Clinical Value of Coronary Computed Tomographic Angiography in Patients With Stable Angina

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Over the past decades, great strides have been made to establish coronary computed tomographic (CT) angiography within the field of cardiovascular medicine. The diagnostic accuracy of CT in comparison with invasive angiography was demonstrated in numerous single- and multicenter studies.[1] From large registry data, an understanding developed of how cardiac CT could affect therapeutic management within different clinical contexts. Most recent clinical practice guidelines support the use of cardiac CT as a primary or secondary diagnostic option for patients with stable chest pain symptoms.[2,3] As a last step toward full recognition, several randomized clinical trials were conducted to investigate the effect of cardiac CT on clinical outcome in comparison with established noninvasive strategies.[4–7]

See Article by Bittencourt et al

In this issue of *Circulation: Cardiovascular Imaging*, Bittencourt et al[8] performed a meta-analysis of all randomized controlled trials published until March 2015 that compared the clinical effectiveness of coronary CT angiography to other noninvasive strategies, and could make several interesting observations for which the separate trials had insufficient power. Although none of the trials demonstrated a statistically significant difference in hard end points, pooling of data from 14 817 patients in this meta-analysis demonstrated that implementation of cardiac CT was associated with a 31% lower myocardial infarction rate compared with usual care. For mortality, no significant difference could be demonstrated between both strategies. Cardiac CT also led to more revascularization procedures (77%), as well as a trend toward more invasive angiograms. We can only speculate whether there is a direct relation between the higher revascularization rate and the lower incidence of myocardial infarction, as other factors may be involved. At first glance the designs of the respective studies seem too different to combine. In terms of size Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) and Scottish Computed Tomography of the HEART Trial (SCOT-HEART) (together 95% of total population) dwarf the other two trials. SCOT-HEART added CT to a strategy that included exercise testing for the majority of patients, Cardiac Computed Tomography for the Assessment of Chest Pain and Plaque (CAPP) compared CT to exercise testing, Min et al[7] compared CT with nuclear imaging, and in PROMISE the choice of test in the usual care arm was left to the clinicians. The mean follow-up period varied from 2 months to >2 years. Recognizing the potential effect of trial heterogeneity on the meta-analysis results, the investigators reanalyzed the data with alternating exclusion of individual studies, which produced largely consistent results.

SCOT-HEART, which demonstrated a trend towards fewer major adverse events after CT, was the only trial where cardiac CT was added to standard care with stress testing, rather than replacing functional testing. The results from SCOT-HEART demonstrated that the combination of anatomic and functional information improves diagnostic certainty. But it also suggests that adding functional information to the CT arm attenuates the higher revascularization rates associated with CT in other trials. Intuitively, that makes sense; more comprehensive information should allow for more appropriate treatment decisions. In PROMISE, costs were similar between the cardiac CT strategy and usual care. Although no cost analysis is available yet for SCOT-HEART, the addition of CT likely increased overall expenses. However, the concept that comprehensive imaging, in some form or another, should improve efficiency and cost–effectiveness of care remains viable.

Interestingly, other observations from the meta-analysis could result in a different conclusion. The disease prevalence in these trials was low, particularly in PROMISE (<12%). The clinical outcome was excellent, whether patients were examined by cardiac CT or underwent functional testing. Despite the relatively high disease prevalence in SCOT-HEART, which included patients with a history of coronary artery disease (CAD), the annual mortality was <5 per 1000. This is comparable with age-adjusted mortality rates in the general population.[9] Identification and treatment of the (albeit small) proportion of patients with severe CAD must have contributed at least to some degree to this excellent outcome. Nevertheless, the low observed disease prevalence and benign outcome have evoked a debate about whether diagnostic testing in patients with stable angina should be abolished entirely.

So the question is should one do comprehensive (multimodality) imaging or no testing at all? Neither position is entirely unreasonable depending on the situation. The challenge is how to predict which patients are at sufficiently low risk to remove the need for (costly) diagnostics, and who would benefit from a comprehensive evaluation to optimize treatment decisions. The conventional methods for estimation

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of coronary disease probability, such as the Diamond and Forrester prediction rule, performed poorly in these trials and overestimated disease prevalence, by perhaps a factor of 4 in PROMISE. Updated prediction rules, ideally validated in low-risk populations and not solely based on an angiographic end point, should allow for more efficient test referral. As an alternative to no testing at all, patients with a low probability of disease could undergo a less expensive test, provided that the test has sufficient sensitivity. Exercise testing is not expensive and provides valuable prognostic information. But justified or not, the test is generally felt to lack sufficient sensitivity to confidently rule out CAD. Although calcium imaging in symptomatic patients remains controversial, preliminary results from the recently published Computed Tomography versus Exercise Testing in Suspected Coronary Artery Disease (CRESCENT) trial suggest that in patients with a low to intermediate probability of disease the calcium scan allows for safe exclusion of CAD, which reduces diagnostic expenses as well as exposure to contrast medium in a substantial proportion of patients.[10]

As the authors discuss in the article, cardiac CT may lead to overtreatment. Coronary CT angiography is still a relatively new technique to many physicians caring for patients with stable angina in daily practice. Unfamiliarity with the technique, both its possibilities and limitations, poses a challenge not always fully appreciated by the ordering physician. Not infrequently patients with (potential) coronary disease on CT are directly referred for invasive confirmation without consideration of initial medical treatment or functional assessment to assess hemodynamic significance. More education is needed to avoid premature referral for invasive angiography and revascularization procedures without clear prognostic (or symptomatic) benefit once CAD has been identified on CT angiography.

Finally, this meta-analysis illustrates how the design and conduct of diagnostic trials remains a challenging task. The quality of the diagnostic intervention (or the comparator) is not generic and depends on various factors, many of which will be difficult to quantify, or extrapolate beyond the specific institutions where it was performed. The relevance of the result may expire before the trial is completed because of perpetual technical development. Contrary to therapeutic interventions, diagnostic tests have no direct impact on outcome. The benefit of testing is measured indirectly by the subsequent changes in management, relying on the assumption that differences in management will actually affect outcome. Most of the trials in this meta-analysis were designed as pragmatic trials where management decisions were left to the caring physicians. It is difficult to extrapolate trial results without knowledge of the test-treatment decision protocol. Likewise, it may be impossible to design an all-inclusive management algorithm that fits all patients and satisfies all participating investigators. What complicates matters further is the apparent phase of transition and challenged paradigms about the management of stable CAD.[11] Given the low incidence of cardiovascular events in contemporary chest pain populations, the question is raised about whether myocardial infarction and death should still be considered the most relevant trial end points. For patients, functional parameters such as relief of symptoms, quality of life, and ability to work may represent more important benefits. Despite its smaller size, the CAPP trial, as well as the CRESCENT trial, demonstrated more improvement in symptoms after cardiac CT.[6,10] Unfortunately, this poses yet one more challenge for diagnostic trials. Because it is virtually impossible to blind patients or physicians to the study allocation, the mechanism by which benefits are achieved may be multifactorial.

In conclusion, the authors should be complimented on their comprehensive data analysis and well-balanced interpretation. This analysis underlines the clinical value of cardiac CT in the management of patients with stable chest pain complaints, with careful consideration of the demographic contexts. Nowadays, society and other specific stakeholders expect demonstrated clinical benefit for diagnostic procedures. Cardiac CT has met this need for scientific evidence in the form of several randomized trials, despite its relatively short existence. Obviously, this is not the end as diagnostic management strategies will continue to evolve. Instead of aiming for a reduction in infrequently occurring major adverse events, future studies are expected to focus on patient-valued parameters and the impact on general well-being. The ideal diagnostic strategy is unlikely to be a one-test-fits-all approach, but will most likely include different (conditional sequences of) tests based on individual characteristics and with consideration of costs.

Disclosures

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