**Institution:** University of Leeds

**Unit of Assessment:** UoA 1

**Title of case study:** Development and validation of Cardiovascular Magnetic Resonance (CMR) imaging for patients with known or suspected coronary artery disease (CAD): superior diagnostic accuracy, prognostication and cost effectiveness compared to the global clinical standard

**Period when the underpinning research was undertaken:** 2001-2016

**Details of staff conducting the underpinning research from the submitting unit:**

| Name(s): | Role(s) (e.g. job title): | Period(s) employed by submitting HEI: |
|---|---|---|
| John P Greenwood | Professor of Cardiology | 2001-current |
| Sven Plein | Professor of Cardiology | 2005-current |

**Period when the claimed impact occurred:** 2013-current

**Is this case study continued from a case study submitted in 2014?** No

**1. Summary of the impact** (indicative maximum 100 words)

Prior to 2006, cardiovascular magnetic resonance (CMR) imaging for stable coronary artery disease (CAD) detection was not a routine NHS test. Our CE-MARC trial provided the largest real-world evidence of the diagnostic accuracy of CMR [1,2], its prognostic ability [3], cost effectiveness [4], and superiority over the existing NHS reference standard. CE-MARC provided the evidence-base that led to the first inclusion of CMR into international clinical guidelines for stable chest pain investigation (European & US). Consequently, CMR for stable CAD detection was rapidly introduced across the NHS, with UK national audit figures showing 24% of all UK CMR was for a CAD indication (BSCMR audit 2019).

**2. Underpinning research** (indicative maximum 500 words)

The Leeds CMR research group is an interdisciplinary research collaboration incorporating clinician scientists, medical physicists, statisticians, and health economists. In 2002, the group showed CMR was a promising technique for the assessment of stable CAD (Plein, *Radiology* 2002). Further pulse sequence optimisation was performed, and the approach validated in patients with acute coronary syndromes (Plein, *JACC* 2004; Greenwood, *Heart* 2007). Three key milestones were then identified so we could take CMR from bench to bedside: (a) demonstration that the diagnostic accuracy of CMR was at least as good as the clinical reference standard MPS-SPECT (myocardial perfusion scanning with single-photon emission computed tomography); (b) determination that CMR was cost effective for the NHS; (c) confirmation that CMR was at least as good as MPS-SPECT in terms of prognostication.

In 2005, a BHF programme grant application was awarded (GBP1.3 Million; Greenwood) to address all three milestones by conducting the largest prospective real-world clinical evaluation of CMR in suspected CAD, compared to MPS-SPECT and X-ray angiography. This programme of work was delivered to time and target, with milestone (a) being published in *The Lancet* and *Circulation* [**1**,**2**]. Milestones (b) and (c) were published subsequently [**3**,**4**]. CE-MARC was described as a landmark diagnostic trial and cited as the underpinning evidence for CMR being incorporated for the first time into EU and US clinical practice guidelines.

Following CE-MARC, we set out to test the hypothesis that CMR was not just a superior diagnostic test to MPS-SPECT, but that it could improve patient management. In 2011, the CE-MARC-2 UK multi-centre randomised trial was funded by the BHF (Greenwood, GBP1.2 Million), comparing head-to-head management strategies of CMR *vs* MPS-SPECT vs UK NICE guidelines (CG95 2010). Presented as a late-breaking clinical trial at the European

Society of Cardiology (Rome, 2016), CE-MARC-2 showed that both CMR and MPS-SPECT significantly out-performed the UK NICE guidelines in terms of reducing the rates of 'unnecessary' invasive coronary angiography [**5**].

Secondary outcome analyses of CE-MARC-2 showed that a CMR strategy was more cost effective for the NHS than the UK NICE guidelines (Walker, *Heart* 2020), resulting in less invasive coronary angiograms with no detriment to patient health-related quality of life or clinical outcomes at 3 years (Greenwood, *JACC* 2020).

Following the CE-MARC trials, the team played a leading role in the MR-INFORM trial, a global multi-centre trial of CMR *vs* invasive angiography+/-FFR. This showed that a CMR-guided investigation strategy in stable chest pain resulted in less invasive angiograms and coronary revascularisation procedures, with no difference in clinical outcomes [**6**].

With the updating of the UK NICE chest pain guidelines in 2016, which now recommend CT coronary angiography first line in all patients with typical and atypical angina, we have obtained funding (Greenwood, Heart Research UK) for a pragmatic UK multi-centre trial (CE-MARC 3, n=4,000) to evaluate this recommendation across the NHS.

**3. References to the research** (indicative maximum of six references)

1. **JP Greenwood**, N Maredia, JF Younger, JM Brown, J Nixon, CC Everett, P Bijsterveld, JP Ridgway, A Radjenovic, CJ Dickinson, SG Ball, **S Plein**. CE-MARC: A prospective evaluation of cardiovascular magnetic resonance and single-photon emission computed tomography in coronary heart disease. *Lancet* 2012; 379(9814): 453-460. doi:10.1016/S0140-6736(11)61335-4

2. **JP Greenwood**, M Motwani, N Maredia, JM Brown, CC Everett, J Nixon, P Bijsterveld, CJ Dickinson, SG Ball, **S Plein**. Comparison of cardiovascular magnetic resonance and single-photon emission computed tomography in women with suspected coronary artery disease from the CE-MARC trial. *Circulation* 2014; 129:1129-1138. doi:10.1161/circulationaha.112.000071

3. **JP Greenwood**, BA Herzog, JM Brown, CC Everett, J Nixon, P Bijsterveld, N Maredia, M Motwani, CJ Dickinson, SG Ball, **S Plein**. 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. doi:10.7326/M15-1801

4. S Walker, F Girardin, C McKenna, SG Ball, J Nixon, **S Plein**, **JP Greenwood**, M Sculpher. 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. doi:10.1136/heartjnl-2013-303624

5. **JP Greenwood**, DP Ripley, C Berry, GP McCann, **S Plein**, C Bucciarelli-Ducci, E Dall'Armellina, A Prasad, P Bijsterveld, JR Foley, K Mangion, M Sculpher, S Walker, CC Everett, DA Cairns, LD Sharples, JM Brown. 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. doi:10.1001/jama.2016.12680

6. E Nagel, **JP Greenwood**, GP McCann, N Bettencourt, AM Shah, ST Hussain, D Perera, **S Plein**, C Bucciarelli-Ducci, M Paul, MA Westwood, M Marber, WS Richter, VO Puntmann, C Schwenke, J Schulz-Menger, R Das, J Wong, DJ Hausenloy, H Steen. C Berry, on behalf of the MR-INFORM Investigators. Magnetic resonance perfusion or fractional flow reserve in coronary disease. *New England Journal of Medicine* 2019;380:2418-28. doi:10.1056/NEJMoa1716734

**4. Details of the impact** (indicative maximum 750 words)

CAD is a leading cause of death and disability worldwide, and the leading single cause of mortality in Europe, responsible for 862,000 deaths a year (19% of all deaths) among men and 877,000 deaths (20%) among women. In the UK, there are an estimated 1.98 million people suffering with symptoms of angina, and CAD costs the UK economy GBP9 billion a year. Our CE-MARC trial provided the largest real-world evidence of the diagnostic accuracy of CMR, its prognostic ability and cost effectiveness, showing superiority over the current NHS reference standard. As a result, CE-MARC provided the evidence base leading to the first inclusion of CMR into international clinical guidelines for chest pain investigation (European & US). This contributed to CMR for stable CAD detection being rapidly introduced across the NHS.

**Inclusion of CMR for the first time in international guidelines**
The CE-MARC trial results underpin the high level of evidence (Class 1) and are cited to support the use of CMR for stable chest pain investigation in the European and US clinical guidelines. US guidelines on appropriate use criteria for the detection and risk assessment of stable CAD cite the CE-MARC trial as evidence supporting the utility and accuracy of stress CMR [**A**]. European guidelines on the management of stable CAD cite the CE-MARC trial as evidence for the diagnostic accuracy of CMR perfusion imaging compared with MPS [**B**]. Additionally, Greenwood is on the writing committee for the *2021 AHA/ACC/ASE/ASNC/ CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain*. Notably, this writing group is normally comprised of American experts. Greenwood was invited to be a part of this group in view of "professional standing, expertise, and track record of managing patients with chest pain, which was superior to any other colleagues in the US and indeed globally" [**C**]. The results of CE-MARC and CE-MARC 2 have been cited as underpinning evidence to support the recommendation for stress CMR to be used as an effective frontline investigation in the diagnosis of stable chest pain.

The CEO of the Society for Cardiovascular Magnetic Resonance has acknowledged the "ground-breaking" CE-MARC and CE-MARC-2 trials, which have significantly impacted the practice of cardiology globally, saving money to healthcare systems, reducing patients' risk and improving patients' quality of life on clinical cardiology practice and improving patients' management using CMR globally [**C**]. The significant contribution the trials have had on international guidelines for the management of chest pain has also been emphasised:

"Stress CMR is now recommended in Class I (which means there is evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective) with the level of evidence A (which means the data is supported by randomised trials). Class IA is the highest level of recommendation and evidence in ESC/AHA/ACC guideline documents. Guidelines from leading scientific societies such as the European Society of Cardiology are the reference documents that cardiologists in Europe and worldwide use to guide clinical practice" [**C**].

**Cost-effectiveness of CMR over other diagnostic strategies**
The availability of a more accurate diagnostic test reduces the need for down-stream investigations, including expensive invasive coronary angiography. Health economic analysis of CE-MARC showed that CMR was more cost effective for the NHS than MPS-SPECT (which was the prior clinical reference standard). The results from this economic evaluation suggest that CMR should be considered as part of a diagnostic strategy for the identification of patients with CAD suitable for revascularisation.

Economic evaluation of CE-MARC 2 to assess the cost-effectiveness of CMR, MPS and NICE guidelines showed CMR had the highest estimated quality-adjusted life year (QALY) gain overall (2.21 (95% credible interval 2.15, 2.26) compared with 2.07 (1.92, 2.20) for NICE and 2.11 (2.01, 2.22) for MPS) and incurred comparable costs (overall GBP1625 (GBP1431, GBP1824) compared with GBP1753 (GBP1473, GBP2032) for NICE and GBP1768 (GBP1572, GBP1989) for MPS) [**D**]. Overall, CMR was the cost-effective strategy, being the dominant strategy (more effective, less costly) with incremental net health benefits per patient

of 0.146 QALYs (−0.18, 0.406) compared with NICE guidelines at a cost-effectiveness threshold of GBP15 000 per QALY (93% probability of cost-effectiveness).

Data from CE-MARC and its economic model have also been used internationally to show CMR cost-effectiveness, e.g. in Switzerland [**E**] and Australia [**F**].

**Dramatic uptake in stress perfusion CMR services across UK**
Results from the CE-MARC and CE-MARC 2 trials showing the high diagnostic accuracy and cost effectiveness of CMR have directly impacted on NHS practice. This is evidenced by the dramatic uptake in stress perfusion CMR services across the UK and also uptake in Europe/globally.

In 2008, survey data revealed 20,597 CMR scans were performed in the UK. This compares to 114,967 scans in 2018, representing a remarkable 5-fold increase over 10-years. Additionally, 100,386 scans were performed in 2017, representing a single year increase of 14.7%. In total, ~24% of all UK CMR was for CAD [**G**]. When focusing on a single Trust, Leeds Teaching Hospitals confirmed that the number of CMR scans has dramatically increased by 135% in the last 10 years (1001 scans in 2010 compared to 2348 in 2020), while numbers of MPS activity have reduced in support of a shift in referrals based on the CE-MARC and CE-MARC-2 trials (1715 scans for the 2014-15 financial year, compared with 1021 for the 2019-20 financial year) [**H**].

The European CMR Registry (EuroCMR) with over 37,000 patients from 57 European centres has demonstrated the impact of CMR on clinical diagnosis and management in Europe. The US multi-centre SPINS registry has shown that CMR in stable chest pain syndromes was a highly effective prognostic test associated with low healthcare costs spent on downstream cardiac testing [**I**].

**5. Sources to corroborate the impact** (indicative maximum of 10 references)

[**A**]. MJ Wolk, SR Bailey, JU Doherty, PS Douglas, RC Hendel, CN Kramer, JK Min, MR Patel, L Rosenbaum, LJ Shaw, RF Stainback, JM Allen, American College of Cardiology Foundation Appropriate Use Criteria Task Force.
ACCF/AHA/ASE/ASNC/HFSA/HRS/SCAI/SCCT/SCMR/STS 2013 multimodality appropriate use criteria for the detection and risk assessment of stable ischemic heart disease: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2014; 63(4): 380-406. doi:10.1016/j.jacc.2013.11.009

[**B**]. Task Force Members; G Montalescot, U Sechtem, S Achenbach, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J* 2013; 34(38): 2949-3003. doi:10.1093/eurheartj/eht296

[**C**]. Testimonial from the CEO of the Society for Cardiovascular Magnetic Resonance

[**D**]. S Walker, E Cox, B Rothwell, C Berry, GP McCann, C Bucciarelli-Ducci, E Dall'Armellina, A Prasad, JRJ Foley, K Mangion, P Bijsterveld, C Everett, D Stocken, **S Plein**, **JP Greenwood**, M Sculpher. Cost-effectiveness of cardiovascular imaging for stable coronary heart disease. *Heart* 2021; 107(5): 381-388. doi: 10.1136/heartjnl-2020-316990

[**E**]. M Pletscher, S Walker, K Moschetti, C Pinget, J Wasserfallen, **JP Greenwood**, J Schwitter, FR Girardin. 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.

doi:10.1093/ehjqcco/qcw008

**[F].** R Kozor, S Walker, B Parkinson, J Younger, C Hamilton-Craig, JBB Selvanayagam, **JP Greenwood**, AJ Taylor. Cost-effectiveness of cardiovascular magnetic resonance in diagnosing coronary artery disease in the Australian health care system. *Heart Lung Circ.* 2021; 30(3): 380-387. doi:10.1016/j.hlc.2020.07.008

**[G].** NG Keenan, G Captur, GP McCann, C Berry, SG Myerson, T Fairbairn, L Hudsmith, DP O'Regan, M Westwood, JP Greenwood. Regional variation in cardiovascular magnetic resonance service delivery across the UK. Heart. Submitted 17 November 2020. doi:10.1136/heartjnl-2020-318667

**[H].** Figures for CMR and MPS from Leeds Teaching Hospitals NHS Trust available on request

**[I].** 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(14):1741-1755. doi:10.1016/j.jacc.2019.07.074