Adding value to myocardial perfusion scintigraphy: A prediction tool to predict adverse cardiac outcomes and risk stratify

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The high global incidence of major adverse cardiac events (MACE) has firmly established cardiovascular disease as an important cause of morbidity, mortality, and healthcare expenditures.¹ The assessment and evaluation of cardiovascular disease is a multi-tiered process incorporating clinical risk factors, patient presentation, and diagnostic testing to evaluate and risk stratify individuals. The identification of key clinical factors for the selection of patients with the highest pre-test probability of disease was first set out in the work by Diamond and Forrester and later modified and adapted to guide noninvasive testing in clinical guidelines as well as the development of appropriate use criteria.^{2–5} Myocardial perfusion imaging (MPI) is a key element in the evaluation of cardiac symptoms and risk stratification given the prognostic power that it has demonstrated.⁶ Previous studies of exercise and pharmacological single photon emission computed tomography (SPECT) MPI have demonstrated sensitivities of 87 and 89% and specificities of 73 and 75%, respectively for angiographically significant coronary artery disease (stenosis > 50%).⁷ Furthermore, an abnormal SPECT MPI (either exercise or pharmacologic) has been shown to portend a significantly increased risk of cardiac death or non-fatal myocardial

infarction as compared to a normal study.⁶ Thus a comprehensive cardiac risk assessment and risk stratification depends on the incorporation of clinical risk factors, patient presentation, and results from diagnostic MPI when appropriate. While the assessment of both risk factors and imaging results are key elements in the cardiovascular risk assessment of a patient, there remains a clinical need for a tool that can seamlessly incorporate these results into a single calculation.

In this issue of the *Journal of Nuclear Cardiology* Leslie et al. report their findings on the retrospective implementation of CRAX2MACE, a prediction tool designed to incorporate patient clinical risk factors and myocardial perfusion imaging variables, to predict the 2-year probability of MACE.⁸ The primary outcome of interest was a composite endpoint of death from any cause, hospitalized acute myocardial infarction, or late coronary revascularization. MACE within 5 years was examined as a secondary outcome. Standard ^{99m}Tc-sestamibi or tetrofosmin rest/stress protocols were completed and processed locally at a single center in Canada. Automated image analysis examining left ventricular segmentation, contour quality, and global perfusion deficit as a percentage of myocardium was performed with QGS-QPS software and later verified in a blinded fashion by researchers at Cedars-Sinai Medical Center in Los Angeles, CA. Clinical risk factors for all patients were gathered electronically via the Canadian Single Public Healthcare system utilizing electronic billing codes.

In their analysis a total of 5842 studies, completed between February 2001 and July 2008, were included and randomly sub-grouped into a development (3896) and validation (1946) cohort. Over the course of the 2-year follow-up, the primary MACE outcome occurred in 589 (15.1%) and 272 (14.0%) of the development and validation groups, respectively. Multivariable logistic regression demonstrated age, diabetes, recent cardiac hospitalization, inability to perform a treadmill exercise,

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stress total perfusion deficit, ischemic total perfusion deficit, left ventricular ejection fraction, and transient ischemic dilatation to be independently associated with the primary outcome. Area under the ROC Curve analyses for MACE prediction at both 2 and 5 years were favorable (0.79 and 0.80 respectively) indicating a fair predictive capability of the model. Lastly, there was a concordant increase in the event rate with increasing risk category.

The current study integrates clinical risk factors and MPI variables to synthesize a tool, CRAX2MACE, that can predict major adverse clinical outcomes. Both clinical risk factors with derived composite scores as well as automated quantitative SPECT variables have separately been well known to have association with cardiovascular outcomes. Earlier studies either generated risk stratification models for cardiovascular outcomes using composite scores derived solely from clinical variable⁹ or have utilized the predictive potential of quantitative MPI technique for evaluation of presence and severity of coronary disease and prediction of cardiac events¹⁰

There are studies regarding the prognostic value of SPECT MPI in patients with individual risk factors, but recently there have been studies that have combined clinical and imaging variables to generate risk stratification tools.^{11–13} CRAX2MACE builds off previous work that examined outcomes on a longer-term interval. Martineau et al. developed an integrated model, CRAX, to predict the cumulative risk of death and acute myocardial infarction in 5842 study patients.¹¹ In their study, age, number of hospitalizations in the 3-year preceding MPI, and left ventricular ejection fraction were predictors of death and acute myocardial infarction; additional predictors of death were the use of pharmacological stress and global stress total perfusion deficit, while transient ischemic dilation, and ischemic total perfusion deficit change were predictive of acute myocardial infarction. The CRAX2MACE scoring tool, in comparison with CRAX, incorporates more clinical variables (e.g., diabetes) in addition to the SPECT MPI predictor variables. CRAX2MACE is primarily developed to predict short-term outcomes by stratifying 2-year risk for MACE, which makes it a useful tool to detect high-risk individuals who are at imminent risk of a cardiac event or require revascularization, compared to the CRAX score that was developed to predict long-term, i.e., 5-year, hard outcomes of death and acute myocardial infarction.

As a risk calculating tool, CRAX2MACE promises to provide a simple, unified risk measure that can be conveniently incorporated into the routine workflow and easily employed in day-to-day practice. It uniquely constructs a combined model that incorporates both

quantitative imaging parameters and simple clinical factors to produce individualized risk profile for predicting future cardiovascular events. Not only does this tool predict MACE, but it distinguishes low and very high-risk groups with high confidence to provide additional risk stratification. This model would be helpful in providing additional, patient-specific, clinical information to the clinicians that might be factored into the decision-making and can stratify patients who need to be more aggressively treated. This risk stratification tool will be pivotal in the adoption of patient-tailored and precision-guided medicine through personalized MACE risk computations, identifying not only those who would be candidates for additional testing or therapeutics but also those who are at low-risk and may not need any further intervention.

This study has some inherent limitations. First, many important clinical cardiovascular risk predictors have not been factored into the CRAX2MACE model. While age, gender, and diabetes have been included in the model—the absence of other common risk factors for coronary disease including hypertension, hyperlipidemia, and smoking would impact the strength of the clinical prediction model and influence the outcome results. In the past, multiparametric prediction models and clinical risk factor calculators have included these well-known risk factors, resulting in better preventative strategies as well as enhanced screening of patients at risk for cardiovascular events.^{14,15} Clinical decision-making with regards to diagnostic testing and/or therapeutic intervention is often guided by taking all the cardiovascular risk factors into consideration. Therefore, selecting some factors at the expense of others may not be in line with the real-world practice. Secondly, since this study was performed on a group from 2001 to 2008, the dataset may not be reflective of the technological advancements that have been made in the field of cardiology and medicine between then and now. With newly emerging therapeutics, recent developments in imaging, and altered practice guidelines—the true applicability of the predictive tool in today's clinical arena is unclear. Furthermore, the internal validation group was drawn from the same population as the development group. Independent prospective validation in a different population could be an important next step.

The era of personalized medicine holds a great number of promises and possibilities for both practitioners and patients. Clinical risk assessment will no longer be limited to a “one size fits all” approach of a laundry list of clinical risk factors, but rather be able to further stratify patients by directly incorporating diagnostic testing results. While there remains work to be done, the evolutionary step forward in coronary artery disease risk assessment offered by tools such as

CRAX2MACE offers an amalgamation of previous clinical experience of the past and 21st century computer processing to enhance risk stratification.

Disclosures

The authors have no disclosures.

References

1. Virani SS, Alonso A, Benjamin EJ et al. Heart disease and stroke Statistics—2020 Update: A report from the American Heart Association. *Circulation* 2020;141:e139–e596. <https://doi.org/10.1161/CIR.0000000000000757>
2. Fihn SD, Gardin JM, Abrams J et al. ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease. *Circulation* 2012;126:e44–e164. <https://doi.org/10.1161/CIR.0b013e3182776f83>
3. Montalescot G, Sechtem U, Achenbach S et al. 2013 ESC guidelines on the management of stable coronary artery disease. *Eur Heart J* 2013;34:296. <https://doi.org/10.1093/eurheartj/ehd296>
4. Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease. *N Engl J Med* 1979;300:1350–8. <https://doi.org/10.1056/nejm197906143002402>
5. Doherty JU, Kort S, Mehran R et al. ACC/AATS/AHA/ASE/ASNC/HRS/SCAI/SCCT/SCMR/STS 2019 appropriate use criteria for multimodality imaging in the assessment of cardiac structure and function in nonvalvular heart disease. *J Am Coll Cardiol* 2019;73:488–516. <https://doi.org/10.1016/j.jacc.2018.10.038>
6. Navare SM, Mather JF, Shaw LJ, Fowler MS, Heller GV. Comparison of risk stratification with pharmacologic and exercise stress myocardial perfusion imaging: A meta-analysis. *J Nucl Cardiol* 2004;11:551–61. <https://doi.org/10.1016/j.nuclcard.2004.06.128>
7. Klocke FJ, Baird MG, Lorell BH et al. ACC/AHA/ASNC guidelines for the clinical use of cardiac radionuclide imaging—executive summary: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASNC Committee to Revise the 1995 Guidelines for the Clinical Use of Cardiac Radionuclide Imaging). *J Am Coll Cardiol* 2003;42:1318–33. <https://doi.org/10.1016/j.jacc.2003.08.011>
8. Leslie WD, Bryanton M, Goertzen A, Slomka P. Prediction of 2-year major adverse cardiac events from myocardial perfusion scintigraphy and clinical risk factors. *J Nucl Cardiol* 2021. <https://doi.org/10.1007/s12350-021-02617-7>
9. He T, Liu X, Xu N et al. Diagnostic models of the pre-test probability of stable coronary artery disease: A systematic review. *Clinics* 2017;72:188–96. [https://doi.org/10.6061/clinics/2017\(03\)10](https://doi.org/10.6061/clinics/2017(03)10)
10. Garcia EV, Slomka P, Moody JB, Germano G, Ficaro EP. Quantitative clinical nuclear cardiology, Part 1: Established applications. *J Nucl Med* 2019;60:1507–16. <https://doi.org/10.2967/jnumed.119.229799>
11. Martineau P, Slomka P, Goertzen A, Leslie WD. CRAX: A simple cardiovascular risk assessment tool to predict risk of acute myocardial infarction or death. *J Nucl Cardiol* 2020;27:2365–74. <https://doi.org/10.1007/s12350-018-01556-0>
12. Betancur J, Otaki Y, Motwani M et al. Prognostic value of combined clinical and myocardial perfusion imaging data using machine learning. *JACC Cardiovasc Imaging* 2018;11:1000–9. <https://doi.org/10.1016/j.jcmg.2017.07.024>
13. Djaileb L, Seiller A, Canu M et al. Prognostic value of SPECT myocardial perfusion entropy in high-risk type 2 diabetic patients. *Eur J Nucl Med Mol Imaging* 2020. <https://doi.org/10.1007/s00259-020-05110-4>
14. Sheridan S, Pignone M, Mulrow C. Framingham-based tools to calculate the global risk of coronary heart disease. *J Gen Intern Med* 2003;18:1039–52. <https://doi.org/10.1111/j.1525-1497.2003.30107.x>
15. Tunstall-Pedoe H. Cardiovascular risk and risk scores: ASSIGN, Framingham, QRISK and others: How to choose. *Heart* 2011;97:442–4. <https://doi.org/10.1136/hrt.2010.214858>

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