Right Answer, Wrong Question
On the Clinical Relevance of the Cardiovascular History

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According to Samuel Johnson, "It is as foolish to make experiments on the constancy of a friend as on the chastity of a wife." Despite this sage admonition, Cheng et al challenge the fidelity of traditional algorithms for estimation of cardiovascular risk based on the quality of symptoms suspicious of angina, asserting that they seriously overstate the actual prevalence of disease. They base their conclusion on a study of some 14,000 patients referred for clinically indicated noninvasive coronary computed tomographic angiography (CCTA) and enrolled in Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry (CONFIRM). Symptoms were elicited largely through a self-administered patient questionnaire and categorized in a manner similar (but not identical) to that used in a number of cardiovascular guidelines.2,3

In a nutshell, the CONFIRM investigators observed that the prevalence of CCTA disease did not correlate well with the presence or type of symptoms. Asymptomatic patients stratified by age and sex had essentially the same prevalence of disease as similarly stratified patients with nonanginal discomfort, atypical angina, or typical angina. Though noting that their population was limited by the use of a self-administered patient questionnaire rather than a physician's history, and that secular patterns of referral might have changed over the 30 years since the introduction of these algorithms—or have been influenced by the availability of additional clinical information— they nevertheless discount these difficulties and leave us with the impression that symptoms don't matter.

At the risk of seeming to construct a straw man argument, ask yourself, "Do symptoms matter?" Is a patient with chest pain more likely to have coronary disease than an asymptomatic patient? Assuming you answered this question in the affirmative, what CONFIRM says is only that noninvasive CCTA doesn't tell us the same thing as conventional invasive coronary angiography. Prevalence of coronary disease by invasive angiography clearly correlates with age, sex, and symptom class when assessed by physician history,4 but not with noninvasive tomographic angiography when assessed by patient questionnaire (the Figure). In essence, the CONFIRM investigators ask us to believe that two 65-year-old men—one with typical angina and the other with musculoskeletal chest pain—have just about the same chance of coronary disease (as shown in the lower left panel of the Figure).

Several lines of argument challenge the veracity of these counterintuitive observations. First, invasive angiographic assessment is known to be highly subjective. It is not uncommon for a given patient to be considered severely diseased by one observer and entirely normal by another,5 and the lower spatial resolution of CCTA images is likely to affect this subjective variability in important ways.

Ironically, the CONFIRM investigators blur the distinction between the 2 methodologies by terming CCTA disease "angiographically significant coronary artery disease."1 The typical clinician, who is inclined to equate this term with conventional invasive coronary angiography rather than noninvasive computed tomography, is likely to be misled by this careless turn of phrase. A computer tomographic image is no more the equivalent of a conventional angiographic image than is a low-resolution scintigram the equivalent of a high-resolution sonogram. Different nets catch different fish.

Without performing a direct comparison of CCTA and conventional angiography in a subgroup of the study population, there is no telling what the magnitude of ascertainment bias was in CONFIRM. Historical comparisons are notoriously unreliable. Even so, previous comparisons of CCTA with conventional angiography reveal substantial variability.7–9 A recent study by several of the CONFIRM investigators disclosed pairwise standardized variations (SD/mean) of 113%, 158%, and 193% among 3 blinded observers reading 221 scans despite superficially impressive statistically significant correlation coefficients.10

There is little doubt that anatomically severe disease is associated with more extreme clinical manifestations of ischemia than is anatomically mild disease. We are not told, however, if any of the patients in CONFIRM underwent historical evaluation, risk factor assessment, or stress testing by their physicians before being referred for anatomic verification. This is important because ischemic symptoms act through their conditional association with the severity of disease. The more severe the disease, the more extreme the clinical manifestations. If patients with more extreme manifestations of ischemia (and therefore more severe disease) were preferentially referred for invasive angiography, whereas patients with less extreme manifestations of ischemia (and therefore less severe disease) were preferentially referred for noninvasive angiography—a practice readily justified as the exercise of good clinical judgment—the
resultant verification bias would be sufficient to account for the poor correlation between symptoms and CCTA disease.

In fact, 25% of the study population (3 of the 12 participating centers) was excluded because information to characterize the patients’ symptoms was absent, and an additional 17% of the patients (3368/19,703) in the 9 remaining centers were excluded because the information was incomplete. The resultant distribution of symptoms is therefore very different from that reported for the traditional algorithm.2–4 On the low end of the spectrum, almost 5000 of the CONFIRM patients (33%) were asymptomatic, and no reason is given why CCTA was considered clinically indicated in these patients. Were the referring physicians using CCTA as a cavalier screening test (something they would never do with invasive coronary angiography)? On the high end of the spectrum, many fewer patients were classified as having typical angina. Among the 9355 symptomatic patients in CONFIRM (including the 1249 patients with dyspnea who would be classified as having nonanginal discomfort by the traditional algorithm), only 17% had typical angina, 56% had atypical angina, and 27% had nonanginal discomfort based on the patient questionnaire. In contrast, among the 13,109 symptomatic patients on which the traditional algorithm was based,2,3 34% had typical angina, 39% had atypical angina, and 27% had nonanginal discomfort based on the physicians’ historical assessments.

This shift in distribution suggests that CONFIRM physicians preferentially referred those with less severe symptoms for CCTA and those with more severe symptoms to alternative management strategies, including invasive coronary angiography. This verification bias is even more pronounced when differences in the defining characteristics for typical angina are considered. The traditional algorithm defines typical angina to be substernal in location,11 but CONFIRM includes jaw pain and arm pain in the definition. In the absence of a substernal component, these latter locations are considered atypical in the traditional algorithm.11 Consequently, an unknown number of patients with typical angina in CONFIRM would be classified as having atypical angina according to the traditional algorithm. Accordingly, fewer than 17% of the symptomatic patients in CONFIRM had typical angina—less than half the number in the studies on which the traditional algorithm was based.

Are we overdiagnosing the disease by our history taking, or are we underdiagnosing the disease by our testing? Bayes theorem helps answer this question. Just as it tells us that the predictive accuracy of any test is conditioned on the overall prevalence of disease in the population tested, it also tells us that test accuracy is conditioned on the overall frequency of abnormal responses in the population tested, those in whom disease status is verified and those in whom it is not. As is well known by several of the CONFIRM investigators,12,13 a test will perform as advertised only if it is applied to patients similar to those in whom its accuracy was first determined, those tested for similar reasons and under similar circumstances. This is clearly not the case here.

The CONFIRM investigators do not tell us how many patients were initially considered candidates for inclusion in the study, but did not then undergo CCTA. Patients undergoing CCTA based on an unspecified clinical suspicion of coronary disease, however, are very different from traditional patients undergoing stress testing and subsequent coronary angiography based on that testing. The latter referrals might also be biased in favor of positive test responders, but this is likely to have occurred much less often decades ago, with electrocardiographic stress testing as the gatekeeper to coronary bypass surgery, than more recently, with stress imaging procedures as the gatekeeper for percutaneous coronary intervention. Different nets catch different fish.6

What else might explain the inability of symptoms to predict disease prevalence in this study? According to Bayes theorem (which states that the posterior odds for disease equal the prior odds times the likelihood ratio of the test observation), there are only 3 ways for this to happen (the Table). Under scenario A, the prior odds must fall and the likelihood ratio must rise in concert to offset that fall. We can readily see how the prior odds would be lower in asymptomatic patients, but not how
the likelihood ratio of the test would be higher. Asymptomatic patients with disease are more likely to have mild disease (that is why they are asymptomatic). Because a test is less able to detect mild disease than severe disease, its likelihood ratio in asymptomatic patients should be lower, not higher. An analogous argument can be posited for patients with typical angina. Under scenario C, the prior odds are expected to be higher, but this means that the likelihood ratio must be lower if the posterior odds are to remain the same, and this is counter to observations showing the likelihood ratio to be higher in patients with more severe (and therefore more symptomatic) disease. Finally, under scenario B, the posterior odds can remain the same if neither the prior odds nor the likelihood ratio change with symptom class, but this runs counter to numerous studies showing that prior odds and likelihood ratios are both higher in symptomatic versus asymptomatic patients. The only rational way to explain the counterintuitive observations in CONFIRM is to indict the method used to select the study population and to characterize their symptoms. In the end, symptoms do matter, but they cannot be elicited accurately by questionnaire. That’s the role of an experienced clinician. Different nets catch different fish.6

Material harm can come of the misunderstandings engendered by the paradoxical observations in CONFIRM. If studies such as this were used to undermine the value of the clinical history in the minds of clinicians, suggesting instead that CCTA can serve as an accurate and efficient replacement for more conventional clinical evaluation, then patients with ischemic symptoms, who might otherwise benefit from preventive cardiovascular care and effective antianginal management, could well go undetected and untreated.

On the other hand, the traditional algorithm should not be used indiscriminately for the assessment of cardiovascular risk. It was developed in patients undergoing cardiovascular stress testing and (current guidelines notwithstanding) is not applicable to the general population undergoing risk factor screening or to patients with suspected acute ischemic syndromes.

In summary, the ascertainment bias resulting from use of self-administered questionnaires and the verification bias caused by the preferential referral of lower-risk patients to CCTA and higher-risk patients to more aggressive alternatives together act to distort the long-established association between cardiovascular symptoms and disease prevalence. In the final analysis, a self-administered questionnaire is not the same as a physician’s history, anatomic screening is not the same as functional testing, and noninvasive tomography is not the same as invasive angiography. Different nets catch different fish.6

Table. Alternative Ways for Posterior Odds to Remain Invariant

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<th>Scenario</th>
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Those beguiled into believing that symptoms do not matter would do well to reflect on an apocryphal story about the great physicist Niels Bohr. A young scientist visiting Bohr at his home was surprised to see a horseshoe hanging over the front door. “Professor,” he exclaimed, “surely you don’t believe in that old superstition!” Bohr thought for a moment and then replied, “They say it works whether you believe in it or not.”

Disclosures

None.

References


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