Combined non-invasive imaging for predicting cardiovascular events

Is three a crowd?

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In this issue of the *Journal*, Nappi et al analyze the incremental prognostic value of coronary artery calcium scoring (CACS), single-photon emission computed tomography myocardial perfusion imaging (SPECT MPI), and coronary CT angiography (CCTA) in a prospective cohort of patients with low-to-intermediate probability of coronary artery disease (CAD) who were referred clinically for all three studies. The authors excluded those who were revascularized within 2 months, setting aside the question of diagnostic accuracy. This is the first study to prospectively and contemporaneously perform all three modalities and compare their prognostic value. The authors are to be applauded for setting out to accomplish such an ambitious goal and for obtaining near-complete follow-up.

Despite low numbers of patients and events, the authors were able to demonstrate incremental prognostic value with SPECT over CACS. But in whom? The population studied by Nappi et al consisted of patients deemed at low or intermediate pre-test probability for CAD according to extended Diamond-Forrester classification. The percentage breakdown between low and intermediate groups is not available. Interestingly, the majority of patients (85/156, 54.5%) were asymptomatic prior to testing. The population studied stands in contrast

to those in other trials of non-invasive imaging, such as PROMISE, in which the patients were symptomatic by study design and had a substantial mean combined Diamond-Forrester and Coronary Artery Surgery Study risk score of $53 \pm 21\%$.¹ The authors do not address the reasons these asymptomatic individuals underwent imaging. Current appropriate use criteria provide limited situations for testing of asymptomatic individuals.² Thus, the authors' indications for testing, as well as the relative order of testing modalities, could provide insight on the role of non-invasive imaging in this patient population.

In the patient population studied, this analysis offers several important results. Using a composite outcome of cardiac death, non-fatal myocardial infarction and unstable angina requiring revascularization, the authors noted that CACS, SPECT MPI, and CCTA all demonstrated prognostic value independently. However, CCTA did not provide incremental prognostic information after CACS and SPECT findings were combined with clinical data. The chi-square value of clinical data in the incremental analysis seems low. It is unlikely that exercise capacity, one of the most powerful prognostic markers in exercise MPI, was included.³ Patients able to achieve a high exercise workload of ≥ 10 -METS have an excellent prognosis, and inclusion of this variable in the clinical model may have altered the incremental value of all three imaging modalities.⁴ However, despite potential limitations, the results highlight a potential role for SPECT MPI. There is an emerging literature on the prognostic value of CACS in patients with normal SPECT, but this report provides a novel demonstration of the additive prognostic value of SPECT over CACS^{5–7} and lends further credibility to the idea that ischemia is an important prognostic marker.⁸

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In this predominately asymptomatic, low-to-intermediate risk cohort, the data make a compelling case for the utility of CACS as an initial modality for risk evaluation in ischemic heart disease; there were no events among patients with a CACS of 0. This finding provides additional confirmation of the excellent prognosis of patients with a negative calcium score.^{9,10} In such patients, there appears to be little role for SPECT MPI or CCTA. In those with CACS >0, there may be incremental value in functional imaging with SPECT MPI. However, the present results suggest that CCTA may find itself the third wheel in prognostication. On the other hand, the finding of a significant reduction in event-free survival in patients with matched defects (MPI defects in a coronary territory supplied by a vessel with CCTA stenosis) vs unmatched defects suggests there is likely a role for hybrid imaging in some patients.^{11,12}

This study has other limitations acknowledged by the authors. It was performed in a single center and included a relatively small number of patients. Furthermore, the combined endpoint was driven largely by unstable angina requiring revascularization, accounting for 73% of all events. There were relatively few cardiac deaths or non-fatal myocardial infarctions. The percentage of “hard” outcomes is lower than in other studies of MPI and prognosis.¹³ While unstable angina requiring revascularization is an important endpoint, the makeup of events further emphasizes the lower risk of this cohort. The low number of events did not prevent SPECT MPI from having incremental value. However, a higher event rate may have resulted in incremental benefit to CCTA, especially given the significant Kaplan–Meier analysis with matched defects and the trend towards significance in the incremental Chi-square analysis ($P = 0.075$).

An important additional finding was that nearly all events (20 of 22, 91%) occurred in men despite women making up 37% of the population. The clustering of events in men further underscores the difficult task of sex-specific prognostication. In patients with abnormal SPECT MPI, a recent study observed higher rates of cardiac death and non-fatal MI as well as coronary revascularization among men, compared with women.¹⁴ Data on CACS have been disparate. An older meta-analysis of 20,178 patients in 3 large studies showed similar CACS-based mortality risk between women and men.¹⁵ However, a more recent study that included 15-year mortality rates suggested increased risk among women with higher CACS.¹⁶ Multi-modal evaluation further complicates this issue and, unfortunately, the findings presented by Nappi et al may not be fully applicable to women.

Many questions persist. It remains to be seen whether the benefit of SPECT MPI over CACS and lack of

value from added CCTA analysis will be found in patients with higher pre-test probability of CAD, or among groups with a greater symptom burden. Factoring in exercise capacity, is there a prognostic role for imaging in patients with good functional capacity (≥ 10 METs)? When should hybrid imaging be performed? Are these results applicable to women? These important questions await the efforts of future investigators to help define optimal risk management in patients at risk for ischemic heart disease.

Disclosure

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