The importance of risk stratification in the management of symptomatic patients with known or suspected coronary artery disease is well recognized. Risk stratification not only informs the clinician’s response to queries regarding prognosis but also helps the clinician choose appropriate therapy. Cardiac computed tomographic angiography (CCTA) is a relatively new tool for this purpose. Single-center studies have suggested its potential utility in estimating the prognosis of patients with known or suspected coronary artery disease (CAD). In this issue of Circulation: Cardiovascular Imaging, Chow et al report the findings of a large international multi-center registry (CONFIRM) that examines the value of CCTA for risk stratification. The strengths of the study include its large size (27,125 patients), its multicenter nature (12 participating centers in 6 different countries), its prospective nature, and the use of all-cause mortality as an end point. Although the authors describe their use of all-cause mortality as a potential limitation, Lauer et al have argued that this end point is actually preferred.

To their credit, Chow et al performed a stepwise analysis incorporating first clinical variables, then clinical variables and the left ventricular ejection fraction (LVEF) by CCTA, and then clinical variables, LVEF, and CAD severity assessed by CCTA. The authors also calculated the net reclassification improvement. This approach tries to quantify the prevalence of clinically meaningful change in individual patients. Past studies considered this concept, but statistical rigor has recently been added. The authors conclude that CCTA measures of LVEF and CAD severity are incremental to clinical variables in predicting all-cause mortality. These results add significantly to the evidence base for CCTA. The remainder of this editorial will consider the implications of these data for the evidence-based clinician evaluating a symptomatic patient with suspected CAD by addressing a series of questions:

**Is the Patient Population Applicable to Clinical Decision-Making?**

The authors correctly excluded patients with a history of myocardial infarction, coronary revascularization, and cardiac transplantation. Most of the patients were symptomatic. More than two-thirds (69.2%) had chest pain and another 8.1% had dyspnea. However, 21.3% of the patients were tested for “other” reasons. They presumably did not have chest pain or dyspnea and may have been asymptomatic. It would have been preferable for this study to focus on patients with chest pain and dyspnea. In addition, we do not know how many other patients with chest pain and dyspnea were seen at these 12 centers during this 6-year period and did not undergo CCTA. It is therefore difficult to know how representative this sample of patients is of the population of symptomatic patients with suspected CAD. This is a common limitation in the literature which is certainly not unique to this study.

**Are Clinical Variables Adequately Considered in the Incremental Analysis?**

The CONFIRM registry included data on risk factors and symptoms. Table 2 in that study shows the pretest likelihood of CAD using age, sex, and chest pain description. However, the authors chose the National Cholesterol Education Project (NCEP) classification of risk to assess clinical risk. As they acknowledge, this parameter is an estimate of both mortality and nonfatal myocardial infarction. However, a more serious limitation is that this parameter is an estimate of both mortality and nonfatal events in asymptomatic individuals. Because the vast majority of the patients in this study were symptomatic, the choice of the NCEP risk seems questionable. Table 2 indicates that pretest likelihood of CAD (categorized as low, intermediate, and high) was not significantly associated with all-cause mortality. However, more than two-thirds of the patients in the study had an intermediate pretest likelihood, which customarily covers a broad range of 10% to 90%. The authors should have been able to calculate the pretest likelihood as a continuous variable using either published tables or equations. The authors’ finding that chest pain was “protective” is surprising because typical angina has been associated with CAD, severe CAD, and subsequent mortality in multiple previous studies. However, because only 4.9% of the patients in CONFIRM were men over age 50 with typical angina, Chow et al may not have had sufficient power to detect this effect.

More importantly, Chow et al do not provide any information about the resting ECG in their patients. ECG Q waves, ST- and T-wave abnormalities, and conduction delays are
prognostically significant and do occur in the absence of a history of myocardial infarction.\textsuperscript{10,11} Even normal versus abnormal ECG is of prognostic significance, as the presence of a normal ECG is associated with normal left ventricular function in nearly all patients.\textsuperscript{8}

**Did the Analysis Adequately Account for Measurement of the Ejection Fraction?**

Unfortunately, only one-half of the patients in the study by Chow et al had absolute LVEF measurements. The remainder had LVEF considered only as normal/abnormal. Chow et al did perform a secondary analysis in those patients with LVEF available as a continuous variable and found that CAD severity was still of incremental prognostic value. However, the reclassification rates presented by the authors are based only on LVEF as normal or abnormal. Thus, they may well overestimate the reclassification rates in patients for whom LVEF is available as a continuous variable.

**Do the Rates of Reclassification Justify the Use of CCTA in Every Patient?**

The answer to this question requires careful review of the data in the lower panel of their Figure 4. CAD severity by CCTA reclassified 380, or 9.32\% of the 4093 patients who were low risk on the basis of clinical parameters and LVEF. Of these 380 patients, 16 died. Using a conservative cost of $200 per CCTA, the cost of testing in these 4093 patients would be $380,000. In contrast, using very similar methodology in patients with normal resting ECGs is controversial.\textsuperscript{6,15,16} Its incremental value in patients with normal exercise ECGs is limited to patients at high clinical risk.\textsuperscript{17} In contrast, the incremental value of SPECT in intermediate-risk patients with abnormal resting ECGs (non-specific ST- and T-wave abnormalities) is considerable.\textsuperscript{18} In patients with normal resting ECGs, Kwok et al reported that SPECT Thallium-201 imaging correctly reclassified only 3\% of the patients. In contrast, using very similar methodology in patients with ST-T abnormalities on their resting ECGs, Kwok \textit{et al} reported that SPECT Thallium-201 reclassified 48\% of the 230 patients in the intermediate-risk group. The absence of resting ECG data in the analysis by Chow et al makes it very difficult to compare their findings to the previous literature.

**Will Improved Risk Stratification by CCTA Lead to Improved Patient Outcomes?**

Clinicians routinely assume that the functional assessment of “borderline” cardiac lesions will lead to the improved selection of patients for revascularization and thereby improve patient outcomes. The existing scientific evidence in support of this premise for any noninvasive modality is remarkably limited. Despite the widespread use of exercise ECG testing, exercise echocardiography, and exercise SPECT imaging for this purpose, there are no prospective studies, demonstrating that the selection of patients for revascularization on the basis of these modalities leads to improved clinical patient outcomes. In contrast, the use of fractional flow reserve during invasive angiography to select patients for percutaneous coronary intervention does lead to improved patient outcomes. A randomized trial\textsuperscript{19} showed that the strategy of fractional flow reserve-guided percutaneous coronary intervention led to improved survival free of major adverse events compared to angiography-guided percutaneous coronary intervention. The challenge for the imaging community is to develop similar evidence for noninvasive approaches. Two randomized trials\textsuperscript{20,21} are currently under way to test the hypothesis that CCTA will lead to improved patient outcomes compared to existing noninvasive methodologies. I would encourage clinicians and imagers in any of the centers participating in these studies to enroll their patients in an effort to answer this critical question.

In the meantime, more studies like this one are needed to better define the prognostic value of CCTA and particularly the specific clinical situations where it has the greatest value. Chow \textit{et al} are to be congratulated on this important contribution. Studies focused on patients with normal and abnormal resting ECGs, with longer clinical follow-up (at least 5 years) and comparisons to other noninvasive modalities are important next steps.

**How Do These Results Compare With Those for Other Existing Noninvasive Modalities?**

The general issue of prognosis is beyond the scope of this editorial. Reviews of the prognostic literature for other modalities, including single-photon computed tomographic (SPECT) perfusion imaging, are available.\textsuperscript{14} There is far less literature regarding reclassification. The incremental value of SPECT perfusion imaging in patients with normal resting ECGs is controversial.\textsuperscript{6,15,16} Its incremental value in patients with normal exercise ECGs is limited to patients at high clinical risk.\textsuperscript{17} In contrast, the incremental value of SPECT in intermediate-risk patients with abnormal resting ECGs (non-specific ST- and T-wave abnormalities) is considerable.\textsuperscript{18} In patients with normal resting ECGs, Christian \textit{et al} reported that SPECT Thallium-201 imaging correctly reclassified only 3\% of the patients. In contrast, using very similar methodology in patients with ST-T abnormalities on their resting ECGs, Kwok \textit{et al} reported that SPECT Thallium-201 reclassified 48\% of the 230 patients in the intermediate-risk group.
Disclosures

None.

References


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