angiography

What's the Prognosis?*

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Computed tomography (CT) has been a source of recurring controversy since its introduction into medical practice in 1973 (1). In those early years, pictures revealing unprecedented structural detail of living brains and bodies, obtained without invasive procedures, were sufficiently compelling to inspire enthusiastic incorporation into clinical practice. The potential economic effects of such enthusiasm, however, prompted regulators in many states to attempt to limit dissemination of these machines, often without success. Concurrently, these developments stimulated health services researchers to consider what evidence was needed to declare CT (or any other imaging technology) validated for routine clinical practice. In 1982, Fryback and Thornbury (2) presented a 6-level hierarchical model of diagnostic test efficacy that continues to shape the approach to test evaluation today (3). In this model, a diagnostic test must first prove it functions as intended at the technical level (level 1). This is followed by evaluation of its diagnostic accuracy (level 2), its effects on diagnostic thinking (level 3), its effects on treatment selection (level 4), its effects on patient outcomes (level 5), and finally its effects on societal outcomes, including cost-effectiveness (level 6).

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More recently, CT has returned to the center of controversy, this time focusing on the use of multidetector CT machines to image coronary arteries (4). Once again, alarmed payers have asserted that use of this technology extends far beyond the available evidence of its value. In December 2007, the Centers for Medicare and Medicaid Services (CMS) proposed a draft national coverage decision that restricted payment for this test to use in 2 select populations (intermediate risk symptomatic stable patients, and unstable angina patients) and required participation in an approved research study as a condition of payment (5). A firestorm of objections forced CMS to retreat from its plan. In a March 2008 decision memorandum, CMS specifically referenced the evidence hierarchy model of Fryback and Thornbury as justification that evidence pertaining to patient outcomes (level 3 or higher) would be required to support a national coverage decision (6). Opponents of the draft Medicare decision countered that most diagnostic studies in current use are not supported by such evidence. Regulators and clinicians are now actively searching for opportunities to justify potential uses of coronary computed tomographic angiography (CTA) in the context of increasingly rigorous standards for evidence-based practice.

Notably, the diagnostic imaging evidence hierarchy model makes no mention of prognostic data. This apparent oversight reflects the scarcity of such data when the model was initially proposed (D.G. Fryback, personal communication, October 2009). Diagnostic accuracy is most often assessed using a convenience sample of patients who undergo both the new test of interest and the reference standard test. Small, single-institution studies of this sort constitute the bulk of the level 2 evidence about coronary CTA to date (7). Prognostic data, in contrast, require years of careful follow-up in much larger cohorts, and significant losses to follow-up can irreparably damage the value of the work (8). Proof that a test provides independent prognostic data does not necessarily prove that its use improves patient outcomes. However, it does provide a signal suggesting that such effects may be possible.

In this issue of the *Journal*, Chow et al. (9) present a large, carefully done, single-institution study on the prognostic value of 64-channel cardiac CTA. Over a 2-year period, these investigators prospectively enrolled 2,076 subjects referred for cardiac CTA into a registry and followed them for an average of 16 months. This study is noteworthy because previous prognostic studies either used obsolete CT machines or involved much smaller cohorts with fewer outcome events (and therefore less statistical power) (8,10). The primary finding that coronary artery disease (CAD) severity assessed as either obstructive disease (≥50% diameter stenosis) or severe disease (≥50% left main, 3-vessel disease, or 2-vessel disease with proximal left anterior descending artery disease) added significant prognostic information to both baseline clinical data and left ventricular ejection fraction bolsters the evidence base for cardiac CTA using contemporary equipment and procedures. These general relationships have been amply demonstrated by decades of invasive angiography. Therefore, it is not surprising that CTA adds some incremental prognostic value to basic clinical risk data, similar to what had been previously seen with invasive catheter-based methods.

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Yet, "similar" is not necessarily "equivalent." One of the questions raised in the 2008 CMS review was whether CTA could replace invasive diagnostic angiography in patients who currently undergo catheterization. Chow et al. (9) did not directly determine whether prognostic estimates from CTA are interchangeable with invasive angiography because this would have required all patients to undergo both tests during their baseline assessment, an enormous challenge for a cohort of this size. On the other hand, many studies have shown that the likelihood of cardiovascular death is primarily driven by events in the patients with the most severe CAD. Only 21% of the cohort assembled by Chow et al. (9) had coronary artery diameter narrowing of ≥70% in ≥1 major coronary artery. Thus, most of the study patients were not likely to contribute any coronary events in follow-up. The weakness of cardiac CTA in CAD diagnosis lies in its tendency to overestimate disease severity relative to invasive angiography (7). This type of misclassification decreases the reliability of prognostic estimates relative to the corresponding findings from invasive angiography.

Anatomic misclassifications are amplified by the fact that the stenosis on any angiogram is a surrogate for the effect of the lesion on coronary blood flow. Although the paramount distinction between structure and function has been recognized for more than 25 years, the visual impression of the angiogram is so powerfully seductive that an obsession with "coronary luminology" still dominates modern cardiovascular practice (11). Unfortunately, sole reliance on angiographic data for treatment decisions leads to substantial overuse of percutaneous revascularization compared with combined structural and functional information (12,13). Although preliminary data suggest that special dual-energy CT techniques can also measure myocardial perfusion (14), cardiac CT in its most common incarnation is very much another anatomic tool.

One distinguishing feature of cardiac CTA is its ability to identify normal and abnormal features of the arterial wall, offering the possibility of a novel perspective into risk stratification for future coronary plaque–related clinical events. Chow et al. (9) used a total plaque score, calculated as the number of coronary segments with a visible plaque of any degree of stenosis, to estimate the burden of CAD. In multivariable analyses, this score added independent prognostic information to both a 4-level CAD severity measure and ejection fraction. In an earlier prognostic study of 16-channel cardiac CTA in 1,127 symptomatic patients, Min et al. (10) found that a similar "segment involvement score" was an independent prognostic factor in multivariable analyses (adjusting only for age, dyslipidemia, and family history). Although the plaque scoring systems are intriguing, their prognostic advantage over a thorough accounting of CAD severity remains equivocal. Resolving the conceptual and statistical properties of these different measures of CAD severity and distribution will require samples with larger numbers of outcome events.

Even the best prognostic data imaginable will not reveal how a test alters physician thinking (level 3) and patient management (level 4). Chow et al. (9) report that CAD severity data altered the 10-year risk predictions for approximately 20% of patients, which addresses how these data might alter clinician thinking, but not whether it actually changes decision making. Indeed, more precise test results will not change patient health outcomes (level 5) unless they influence physician or patient behavior. Very few modern diagnostic tests have evidence directly connecting their findings with changes in patient outcomes. Ongoing comparative effectiveness initiatives seek to overcome this gap. In October 2009, the National Heart, Lung, and Blood Institute funded PROMISE (PROspective Multicenter Imaging Study for Evaluation of Chest Pain), a randomized trial of initial ≥64-channel cardiac CTA versus initial functional stress testing in 10,000 low- to intermediate-risk patients. Designed as a real-world pragmatic trial, the PROMISE trial will test whether an initial anatomic strategy with cardiac CTA will reduce a composite clinical outcome event (including death and myocardial infarction) by 20% compared with an initial functional testing strategy over an average follow-up of 2.5 years (15).

To improve clinical outcomes, a cardiac CTA-based strategy must provide clinicians with actionable information to direct prognosis-modifying treatments efficiently and accurately. The data from Chow et al. (9) together with ongoing investigations should help us to determine whether the tomographic noninvasive denomination of luminology offers a "PROMISEing" prognosis or simply another opportunity to recite the catechisms of the past.

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