**Stress CMR Imaging for Stable Chest Pain Syndromes: under-used and undervalued?**

**Running title: Stress CMR: under-used and undervalued?**

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Over the past decade, in many developed healthcare systems, there has been dramatic increase in the use of stress CMR to aid both diagnosis and further management decisions in patients with stable chest pain syndromes. This has been driven by a strong evidence base and contemporary high-quality randomised trials that have led to a Class I recommendation by the European Society of Cardiology for the use of stress CMR as a first-line investigation [1].

CMR has a high diagnostic accuracy for the identification of significant obstructive coronary artery disease (CAD) [2,3] compared to invasive coronary angiography (ICA). More importantly, it is highly concordant with the reference standard invasive FFR for myocardial ischemia detection [4], which has been shown in clinical trials to deliver better patient outcomes compared to revascularisation decisions made by visual angiographic interpretation [e.g.5]. A first-line strategy of stress CMR in patients with chest pain and suspected or known CAD, has recently been evaluated in two large, multi-centre, clinical trials. These showed that stress CMR is 1) a highly effective gatekeeper for the catheter-lab, significantly reducing the rates of ‘unnecessary’ ICA compared to management according to the UK NICE 2010 chest pain guideline [6], and 2) non-inferior to a strategy of direct to ICA+/-FFR as needed, in terms of clinical outcomes at 12-months [7]. Furthermore, in terms of prognostication, when adjusted for multiple cardiovascular risk factors and revascularisation, CMR was more closely associated with 5 year MACE than MPS-SPECT [8].

So why is CMR not used more frequently in some healthcare systems; perhaps it is related to the index procedural costs? Certainly in some countries, the index cost of stress CMR is higher than other functional tests, but in the US this is not strictly the case, with CMR being less costly than MPS-SPECT ($807 vs. $1,219; based on Medicare reimbursement) and PET. However, this is not the complete picture. To understand the true cost and hence value of a test, one needs to consider the false positive and false negative rates, and their impact on downstream investigations and resource use, including impacts on health resulting from delayed and incorrect treatments. Only by conducting a rigorous health economic analysis of the investigation and treatment pathway can one get a clear idea of a tests cost-effectiveness in a particular healthcare system, and start to understand the value of that test in terms of willingness to pay thresholds. Typically, the standard unit of measurement is the quality-adjusted life-year (QALY), a generic measure of health, capturing both quality and quantity of life lived, where one QALY equates to one year in perfect health. On this basis, stress CMR has been shown to be cost-effective as an investigation for stable chest pain in healthcare systems across Europe, UK and US [9-11].

In this issue of *iJACC*, Ge et al. [12] describe their cost effectiveness analysis of stress CMR for stable chest pain syndromes, using data derived from the multi-center Stress CMR Perfusion Imaging in the United States (SPINS) Study. SPINS was a registry conducted between 2008 and 2013, of patients with known or suspected obstructive CAD, aged between 35 and 85 years, referred for clinical stress CMR at 13 US centres [13]. Using a decision analytic model to estimate lifetime healthcare costs and QALYs, they assessed the cost-effectiveness of a stress CMR first-line strategy, against four other first-line strategies: 1) Immediate ICA with selective FFR, 2) MPS-SPECT, 3) CTCA with selective CT-FFR, and 4) no imaging. The analyses were conducted from a US health system perspective over a lifetime horizon, with all costs in 2017 dollars, and a threshold for willingness to pay for health of $100,000/QALY. SPINs follow-up was for at least 4 years, for MACE (cardiovascular death, acute non-fatal myocardial infarction (AMI), hospitalization for unstable angina (UA) or congestive heart failure (CHF), and late coronary artery bypass grafting (CABG) (MACEAll)), with ‘hard’ endpoints defined as cardiovascular death and AMI (MACEHard).

Predictably, doing ‘no imaging’ investigations was the cheapest of the five strategies, but produced the lowest lifetime QALYs. However, in terms of MACEHard, compared to a ‘no imaging’ strategy, CMR strongly dominated (i.e. was associated with lower costs and more QALYs) both MPS-SPECT and CTCA, with an incremental cost-effectiveness ratio (ICER) of $52,000/QALY. When MACEAll was considered, the CMR-based strategy remained the preferred strategy in the base-case, with ICER of $58,000/QALY compared to the ‘no imaging’ strategy, and again dominated both MPS-SPECT and CTCA. As these model-based analysis techniques rely on multiple assumptions, the authors performed multiple sensitivity analyses, and showed that the results remained consistent for CMR. Finally, using probabilistic sensitivity analysis (PSA) and a cost-effectiveness threshold of $100,000/QALY, the CMR-based strategy was optimal in 84% of draws and a ‘no-imaging’ strategy in 16%; MPS-SPECT, CTCA and immediate ICA were optimal strategies in 0%.

How do we interpret these findings? Firstly, the authors should be congratulated for their efforts in developing a coherent decision analytic model synthesising contemporary US data from the SPINS study with other literature. Importantly, their conclusions appears robust and we commend the use of PSA to address the joint uncertainty across all parameters, which demonstrates a high probability of CMR being cost-effective at $100,000/QALY. Nonetheless, there are potential weaknesses which could be addressed in future analyses, for example, a failure to reflect higher MACE risk in the year following a previous MACE is not in line with previous analyses, and assuming a constant long-term MACE risk, does not reflect increasing risk with age [14,15]. Similarly, the model does not reflect increasing costs of patients with increasing age [16]. The use of common utility values for those with and without obstructive CAD and the failure to consider disutility arising from non-fatal adverse events associated with ICA, or from recovery from revascularisation is questionable, the impact of which has not been considered in the uncertainty analysis. Finally, the divergence between the results based on ‘hard’ and ‘all’ MACE outcomes needs further consideration, as does the use of common mortality multipliers across these two different MACE outcomes.

The lack of accepted cost-effectiveness thresholds in the US makes conclusions on cost-effectiveness of interventions challenging, however, the ICERs suggested here for CMR fall well below most accepted values, although exceed the historic and widely used, if also much maligned, $50,000 per QALY [17]. The authors recommend the use of future RCTs to further evaluate these modalities, however, there are challenges in conducting such trials given the size required to demonstrate impacts on final endpoints, and the potential that the evidence already demonstrates a lack of clinical equipoise. The use of PSA in the model could be extended to consider the importance of the uncertainty of different parameters to help focus where the most valuable future research could be conducted [18].

In summary, from a US perspective the study by Ge et al., adds the final piece to the jigsaw. CMR has high diagnostic accuracy for obstructive CAD detection, is closely concordant with the invasive reference standard of FFR for ischemia detection, is a strong prognosticator, and in the US, the index reimbursement cost of stress CMR is lower than MPS-SPECT, with CMR being a cost effective first-line investigation for suspected CAD in multiple scenarios [12]. For these reasons, and the fact that a comprehensive ischemia/LV function/viability CMR scan can be performed in as little as 20mins [19], there really is no logic as to why CMR should be under-used or undervalued anymore.

**References**

1. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J. 2020;41(3):407-477.
2. JP Greenwood, N Maredia, JF Younger, et al. Cardiovascular magnetic resonance and single-photon emission computed tomography for diagnosis of coronary heart disease (CE-MARC): a prospective trial. Lancet 2012; 379(9814): 453-460.
3. Jaarsma C, Leiner T, Bekkers SC, et al. Diagnostic performance of noninvasive myocardial perfusion imaging using single-photon emission computed tomography, cardiac magnetic resonance, and positron emission tomography imaging for the detection of obstructive coronary artery disease: a meta-analysis. J Am Coll Cardiol. 2012; 59:1719–1728
4. Danad I, Szymonifka J, Twisk JWR, et al. Diagnostic performance of cardiac imaging methods to diagnose ischaemia-causing coronary artery disease when directly compared with fractional flow reserve as a reference standard: a meta-analysis. Eur Heart J. 2017;38(13):991-998.
5. Tonino PA, De Bruyne B, Pijls NH, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med. 2009;360(3):213-24.
6. JP Greenwood, DP Ripley, C Berry, et al. Effect of care guided by cardiovascular magnetic resonance, myocardial perfusion scintigraphy, or NICE guidelines on subsequent unnecessary angiography rates: a randomized trial (CE-MARC 2). JAMA 2016; 316(10):1051-1060.
7. E Nagel, JP Greenwood, GP McCann, et al. Magnetic Resonance Perfusion or Fractional Flow Reserve in Coronary Disease. New England Journal of Medicine 2019;380:2418-28.
8. JP Greenwood, BA Herzog, JM Brown, et al. Prognostic Value of CMR and SPECT in Suspected Coronary Heart Disease: Long Term Follow-Up of the CE-MARC Study. Annals of Internal Medicine 2016; 165(1):1-9.
9. S Walker, F Girardin, C McKenna, et al. Cost-effectiveness of cardiovascular magnetic resonance in the diagnosis of coronary heart disease: an economic evaluation using data from the CE-MARC study. Heart 2013; 99(12):873-81.
10. M Pletscher, S Walker, K Moschetti, et al. Cost-effectiveness of functional cardiac imaging in the diagnostic work-up of coronary heart disease. Eur Heart J Qual Care Clin Outcomes. 2016; 2(3):201-207.
11. Moschetti K, Favre D, Pinget C, et al. Comparative cost-effectiveness analyses of cardiovascular magnetic resonance and coronary angiography combined with fractional flow reserve for the diagnosis of coronary artery disease. Journal of Cardiovascular Magnetic Resonance 2014, 16:13.
12. Ge Y, Pandya A, Steel K, et al. Cost Effectiveness Analysis of Stress Cardiac Magnetic Resonance Imaging for Stable Chest Pain Syndromes. JACC imaging 2020 (in press).
13. RY Kwong, Y Ge, K Steel, et al. Cardiac Magnetic Resonance Stress Perfusion Imaging for Evaluation of Patients With Chest Pain. J Am Coll Cardiol 2019;74:1741–55.
14. Briggs A, Mihaylova B, Sculpher M, et al. Cost effectiveness of perindopril in reducing cardiovascular events in patients with stable coronary artery disease using data from the EUROPA study. Heart 2007;93:1081–6.
15. Asaria M, Walker S, Palmer S, et al. Using electronic health records to predict costs and outcomes in stable coronary artery disease. Heart 2016;102:755–62.
16. Walker S, Asaria M, Manca A, et al. Long-term healthcare use and costs in patients with stable coronary artery disease: a population-based cohort using linked health records (CALIBER). Eur Hear J - Qual Care Clin Outcomes 2016;2:125–40.
17. Neumann PJ, Cohen JT, Weinstein MC. Updating Cost-Effectiveness — The Curious Resilience of the $50,000-per-QALY Threshold. N Engl J Med 2014;371:796–7.
18. Rothery C, Strong M, Koffijberg HE, et al. Value of Information Analytical Methods: Report 2 of the ISPOR Value of Information Analysis Emerging Good Practices Task Force. Value Health 2020;23:277–286.
19. JRJ Foley, C Richmond, GJ Fent, et al. Rapid Cardiovascular Magnetic Resonance for Ischemic Heart Disease Investigation (RAPID-IHD). JACC Img 2020; (in press).