Myocardial stress perfusion in asymptomatic patients: the silent ischemia makes the loudest sound

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The last 50 years have seen unprecedented success in tackling heart disease with cardiovascular mortality rates falling by up to 60% [1]. This has been driven by leaps forward in public health and in the development and routine utilization of primary and secondary preventative therapies. Despite these significant advances, coronary heart disease remains the cause of 1 in 7 deaths [1], with an ST-elevation myocardial infarction (STEMI) still the first presentation of coronary artery disease in > 80% of patients. Fortunately, 80% of patients presenting with an acute MI have antecedent cardiovascular risk factors [2], presenting a key opportunity to enable identification and early preventative treatment of patients at greatest risk of future cardiovascular events.

Cardiovascular magnetic resonance imaging (MRI) holds great potential for the detection and quantification of myocardial disease due to its high spatial and temporal resolution, and the ability to assess myocardial function, perfusion, and scar in the same examination. The CE-MARC study showed a greater accuracy for the detection of coronary artery disease for adenosine stress perfusion MRI compared with SPECT, as well as providing greater risk discrimination of future cardiovascular events [3]. Subsequent to this study, the prognostic power of MRI has been replicated in symptomatic patients in multiple large registries [4]. It is therefore a technology that might help to further stratify cardiovascular risk in asymptomatic cohorts as well.

It is this hypothesis that Pezel and colleagues [5] seek to address. They do so by examining the prognostic value of stress perfusion MRI in asymptomatic patients with elevated cardiovascular risk. They retrospectively identified 903 patients with ≥ 2 cardiovascular risk factors referred for dipyridamole stress perfusion MRI between 2009 and 2011, providing a median of 9 years follow-up to examine the prognostic significance of any findings. To their credit, the authors focused on hard end points in their definition of major adverse cardiovascular events (MACE), including only cardiovascular mortality and non-fatal MI as their primary endpoint, avoiding revascularization which is open to significant confirmation bias. In this asymptomatic cohort, 12% of patients had an inducible perfusion defect and 11% had evidence of a prior unrecognized MI, with a third of those with MI having an additional inducible perfusion defect beyond the territory of their infarct.

Over the 9 years of follow-up, 91 major adverse cardiovascular events occurred (72 cardiovascular mortality and 19 non-fatal MI). The presence of a perfusion defect was associated with an approximately 6-fold increase in the risk of MACE on multivariate analysis, with unrecognized MI conferring a 2-fold increase in risk in the same model. These results held true in two different multivariate models, and in an additional competing risk model with cardiovascular mortality and non-fatal MI considered separately, with hazard ratios persisting in the model suggesting the findings are robust. Furthermore, while the prognosis of silent perfusion defects on MRI has not been reported, that of unrecognized MI is well reported, with the current 2.4-fold risk in close agreement with that of a recent meta-analysis including 3018 patients in which there was a 3.2-fold risk of MACE in those with unrecognized MI [6].

It should be noted that the 2.2% annualized event rate in the current study is relatively high for an asymptomatic cohort with no prior cardiovascular events. This is double the event

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rate observed in the SPINS registry (a study of symptomatic patients), and lies closer to the 3.6% event rate of MR-INFORM which exclusively enrolled high pre-test probability patients with chest pain [4, 7]. This will partially be accounted for by the older age of the current cohort compared with these prior studies but is also likely driven by referral bias. One-third of the study cohort were referred due to an inconclusive stress test, suggesting there is a wider cohort of negative stress tests that have been screened out prior to MRI. Inconclusive stress tests are themselves a marker of elevated risk, with a two-fold risk of cardiovascular events compared with normal stress tests [8]. This will likely reduce the diagnostic yield if routine screening was to be implemented in a general population with multiple risk factors; however, it should have a relatively minimal impact on the relative risk of a positive test leaving the significance of such findings intact.

A critical question remains as to what to do with this knowledge of high risk? Answering this question is hampered somewhat by one of the key omissions of the current study, with no detail provided on the prevalence of preventative medications. Thus, it is not clear whether these results are driven by poor rates of preventative therapies in this high-risk population, or in spite of optimal medical therapy. Assuming the latter, how does one escalate therapy in this high-risk cohort? While the results of the ISCHEMIA trial were derived in a high-risk symptomatic cohort, there is little reason to believe that its findings of no additional prognostic benefit of revascularization compared with optimal medical therapy would be any different in an asymptomatic cohort [9].

In the era of precision medicine, detailed phenotyping with imaging could result in more effective targeting of expensive emerging therapies such as the growing array of new monoclonal antibody therapies targeting both the lipid and inflammatory pathways in CAD [10]. While statin therapy is cheap and using advanced imaging to select patients for this is unlikely to ever be cost-effective [11], these new therapies are extremely expensive, and better risk stratification with imaging may help better identify those with most to gain. In such an endeavor, MRI-guided precision medicine will have to prove its mettle against cardiac computed tomography. This latter technique provides a direct assessment of the severity of atherosclerosis rather than the surrogate of reduced blood flow, and rules out left main disease in less than half the time it takes to perform a stress MRI [12]. Prospective studies are now required, which will be much aided in both justification and determining study sample size by the insights gleaned from the current robust analysis.

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Methodology

• Editorial

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