

**Cardiovascular Magnetic Resonance Imaging for the  
Investigation of Patients with Coronary Heart Disease**

Dr David Paul Ripley

Submitted in accordance with the requirements for the degree of  
Doctor of Philosophy (PhD)

The University of Leeds  
Division of Cardiovascular and Diabetes Research  
Leeds Institute of Cardiovascular and Metabolic Medicine  
School of Medicine

November 2019

## Intellectual Property and Publications Statements

The candidate confirms that the work submitted is his/her own, except where work which has formed part of jointly-authored publications has been included. The contribution of the candidate and the other authors to this work has been explicitly indicated below. The candidate confirms that appropriate credit has been given within the thesis where reference has been made to the work of others.

### Chapter 1

**Ripley DP**, Motwani M, Plein S, Greenwood JP. Established and Emerging Cardiovascular Magnetic Resonance Techniques for the Assessment of Stable Coronary Heart Disease and Acute Coronary Syndromes. *Quant Imaging Med Surg.* 2014;4(5):330-44

Author contributions:

**D.P.R.** Concept, design, literature search, drafting of manuscript. **M.M.** Drafting and revision of the manuscript. **S.P.** Critical revision of the manuscript. **J.P.G.** Concept and critical revision of the manuscript.

**Ripley DP**, Musa TA, Dobson LE, Plein S, Greenwood JP. Cardiovascular magnetic resonance imaging - What the general cardiologist should know. *Heart.* 2016;102(19):1589-603

Author contributions:

**D.P.R.** Concept, design, literature search, drafting of manuscript. **T.A.M.** Drafting and revision of the manuscript. **L.E.D.** Drafting and revision of the manuscript. **S.P.** Critical revision of the manuscript. **J.P.G.** Concept and critical revision of the manuscript.

## Chapter 2

**Ripley DP**, Motwani M, Brown JM, Nixon J, Everett CC, Bijsterveld P, Maredia N, Plein S, Greenwood JP. Individual component analysis of the multi-parametric cardiovascular magnetic resonance protocol in the CE-MARC trial. *J Cardiovasc Magn Reson*. 2015 Jul 15;17(1):59.

Author contributions:

**D.P.R.** Analysis & interpretation of data, literature search, drafting of manuscript. **M.M.** Critical revision of the manuscript. **J.M.B.** Concept and design, analysis of data, critical revision of the manuscript **J.N.** Concept and design, analysis of data, critical revision of the manuscript **C.C.E.** Analysis & interpretation of data, critical revision of the manuscript. **P.B.** Critical revision of the manuscript. **N.M.** Analysis & interpretation of data, critical revision of the manuscript. **S.P.** Concept and design, analysis & interpretation of data, critical revision of the manuscript. **J.P.G.** Concept and design, analysis & interpretation of data, critical revision of the manuscript.

## Chapter 3

**Ripley DP**, Herzog BA, Maredia N, Motwani M, Kidambi A, Uddin A, Bijsterveld P, Brown JM, Everett CC, Nixon J, Dickinson CJ, Plein S, Greenwood JP. Ischaemia and Scar Burden Measured by Cardiac Magnetic Resonance Imaging in Patients with Coronary Heart Disease - a CE-MARC Sub-study. Submitted to *J Cardiovasc Magn Reson*

Author contributions:

**D.P.R.** Analysis & interpretation of data, literature search, drafting of manuscript. **B.A.H.** Analysis & interpretation of data, literature search, drafting of manuscript. **N.M.** Analysis & interpretation of data, critical revision of the manuscript. **M.M.** Critical revision of the manuscript. **A.K.** Critical revision of the manuscript. **A.U.** Critical revision of the manuscript. **P.B.** Critical revision of the manuscript. **J.M.B.** Concept and design, analysis of data, critical revision of the manuscript. **C.C.E.** Analysis & interpretation of data, critical revision of the manuscript. **J.N.** Concept and design, analysis of data, critical revision of the manuscript. **C.J.D.** Analysis & interpretation of data. **S.P.** Concept and design, analysis & interpretation of data, critical revision of the manuscript. **J.P.G.** Concept and design, analysis & interpretation of data, critical revision of the manuscript.

## Chapter 4

**Ripley DP**, McDiarmid AK, Kidambi A, Uddin A, Swoboda PP, Musa TA, Erhayiem B, Bainbridge GJ, Greenwood JP, Plein S, Higgins DM. Patient adaptive maximal resolution magnetic resonance myocardial stress perfusion imaging. *J Magn Reson Imaging*. 2015 Oct;42(4):946-53.

Author contributions:

**D.P.R.** Concept, design, analysis & interpretation of data, literature search, drafting of manuscript. **A.K.M.** Analysis & interpretation of data, critical revision of the manuscript. **A.K.** Critical revision of the manuscript. **A.U.** Critical revision of the manuscript. **P.P.S.** Critical revision of the manuscript. **T.A.M.** Critical revision of the manuscript. **B.E.** Critical revision of the manuscript. **G.J.B.** Analysis & interpretation of data. **J.P.G.** Critical revision of the manuscript. **S.P.** Concept, design & critical revision of the manuscript. **D.M.H.** Concept, design, analysis, interpretation of data & critical revision of the manuscript.

## Chapter 5

**Ripley DP**, Brown JM, Everett CC, Bijsterveld P, Walker S, Sculpher M, McCann GP, Berry C, Plein S, Greenwood JP. Rationale and design of the Clinical Evaluation of Magnetic Resonance imaging in Coronary heart disease 2 trial (CE-MARC 2): A prospective, multi-centre trial of diagnostic management of coronary heart disease. *Am Heart J.* 2015;169(1):17-24.

Author contributions: see below.

## Chapter 6

Greenwood JP, **Ripley DP**, Berry C, McCann GP, Plein S, Bucciarelli-Ducci C, Dall'Armellina E, Prasad A, Bijsterveld P, Foley JR, Mangion K, Sculpher M, Walker S, Everett CC, Cairns DA, Sharples LD, Brown JM; CE-MARC 2 Investigators. Effect of Care Guided by Cardiovascular Magnetic Resonance, Myocardial Perfusion Scintigraphy, or NICE Guidelines on Subsequent Unnecessary Angiography Rates: The CE-MARC 2 Randomized Clinical Trial. *JAMA.* 2016;316(10):1051-60.

Author contributions:

Concept and design: Greenwood, Ripley, Berry, McCann, Plein, Bijsterveld, Sculpher, Walker, Brown.

Acquisition, analysis, or interpretation of data: All Authors.

Drafting of the manuscript: Greenwood, Ripley, Bucciarelli-Ducci, Prasad, Foley, Everett, Cairns, Sharples, Brown.

Critical revision of the manuscript for important intellectual content: Greenwood, Berry, McCann, Plein, Bucciarelli-Ducci, Dall'Armellina, Bijsterveld, Foley, Mangion, Sculpher, Walker, Everett, Cairns, Sharples, Brown.

Statistical analysis: Everett, Cairns, Sharples, Brown.

Obtained funding: Greenwood, Berry, McCann, Plein, Brown.

Administrative, technical, or material support: Greenwood, Berry, Plein, Dall'Armellina, Bijsterveld, Foley, Mangion, Walker, Sharples.

Study supervision: Greenwood, Ripley, Berry, McCann, Bucciarelli-Ducci, Prasad, Bijsterveld, Foley, Mangion, Walker, Sharples, Brown.

Other - Economic analysis: Sculpher.

This copy has been supplied on the understanding that it is copyright material and that no quotation from the thesis may be published without proper acknowledgement.

© 2019 The University of Leeds and David Paul Ripley

## **Acknowledgements**

I would like to specifically thank my supervisors Professors Greenwood and Plein for the guidance and support. For providing the opportunity to research and explore this exciting area of cardiovascular medicine. I would like to extend my thanks to the CMR research department. Thanks to Gavin, Petra, Margaret, Caroline, Lisa, Anne, Debbie and Fiona for their assistance and help with recruitment and scanning.

I'm particularly grateful to my wife, Anne-Marie, for her enduring support throughout my career (and multiple house moves around the country). To my parents who taught me the value of hard work and without that early guidance I would not be where I am.

I would like to thank the British Heart Foundation and Heart Research UK for supporting this research.

Finally I dedicate this work to my children Harry and Isabella. They will both receive a bound copy of this thesis, which I'm absolutely sure they will never read, but hopefully may inspire them in the future to understand that with hard work anything is possible.

## **Abstract**

### **Objectives**

To evaluate the role of stress perfusion cardiovascular magnetic resonance (CMR) in the investigation of stable coronary artery disease (CAD).

### **Background**

Coronary artery disease remains the biggest cause of morbidity and mortality. The multi-parametric CMR examination is established as an investigative strategy for the investigation of CAD.

### **Methods**

Study 1 & 2: Patients with stable coronary artery disease underwent a multi-parametric CMR protocol assessing 4 components: i) left ventricular function; ii) myocardial perfusion; iii) viability (late gadolinium enhancement (LGE)) and iv) coronary magnetic resonance angiography (MRA). The diagnostic accuracy of the individual components were assessed. The ischaemic burden of stress CMR Vs. Single Photon Emission Computed Tomography (SPECT) was determined.

Study 3: Volunteers and patients were scanned with perfusion sequence which adapts the spatial resolution to the available scanning time and field-of-view.

Study 4: A multi-centre pragmatic randomised controlled trial of patients with stable angina comparing CMR guided-care Vs. SPECT guided-care Vs. National Institute of Health and Care Excellence guided-care.

### **Results**

Study 1 demonstrated the stress perfusion component of the multi-parametric CMR exam was the single most important component for overall diagnostic accuracy. However, the full combined multi-parametric protocol



was the optimal approach for disease rule-out, and the LGE component best for rule-in. Study 2 showed that there was reasonable agreement of the summed stress scores between CMR and SPECT (a well established investigation with significant amounts of prognostic data).

In study 3, a perfusion pulse sequence which automatically adapts the acquisition sequence to the available scanning time results in spatial resolution improvement and reduction in dark rim artefact.

Finally in study 4 in patients with suspected angina using CMR as an initial investigative strategy produced a significantly lower probability of unnecessary angiography compared to NICE guidance. There were similar rates of CAD detection were comparable suggesting no penalty for using functional imaging as a gatekeeper for angiography.

## **Conclusion**

CMR has high diagnostic accuracy for the detection of coronary artery disease; with similar detection of ischaemic burden to established tests and can be used safely and effectively as a gate keeper to invasive coronary angiography.

## Table of Contents

<b>Acknowledgements</b> .....	<b>vii</b>
<b>Abstract</b> .....	<b>viii</b>
Objectives .....	viii
Background .....	viii
Methods .....	viii
Results .....	viii
Conclusion .....	ix
<b>Table of Contents</b> .....	<b>x</b>
<b>List of Tables</b> .....	<b>xvi</b>
<b>List of Figures</b> .....	<b>xvii</b>
<b>Chapter 1 Background</b> .....	<b>2</b>
1.1 Coronary Heart Disease.....	2
1.2 Cardiovascular Magnetic Resonance.....	2
1.3 CMR in National & International Guidelines .....	3
1.4 CMR Physics, Methodology & Safety.....	7
1.4.1 Basic CMR Physics .....	7
1.4.2 Image Quality and Artefacts .....	10
1.4.3 CMR Safety and the Safety of Implanted Medical Devices .....	11
1.4.3.1 Safety of Implanted Medical Devices .....	11
1.4.4 CMR Contrast Agents: Indications and Safety .....	12
1.5 Cardiovascular Magnetic Resonance for the Investigation of Stable Coronary Heart Disease.....	12
1.5.1 Global and Regional LV Volumetric Assessment .....	13
1.5.2 Stress Cardiovascular Magnetic Resonance.....	13
1.5.2.1 Vasodilatory Stress CMR .....	14
1.5.2.2 Inotropic Stress CMR .....	17
1.5.2.3 Pushing the boundaries: improving stress technology.....	18
1.5.3 Coronary Artery Imaging .....	20
1.6 Cardiovascular Magnetic Resonance after Acute Coronary Syndromes.....	20
1.6.1 Acute Myocardial Infarction .....	21

1.6.1.1 Myocardial Oedema .....	21
1.6.1.2 Microvascular obstruction.....	22
1.6.1.3 Intramyocardial haemorrhage .....	24
1.6.1.4 Other sequelae of myocardial infarction .....	25
1.6.2 Assessment of Myocardial Viability after Myocardial Infarction .....	25
1.6.2.1 Transmurality of LGE .....	26
1.7 Prognostic Value of CMR in Coronary Heart Disease .....	27
1.8 Conclusion .....	29
<b>Chapter 2 Individual Component Analysis of the Multi-Parametric Cardiovascular Magnetic Resonance Imaging Protocol in the CE-MARC Trial.....</b>	<b>30</b>
2. 1 Abstract .....	30
2.1.1 Background .....	30
2.1.2 Methods .....	30
2.1.3 Results .....	30
2.1.4 Conclusions.....	31
2.2 Background .....	32
2.3 Methods .....	33
2.3.1 Study Design.....	33
2.3.2 CMR imaging and analysis.....	34
2.3.3 X-Ray Angiography .....	34
2.3.4 Statistical Analysis.....	36
2.4 Results .....	36
2.4.1 Study Population .....	36
2.4.2 Diagnostic Accuracy.....	36
2.4.2.1 Sensitivity .....	39
2.4.2.2 Specificity .....	39
2.4.2.3 Overall Diagnostic Performance.....	39
2.4.3 The Value of Components as Individual and Add On Tests: Likelihood Ratios .....	42
2.5 Discussion.....	42
2.5.1 Likelihood Ratios.....	44
2.5.2 Comparative Literature.....	47
2.6 Conclusions.....	50

<b>Chapter 3 Ischaemia and Scar Burden Measured by Cardiac Magnetic Resonance Imaging in Patients with Coronary Heart Disease - a CE-MARC Sub-study .....</b>	<b>51</b>
3.1 Abstract.....	51
3.1.1 Background .....	51
3.1.2 Methods .....	51
3.1.3 Results .....	51
3.1.4 Conclusions.....	52
3.2 Introduction .....	53
3.3 Methods .....	54
3.3.1 Patients .....	54
3.3.2 CMR imaging and analysis.....	55
3.3.3 SPECT imaging and analysis.....	56
3.3.4 X-ray angiography .....	57
3.3.5 Statistical Analysis.....	57
3.4 Results .....	58
3.4.1 Study Population .....	58
3.4.2 Image Quality .....	58
3.4.3 Summed Scores.....	58
3.4.3.1 Primary Analysis: All Angiographic Positive Population .....	58
3.4.3.2 Secondary Analysis: All 3-Tests Positive Population .....	60
3.4.4 Correlation and Agreement of Summed Scores.....	60
3.5 Discussion.....	66
3.6 Study Limitations.....	69
3.7 Conclusion .....	70
<b>Chapter 4 Patient Adaptive Maximal Resolution Magnetic Resonance Myocardial Stress Perfusion Imaging .....</b>	<b>71</b>
4.1 Abstract.....	71
4.1.1 Background .....	71
4.1.2 Methods .....	71
4.1.3 Results .....	71
4.1.4 Conclusion .....	72
4.2 Introduction .....	73
4.3 Methods .....	76
4.3.1 Patient Selection .....	76

4.3.2 Magnetic Resonance Imaging.....	77
4.3.3 Image Analysis.....	79
4.3.3.1 Quantitative measurements of SNR.....	80
4.3.4 Statistical Analysis.....	80
4.4 Results.....	82
4.4.1 Scan Parameters and Image Attributes.....	82
4.4.2 Signal-to-Noise Ratio.....	87
4.5 Discussion.....	87
4.5.1 Limitations.....	92
4.5.2 Conclusions.....	93

**Chapter 5 Rationale and design of the Clinical Evaluation of  
Magnetic Resonance imaging in Coronary heart disease 2  
trial (CE-MARC 2): A prospective, multi-centre, randomized  
controlled trial of diagnostic strategies for suspected  
coronary heart disease..... 94**

5.1 Abstract.....	94
5.1.1 Background.....	94
5.1.2 Trial Design.....	94
5.2 Background.....	96
5.3 Study Objectives.....	97
5.4 Methods.....	98
5.4.1 Study Design.....	98
5.4.2 Patient Population, Recruitment & Randomisation.....	99
5.4.3 Funding.....	104
5.4.4 Investigation Details.....	104
5.4.4.1 CMR.....	104
5.4.4.2 SPECT.....	106
5.4.4.3 Cardiac CT.....	107
5.4.4.4 X-ray angiography and FFR.....	108
5.4.5 Investigation Reporting.....	109
5.4.5.1 CMR.....	109
5.4.5.2 SPECT.....	110
5.4.5.3 Cardiac CT.....	111
5.4.5.4 X-ray angiography and FFR.....	111
5.4.6 Protocol deviations.....	112
5.4.7 Annual Follow-up.....	112

5.4.8 Primary Endpoint.....	113
5.4.8.1 Unnecessary invasive coronary angiography occurring within 12 months in each arm.....	113
5.4.9 Secondary Endpoints .....	114
5.4.9.1 Major adverse cardiovascular events.....	114
5.4.9.2 Positive coronary angiogram.....	114
5.4.9.3 Economic Evaluation.....	114
5.4.9.4 Quality of Life .....	115
5.4.9.5 Complications.....	115
5.4.10 Statistical Considerations .....	115
5.4.10.1 Sample Size .....	115
5.4.10.2 Analysis Plan.....	116
5.4.10.3 Primary Endpoint Analysis .....	117
5.4.10.3 Secondary Endpoint Analysis.....	117
5.4.11 Data monitoring.....	118
5.4.11 Conclusion .....	119
<b>Chapter 6 Results from the Clinical Evaluation of MAgnetic Resonance imaging in Coronary heart disease 2 trial (CE- MARC 2): A prospective, multi-centre, randomized controlled trial of diagnostic strategies for suspected coronary heart disease .....</b>	<b>120</b>
6.1 Results .....	120
6.1.1 Trial Population .....	120
6.1.2 Baseline Characteristics.....	120
6.1.3 Test Conduct.....	123
6.1.4 Primary End Point .....	124
6.1.5 Secondary End Points.....	126
6.1.6 Functional Imaging Assessment .....	129
6.2 Discussion.....	129
6.2.1 Limitations .....	133
6.2.2 Conclusions.....	134
<b>Chapter 7 Final Conclusions.....</b>	<b>136</b>
7.1 Diagnostic Accuracy of Cardiovascular Magnetic Resonance ....	136
7.2 Comparison of Ischaemic Burden between CMR and SPECT....	137
7.3 Developing a new perfusion pulse technique to maximise spatial resolution. ....	137

7.4 The Use of CMR as a Gate keeper to Invasive Coronary Angiography .....	138
7.5 Future Directions .....	139
<b>List of References .....</b>	<b>140</b>
<b>List of Abbreviations.....</b>	<b>152</b>
<b>Appendices .....</b>	<b>155</b>
9.1 Appendix 1 .....	155
9.1.1 Ethics Committee Approval for Study 1 & 2 .....	155
9.1.2 Ethics Committee Approval for Study 3.....	157
9.1.3 Ethics Committee Approval for Study 4.....	161
9.2 Appendix 2 .....	166
9.2.1 Patient Information Leaflet Study 1 & 2 .....	166
9.2.1 Patient Information Leaflet Study 3 .....	171
9.2.2 Patient Information Leaflet Study 4 .....	175
9.3 Appendix 3 .....	183
9.3.1 Consent Form for Study 1& 2.....	183
9.3.2 Consent Form for Study 3 .....	185
9.3.1 Consent Form for Study 4 .....	187

## List of Tables

<b>Table 2.1 Criteria for a Positive CMR result in the CE-MARC study[91, 92].</b>	<b>35</b>
<b>Table 2.2 Summary of demographic and angiographic characteristics.</b>	<b>40</b>
<b>Table 2.3 Diagnostic accuracy of a multi-parametric CMR exam and its individual components, paired and triplet combinations compared to the reference test X-ray angiography.</b>	<b>41</b>
<b>Table 2.4 Likelihood ratios positive and negative for the multi-parametric CMR exam and its individual components, paired and triplet combinations compared to the reference test X-ray angiography.</b>	<b>43</b>
<b>Table 2.5 Relative likelihood ratios and the numbers of new true positive and false positive cases produced by adding on further components sequentially to stress perfusion imaging in isolation.</b>	<b>45</b>
<b>Table 3.1 Baseline characteristics</b>	<b>59</b>
<b>Table 3.2 Image Quality for CMR and SPECT</b>	<b>60</b>
<b>Table 4.1 Demographic and Haemodynamic Data</b>	<b>84</b>
<b>Table 4.2 Comparison of Stress Haemodynamic Data</b>	<b>85</b>
<b>Table 4.3 Comparison of Scan Parameters and Image Scores</b>	<b>86</b>
<b>Table 5.1 Inclusion and Exclusion Criteria into the CE-MARC2 Study</b>	<b>103</b>
<b>Table 6.1 Baseline Characteristics of Participants With Suspected Coronary Heart Disease (CHD) by Study Group</b>	<b>122</b>
<b>Table 6.2 Summary of the CE-MARC 2 Trial Endpoints.</b>	<b>125</b>



## List of Figures

Figure 1.1 CMR in Stable Coronary Artery Disease .....	5
Figure 1.2 CMR in Acute Myocardial Infarction .....	6
Figure 1.3 Multi Parametric CMR Protocols in Coronary Artery Disease.....	15
Figure 1.4 CMR in Acute Myocardial Infarction .....	23
Figure 2.1. Diagnostic accuracy of the individual components and their combinations compared to the full multi-parametric CMR examination. ....	38
Figure 3.1 Median Summed Stress Score and Distribution.....	61
Figure 3.2 Median Summed Rest Score and Distribution.....	61
Figure 3.3 Median Summed Difference Score and Distribution.....	61
Figure 3.4 Case examples of patients undergoing CMR and SPECT .....	62
Figure 3.5 Bland-Altman limits of agreement for summed stress score, summed rest score and summed difference scores. ....	64
Figure 3.6 Regression analysis fitting of cardiovascular magnetic resonance (CMR) summed difference score (SDS) to single photon emission computed tomography (SPECT) SDS .....	65
Figure 4.1 Schematic representing standard and adaptive resolution pulse sequences. ....	75
Figure 4.2 Stress perfusion imaging in a health volunteer: standard imaging vs. adaptive resolution pulse sequence.....	89
Figure 4.3 Stress perfusion imaging in a patient: standard imaging vs. adaptive resolution pulse sequence.....	90
Figure 5.1 CE MARC 2 study flow diagram illustrating the recruitment process.....	101
Figure 5.2 CE-MARC 2 study flow diagram illustrating randomization, investigative strategy and study end- points.[139].....	102
Figure 6.1 Flow of Patients Through the Study of Noninvasive Imaging and Angiography Rates. ....	121
Figure 6.2 Effect of Specific Patient Characteristics on Results for CMR-Guided Care vs NICE Guidelines-Directed Care and MPS-Guided Care Among Patients With Suspected Coronary Heart Disease .....	127

**Figure 6.3 Time to First Major Adverse Cardiovascular Event  
After a Minimum of 12-Month Follow-Up From Randomization  
Among Patients With Suspected Coronary Heart Disease  
(Median, 16 Months)..... 128**

**Cardiovascular Magnetic Resonance Imaging for the  
Investigation of Patients with Coronary Heart Disease**

## **Chapter 1 Background**

### **1.1 Coronary Heart Disease**

Coronary heart disease (CHD) is a leading cause of death and disability worldwide. In the United States (US) 15.4 million people have CHD costing the US economy \$108.9 billion/yr[1] and each year 715,000 have a myocardial infarction[2]; whilst in the United Kingdom (UK) there are an estimated 2 million people with angina costing £9.0 billion/yr[3]. In a typical hospital setting a variety of investigations may be used to diagnose CHD, as well as risk stratify the individual and determine the need for coronary revascularization. These may involve anatomical imaging of the coronary arterial tree with computed tomography coronary angiography (CTCA) or invasive X-ray coronary angiography; or assessment for functionally significant coronary artery stenosis with single-photon emission computed tomography (SPECT), stress echocardiography, cardiovascular magnetic resonance (CMR) or positron emission tomography (PET).

### **1.2 Cardiovascular Magnetic Resonance**

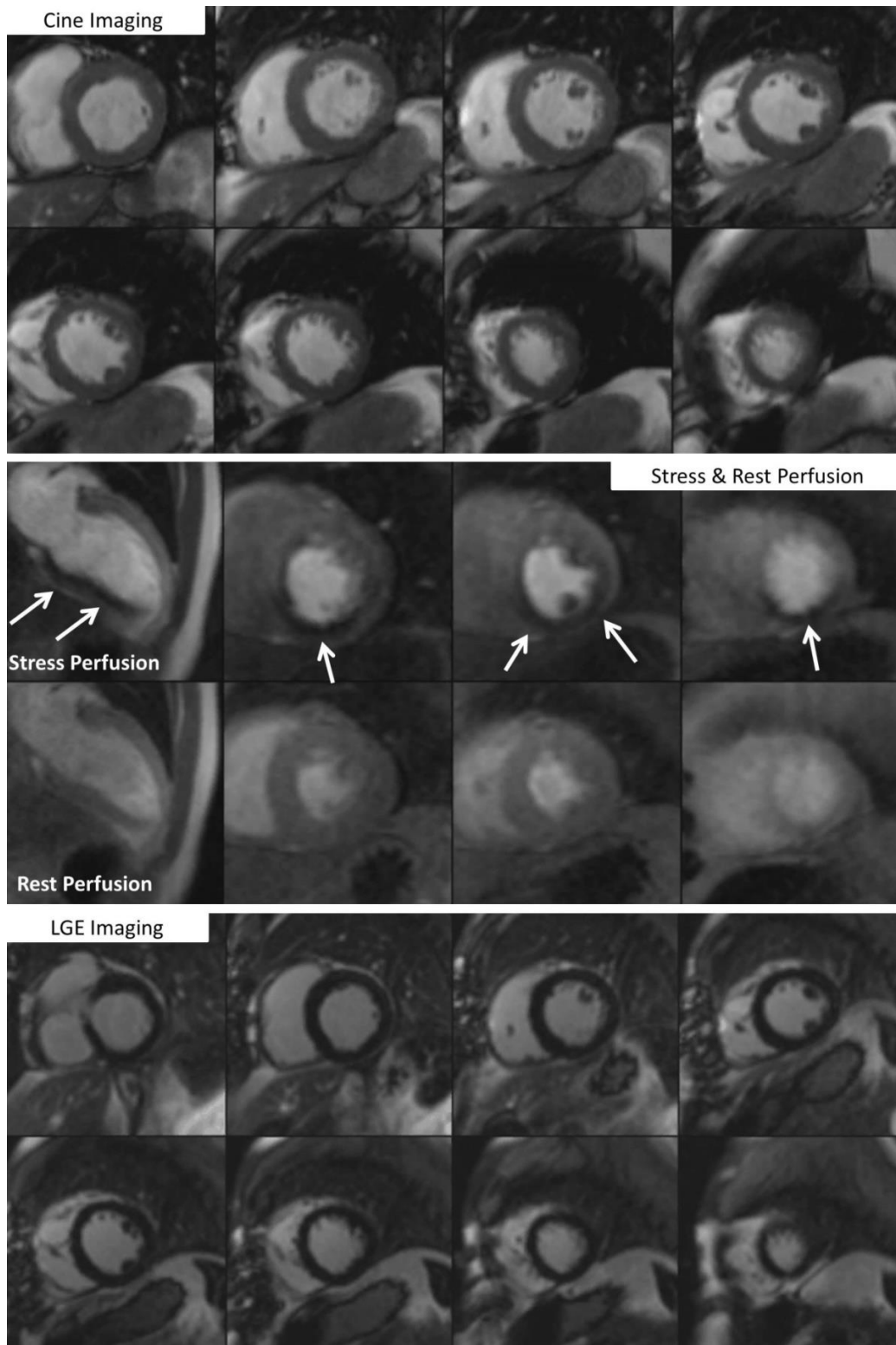
Cardiovascular magnetic resonance (CMR) is an established advanced cross-sectional imaging modality for the functional and anatomical assessment of a wide range of cardiovascular disease. CMR produces high resolution images which can be acquired in any plane and allows the assessment of global and regional cardiac function, myocardial perfusion,

myocardial viability, tissue characterisation and proximal coronary anatomy - all within a single study and without the use of ionising radiation. This unique multi-parametric approach leads to a high diagnostic accuracy for the detection of CHD and an important role in the management of both the stable and acute patient. In patients with stable CHD, CMR can detect and localise ischemia, quantify ischemic burden and determine myocardial viability, all of which can be used to risk-stratify patients and guide revascularization (Figure 1.1). In patients presenting with acute coronary syndromes, CMR can accurately determine ischemia and infarction and provide prognostic information such as the size and location of myocardial infarction, the area at risk (myocardial oedema) and the presence or absence of microvascular obstruction (MO), intramyocardial haemorrhage (IMH) or sequelae such as left ventricular thrombus (Figure 1.2). There is an extensive and growing evidence base for CMR and for many cardiovascular conditions it is the reference standard imaging test.

### **1.3 CMR in National & International Guidelines**

CMR is therefore firmly established in both national and international guidelines, which recommend a variety of investigative strategies for the diagnosis of CHD[4-6] with recognised international training syllabi and accreditation/certification processes[7-9]. The 2013 European Society of Cardiology (ESC) guidelines on the management of stable CHD [5] give a Class I recommendation for non-invasive stress testing and recommend CMR as an imaging option for the initial diagnostic assessment of angina. The American College of Cardiology Foundation/American Heart Association

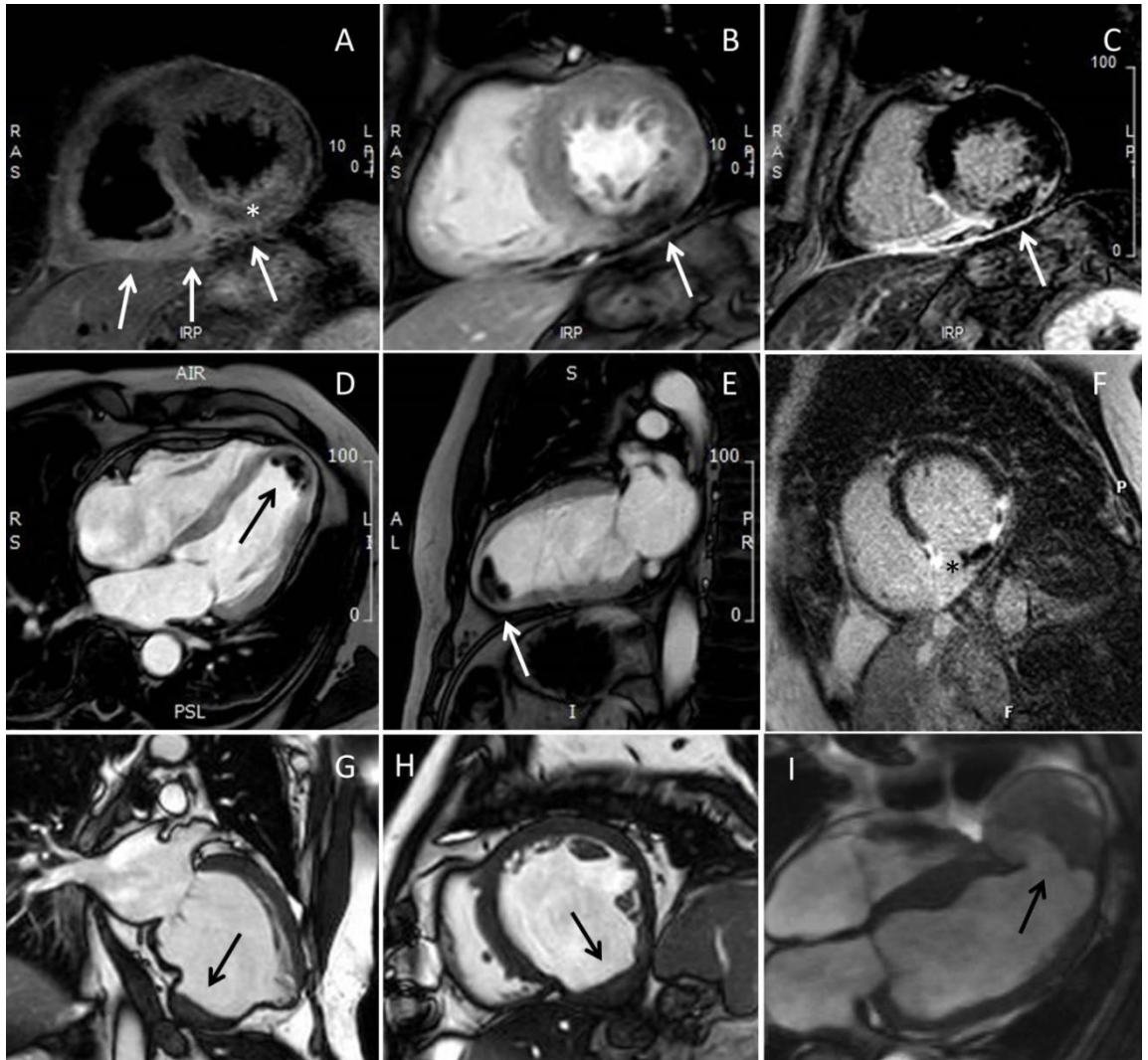
(ACCF/AHA) guidelines give CMR a class IIa recommendation for the investigation of those with intermediate to high pre-test probability of obstructive CHD in those physically able to exercise but with an ECG which would be un-interpretable during an exercise test; and class IIb in those intermediate to high risk unable to exercise[4]. There is also a role for ischemia and viability testing with CMR in those with known CHD and after myocardial infarction (MI), particularly in those with multi-vessel disease.[10] The ACCF/AHA gives CMR a Class I recommendation in those with known CHD of unclear physiological significance considered for revascularization and the ESC guidelines give non-invasive stress imaging IIa classification for this indication[5].



**Figure 1.1 CMR in Stable Coronary Artery Disease**

Top Panel) Short axis cine stack used for demonstration of global and regional ventricular function. Middle Panel) Adenosine stress (top row) and rest (bottom row) first pass perfusion demonstrating inducible inferior and infero-lateral hypoperfusion (ischaemia) (arrows) consistent with severe stenosis of the right coronary artery (Video 1). Bottom Panel) Late

gadolinium enhancement image demonstrating no evidence of myocardial infarction.



**Figure 1.2 CMR in Acute Myocardial Infarction**

A) T2w image with high signal (oedema) of the inferior LV and RV wall (arrow) with an area of hypointense core representing intra-myocardial haemorrhage (star). B) Early gadolinium enhancement (EGE) image with dark central core of the inferior wall representing an area of microvascular obstruction (MO). C) Late gadolinium enhancement (LGE) image with full thickness myocardial infarction demonstrated by hyperintense (white) areas of the inferior wall and inferior septum extending into the RV. The central dark area (arrow) is MO. D&E) LV apical thrombus on EGE image (arrows). F) Short axis LGE image with ventricular septal defect (star). G&H) Inferior aneurysm (arrows) with thrombus. I) Contained apical LV rupture with thrombus (arrow).



## **1.4 CMR Physics, Methodology & Safety**

### **1.4.1 Basic CMR Physics**

CMR imaging uses a strong superconducting magnet (cooled in liquid helium) to construct images with high spatial resolution and excellent soft tissue contrast[11]. This magnet operates at a field strength measured in units of Tesla (T), with  $1T \approx 20,000$  times the earth's magnetic field. Three types of magnetic fields are used to produce images: a strong, static magnetic field ( $B_0$ ), a gradient magnetic field (which can be rapidly switched on and off) and a radiofrequency (RF) field.

CMR uses the signal generated from magnetising hydrogen nuclei (single protons) as they are in abundance. When a patient is placed into the scanner the protons within free water and lipid molecules align themselves either parallel or anti-parallel to the static field  $B_0$ . For imaging purposes a RF pulse is applied, delivering energy to the protons, which tilt them away from their alignment with  $B_0$ . When this extrinsic RF pulse is removed, protons return to their resting state, releasing this energy in the form of a radio signal, a process that is used to generate the image.

The relaxation of protons back to their equilibrium state after withdrawal of the RF pulse is defined by two important parameters known as T1 and T2[12]. The T1 relaxation time (ms) is defined as the duration for longitudinal magnetization of excited tissues to recover to approximately 63% of their original value. This increases with increasing magnetic field strength. T2 relaxation (ms) is the time when 63% of the transverse magnetisation of excited tissues has recovered and this is essentially unaffected by

increasing magnetic field strengths. In biological tissues, T2 values are substantially shorter than T1. Fat has short T1 and T2 relaxation; fluids have long T1 and T2 relaxation.

Both the delay between successive RF applications (Repetition Time, TR) and between each RF application and subsequent signal readout (Echo Time, TE) can be specified by the operator[12]. This is exploited for purposes of tissue characterisation by permitting imaging sequences preferentially weighted to T1 (T1w: short TE and TR,) or T2 (T2w: long TE and TR).

The two most commonly used pulse sequence types in CMR are Spin Echo (SE) and Gradient Echo (GE). SE sequences are generally used for static anatomical definition. SE produces high quality T1w and T2w images and is termed black-blood imaging (as blood is usually black and fat white).[13] On T1w SE images, fluid typically appears dark and fat bright, whereas both are bright on T2w images.

GE sequences permit fast cine acquisition (motion) with high temporal resolution and generally generate bright-blood images (both blood and fat are bright)[14]. In addition to standard cine imaging, it is also possible to assess intra-myocardial motion by “tagging” the myocardium with a grid pattern and then track its deformation through the cardiac cycle[15]. The displacement of tagging features permits measurement of myocardial strain, strain rate and torsion[16].

Phase-encoded GE sequences (also called phase-contrast or velocity encoded sequences) are a technique whereby the net direction of the moving blood is displayed as a phase map. Pixels travelling in different directions and at different velocities are displayed as either black (moving away from the phase encoding direction), white (moving towards the phase encoding direction) or grey (stationary). Phase-contrast velocity mapping is typically used to measure blood flow e.g. aortic or pulmonary valvular regurgitation[17] and total flow volumes per cardiac cycle with both forward and reverse flow components measurable. CMR allows precise alignment of the imaging plane (in-plane or through-plane) with the direction of flow but is limited by temporal resolution (typically 25-45ms, 10-fold lower than Doppler echocardiography) and thus may underestimate peak values in high velocity jets (e.g. severe aortic stenosis).

The duration of a CMR scan typically ranges from 30 minutes to an hour depending on the complexity of the referral question. Patients are breath-held for the acquisition of most images, which with modern fast scanners can be just a few seconds in duration, and can be adjusted according to patient ability. Vector-cardiogram (equivalent to ECG) triggering and gating are used to prevent image distortion due to cardiac motion[18]; with cine images acquired during the entire cardiac cycle (prospective or retrospective gating[19]) and static images preferentially acquired during diastole (prospective triggering). Arrhythmias and poor breath holding can thus degrade image quality[20], although in most cases diagnostic quality information can still be obtained by using arrhythmia rejection algorithms and non-breath holding (free breathing) techniques.

### **1.4.2 Image Quality and Artefacts**

CMR image acquisition can be associated with a number of classical artefacts[21], although in the vast majority of cases an experienced technologist can minimise these to produce diagnostic quality images. The most common include:

- Image aliasing: indicative of too small a field a view with signal from peripheral parts of the body wrapping centrally into the main image.
- Ghosting artefact from respiratory motion: caused by movement of tissue between each TR with subsequent misplacement of signal in the image.
- Arrhythmia artefact: Poor quality ECG triggering generates cardiac motion artefacts during cine acquisition due to jumps in TR and variation in R-R intervals.
- Chemical shift artefact: typically a signal void at the interface between fat layers and surrounding water-based tissue. It is important to recognise in order to avoid misinterpretation e.g. the false impression of aortic wall dissection “flap”.
- Metallic artefact: can significantly degrade images, appearing as a large signal void; particularly affecting GE based pulse sequences.
- Dark-rim artefact: refers to a band of transient low signal in the endocardium during first-pass perfusion when contrast first enters the LV cavity. It does not indicate hypo-perfusion and subsequently resolves within a few heartbeats as myocardial enhancement occurs.
- Complex flow signal loss: Turbulent blood flow commonly associated with valvular pathology can cause phase shift dispersion and appear

as signal loss artefact. Caution is required as the area of signal void may not be directly related to the severity of the valve lesion.

### **1.4.3 CMR Safety and the Safety of Implanted Medical Devices**

The magnetic field of the MR scanner is always on and although the magnetic field is strongest within the bore of the magnet, the surrounding fringe field can also adversely affect pacemakers and other implants. Importantly, any ferromagnetic objects will accelerate towards the magnet core, posing a projectile hazard with potentially fatal consequences. For these reasons, health and safety regulations dictate a controlled area must be defined enclosing the 0.5mTesla fringe field (the “pacemaker” line)[22]. Access to this area is restricted to trained staff, and patients who have been screened in particular for pacemakers, cerebral aneurysm clips and ocular foreign bodies. Items of hospital equipment and medical devices should all be classified using the American Society for Testing Materials (ASTM) guidance as MR Safe, MR conditional or MR unsafe[23].

#### **1.4.3.1 Safety of Implanted Medical Devices**

Both mechanical and bioprosthetic heart valves, including transcatheter aortic valve implants, and intracoronary and aortic stents are all generally considered safe to scan shortly after implantation. The online resource [www.MRISafety.com](http://www.MRISafety.com) provides an extensive list of tested medical devices/implants. MR conditional pacemakers and defibrillators are now increasingly being implanted. However, MR imaging remains conditional on meeting stringent manufacturer safety criteria and requires prior

reprogramming and also immediate post-imaging parameter checks to ensure safe device operation before the patient leaves the department.

#### **1.4.4 CMR Contrast Agents: Indications and Safety**

Intravenously administered gadolinium chelate-based contrast agents (0.1-0.2mmol/Kg), are typically extracellular and highly paramagnetic[24], shortening T1 relaxation times and increasing signal intensity of adjacent water molecules on T1w images.

The reported incidence of allergic reactions to gadolinium is very low (~1:10,000); at least one order of magnitude lower than that of iodinated contrast agents[25]. No harm has been reported during pregnancy, although scanning during 1<sup>st</sup> trimester is generally avoided. The use of several gadolinium-based contrast agents in patient with advanced renal failure has been associated with Nephrogenic Systemic Fibrosis[26]. Several cyclic contrast agents appear not to cause this condition and it has never been reported in those with an eGFR>30ml/min/1.73m<sup>2</sup>. The FDA advises avoiding gadolinium based contrast agents when the eGFR is below 30 ml/min/1.73m<sup>2</sup>, unless diagnostic information is essential and otherwise unattainable.

### **1.5 Cardiovascular Magnetic Resonance for the Investigation of Stable Coronary Heart Disease.**

CMR is an established method for demonstrating myocardial ischemia and in some UK and European centres has become the preferred investigation

for patients with suspected stable angina. A CMR study for this purpose takes between 30 and 60 minutes and typically includes cine images in multiple planes for assessment of left ventricular (LV) volumes and function, stress and rest perfusion for myocardial ischemia and late gadolinium enhancement (LGE) for delineation of scar and assessment of viability. The combination of the above techniques in a single multi-parametric exam allows the quantification of ischemic burden and determines myocardial viability, which can be used to risk-stratify patients and guide revascularisation.

### **1.5.1 Global and Regional LV Volumetric Assessment**

CMR is the reference standard in terms of accuracy and reproducibility of quantitation of LV volumes, mass and for the assessment of regional and global systolic function[27]; the latter remains the most powerful predictor of mortality in cardiovascular disease. LV volumes are performed with a contiguous stack of cine images parallel to the mitral valve annulus covering the whole of the left ventricle, providing a full three dimensional (3D) dataset. Full acquisition typically takes only a couple of minutes using breath hold techniques, and free breathing approaches are also possible.

### **1.5.2 Stress Cardiovascular Magnetic Resonance**

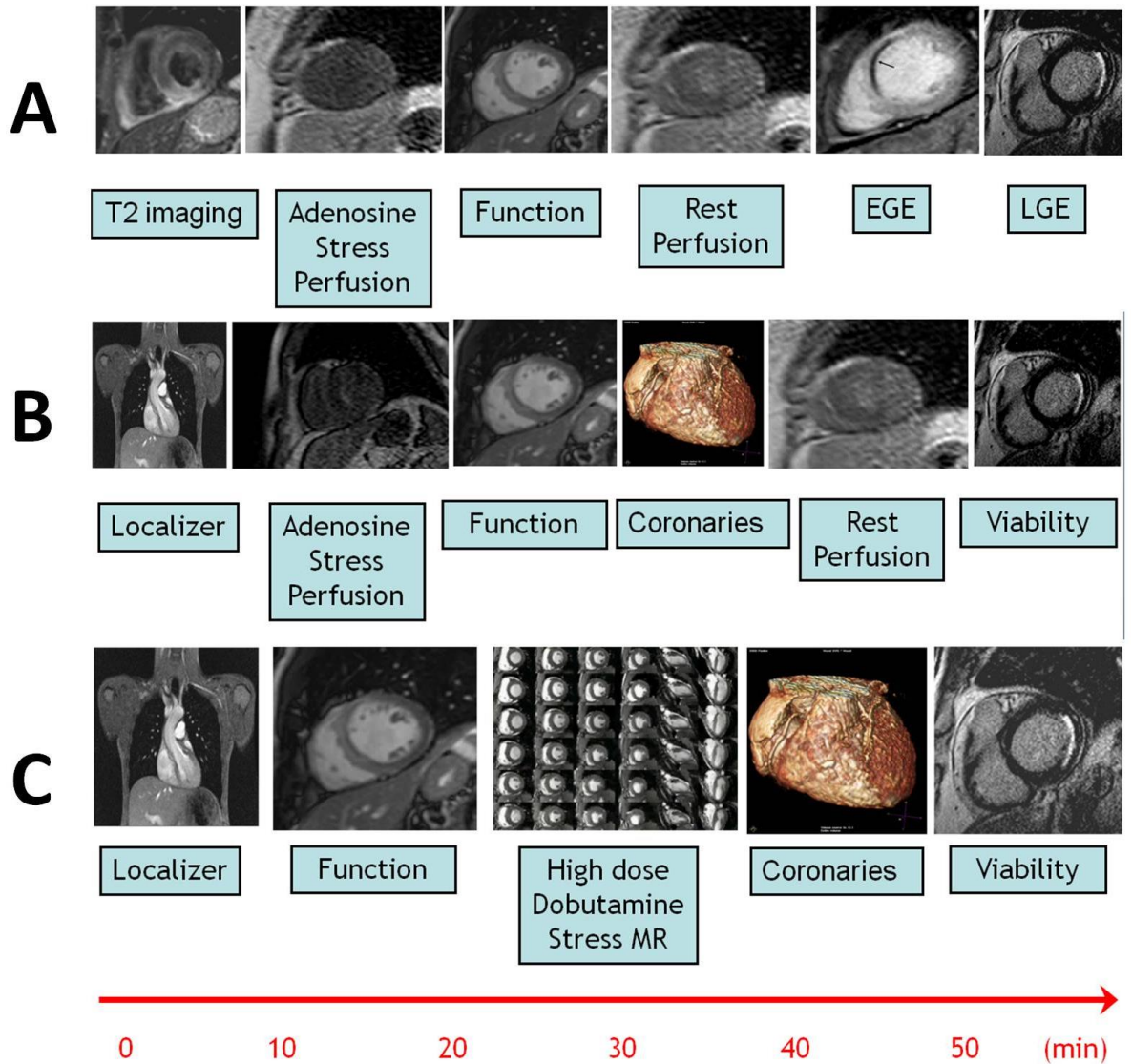
Stress assessment with CMR for myocardial ischemia can be performed with vasodilatory or inotropic stress agents. Vasodilatory stress with adenosine, regadenoson (and less commonly dipyridamole or nicorandil) uses gadolinium based contrast agents to demonstrate myocardial

hypoperfusion. Dobutamine stress CMR, like stress echocardiography, induces wall motion abnormalities in the presence of functionally significant coronary stenoses without the need for a gadolinium based contrast agent (although first pass perfusion can be performed at peak stress for additional value). Typical multi-parametric CMR protocols can be seen in Figure 1.3.

#### **1.5.2.1 Vasodilatory Stress CMR**

Vasodilatory stress CMR has high diagnostic accuracy for the detection of CHD and a recent meta-analysis of 37 studies demonstrated a combined sensitivity of 89% (95%CI: 88%-91%) and specificity of 76% (95%CI: 73%-78%)[28]. The largest prospective randomized controlled trial, the CE-MARC study, which was not included in the meta-analysis, demonstrated similar results and comprehensively established superiority over SPECT with a higher sensitivity (87% vs. 67%,  $p < 0.0001$ ) and negative predictive value (91% vs. 79%,  $p < 0.0001$ ) but similar specificity (83% vs. 83%  $p = 0.916$ ) and positive predictive values (77% vs. 71%,  $p = 0.061$ )[29, 30]. A recent pre-specified CE-MARC gender sub-analysis has shown that in terms of sensitivity, CMR outperformed SPECT in both males and females, whereas the sensitivity of SPECT in females was significantly worse than in males[31].





**Figure 1.3 Multi Parametric CMR Protocols in Coronary Artery Disease**

Panel A – Typical multi-parametric CMR protocol for the assessment of acute coronary syndromes involving T2w imaging demonstrating oedema, stress and rest perfusion for hypoperfusion (ischaemia), cine imaging for regional and global ventricular function, EGE for thrombus and MO and LGE for viability assessment and demonstration of scar. Panel B&C – Typical multi-parametric CMR protocols for the assessment of stable coronary artery disease with adenosine stress perfusion (B) or high dose dobutamine stress (C). EGE – early gadolinium enhancement; LGE – late gadolinium enhancement; MO – microvascular obstruction; T2w – T2 weighted

Like CE-MARC, the subsequently published multi-centre MR-IMPACT II trial also showed a greater sensitivity of CMR compared to SPECT (67% vs. 59%,  $p=0.024$ ) but a lower specificity (61% vs. 72%,  $p=0.038$ )[32]. However in this trial only the perfusion components of the CMR examination were analysed and as a result, diagnostic accuracy was comparatively lower. This may also be explained by the multicenter, multivendor, non-standardized pulse sequence trial design of MR-IMPACT II with reporting performed by an independent core laboratory without clinical details, and emphasizes the incremental value of reporting imaging studies in their clinical context and with experience and knowledge of the techniques used.

Whilst both CE-MARC and MR-IMPACT II assessed the ability for CMR and SPECT to detect inducible myocardial perfusion deficits with adenosine stress, CE-MARC also evaluated the incremental value of the addition of infarction detection with late gadolinium enhancement (LGE), cine imaging for regional ventricular function and magnetic resonance angiography (MRA) for coronary artery anatomy. The value of combining such components in one single multi-parametric CMR examination added to the increased specificity in the CE-MARC trial. Indeed this issue has been examined in small scale studies with ventricular function and LGE improving the specificity and diagnostic accuracy above the stress perfusion examination alone. The clinical utility of imaging coronary artery anatomy by MRA within already lengthy protocols however still remains to be established[33]. In CE-MARC the overall diagnostic accuracy did not alter whether or not the results of the MRA were included in the analysis. Other investigators have

evaluated the effect of adding coronary MRA to stress perfusion CMR on diagnostic performance; when compared to invasive pressure-wire derived fractional flow reserve (FFR) at 1.5T there was no significant improvement in diagnostic accuracy[34].

Whilst the CE-MARC study proved the superiority of CMR over SPECT in terms of diagnostic accuracy of CHD detection, questions were raised over the availability and cost benefit of the technology[35]. Subsequent health economic analysis demonstrated that a diagnostic strategy which includes CMR is cost effective falling between the lower and upper limits thresholds (£20-30,000) per quality adjusted life year (QALY) as defined by National Institute for Health and Care Excellence (NICE)[36]. Furthermore the cost effectiveness of CMR has been corroborated in other international models against both direct to invasive coronary angiography and SPECT, although direct referral to invasive coronary angiography may be more cost effective in those with a high pre-test probability of having underlying CHD[37, 38].

#### **1.5.2.2 Inotropic Stress CMR**

Inotropic stress CMR with dobutamine for the detection of significant CHD relies on the induction of wall motion abnormalities and therefore evaluating a later stage of the ischemic cascade than perfusion imaging. Nevertheless dobutamine stress CMR also has a high diagnostic accuracy for the detection of CHD with one meta-analysis of 14 studies showing a pooled sensitivity of 0.83 (95%CI: 0.79-0.88) and specificity of 0.86 (95%CI: 0.81-0.91)[39]. One single centre study demonstrated dobutamine stress CMR to

be superior to dobutamine stress echocardiography (DSE) with sensitivity of 86% vs. 74%,  $p < 0.05$  and specificity 86% vs. 70%,  $p < 0.05$ , although this benefit of dobutamine stress CMR above DSE was limited to those with suboptimal echocardiographic images[40]. In terms of prognostic value, those with a negative DSCMR have an excellent prognosis with an event rate of only 1.2% in the first year after the test, [41-43] which is similar to that published annual event rate of 1.3% of a negative DSE[44]. Dobutamine stress CMR has been demonstrated to be extremely safe with a comparable safety profile to DSE[45, 46].

### **1.5.2.3 Pushing the boundaries: improving stress technology**

Since the inception of the CE-MARC and MR-IMPACT II studies, which used perfusion sequences with an in-plane spatial resolution of 2-3mm, there have been major advances in CMR technology. Notably, there have been improvements in acquisition techniques such as highly accelerated pulse sequences based on spatio-temporal undersampling (for example *k-t* sensitivity encoding (SENSE) and highly constrained back projection (HYPR)) and improvements in hardware, such as higher field strengths and improved cardiac phase-array coils for higher signal-to-noise[47]. Perfusion CMR at 1.5 Tesla (T) using *k-t* SENSE acceleration to achieve an in-plane spatial resolution of 1.6mm has been demonstrated to have a greater overall diagnostic accuracy than standard resolution (2.5mm) for identifying both single ( $p < 0.001$ ) and multi vessel disease ( $p = 0.002$ ), with an area under the curve (AUC) of 0.93 vs. 0.83;  $p < 0.001$ [47]. Similarly, diagnostic performance at 3.0T exceeds that at 1.5T for both single-vessel disease (AUC: 0.89 vs

0.70;  $p < 0.05$ ) and multivessel disease (AUC: 0.95 vs. 0.82;  $p < 0.05$ )[48]. Using similar high resolution techniques at 3.0T can regularly achieve an in-plane spatial resolution of  $< 1.5\text{mm}$ , which is the basis for improved detection of subendocardial ischemia, and this advance is now beginning to make the transition into clinical practice[49].

Conventional stress perfusion CMR images are typically acquired in 3 short axis slices to assess 16 of the 17 segments in the AHA/ACC model (excluding the apical cap). Faster image acquisition also allows 3-dimensional (3D) whole heart myocardial perfusion imaging with full left ventricular coverage and therefore overcomes assumptions made about the myocardium between slices seen with the conventional approach [47]. An additional advantage of 3D perfusion CMR is that all the data are acquired in one shot and thus in the same cardiac phase. Two recent studies have validated 3D perfusion CMR against FFR and shown high diagnostic accuracy[50, 51]. Manka *et al* demonstrated 3D perfusion CMR at 1.5T was found to have a sensitivity, specificity and diagnostic accuracy of 90%, 82% and 87% respectively[50]. Jogiya *et al* found similar figures of 91%, 90% and 91% respectively at 3.0T[51]. Both of these studies also verified the feasibility and reproducibility of myocardial ischemic burden quantification from 3D data using volumetry of myocardial hypo-enhancement expressed as a percentage of total myocardium. 3D myocardial stress perfusion CMR is therefore a highly promising development with high diagnostic accuracy, with a potential additional role in the assessment and follow-up of total myocardial ischemic burden.

### **1.5.3 Coronary Artery Imaging**

Unlike cardiac CT coronary angiography which produces exquisite anatomical images of the coronary arteries, the clinical utility of detection coronary artery stenosis by magnetic resonance angiography (MRA) remains to be established. This is due to the required long imaging times, more limited spatial resolution, and the impact of cardiac and respiratory motion on MRA image quality. One question unanswered from the CE-MARC multi parametric protocol is the value of the addition of the MRA on the diagnostic accuracy. Other data has suggested that there is no incremental value on including the MRA[33]. Coronary MRA, however, is useful for detecting the location of coronary aneurysms (such as those seen in Kawasaki disease), and the presence of anomalous coronary arteries with accurate delineation of their anatomical course[52]; the principal advantage of MRA being the lack of ionising radiation in children and younger adults.

### **1.6 Cardiovascular Magnetic Resonance after Acute Coronary Syndromes**

The pathophysiology and prognosis of both acute and chronic MI are highly variable. Multi-parametric imaging with CMR has high diagnostic accuracy for the detection of CAD in the assessment of both ST-segment and non-ST-segment elevation acute coronary syndromes [53, 54]. CMR can uniquely determine the likelihood of functional recovery after revascularization, assess the area of myocardium at risk (and myocardial salvage), differentiate acute from chronic infarction, demonstrate microvascular obstruction (MO) and intramyocardial haemorrhage (IMH), as well as being

able to detect several sequelae of MI. These individual features may be more powerful surrogate markers of outcome than the traditionally used left ventricular ejection fraction.

### **1.6.1 Acute Myocardial Infarction**

After an acute coronary syndrome, LGE imaging confirms the presence of myocardial infarction (MI), which is seen as hyperenhancement, and can determine its size and location. In acute MI, the distribution volume of extracellular gadolinium-based contrast agents is increased within myocardium due to the destruction of sarcolemmal membranes and abnormal washout kinetics. Similarly, in chronic MI, the presence of replacement fibrotic tissue increases the contrast distribution volume. The resulting differences in contrast distribution between normal and injured myocardium can therefore be used to delineate MI (whether it be acute or chronic) using a T1-sensitive inversion-recovery sequence performed 10-15mins after contrast injection – i.e. LGE imaging (Figures 1.1, 1.2 & 1.4).

#### **1.6.1.1 Myocardial Oedema**

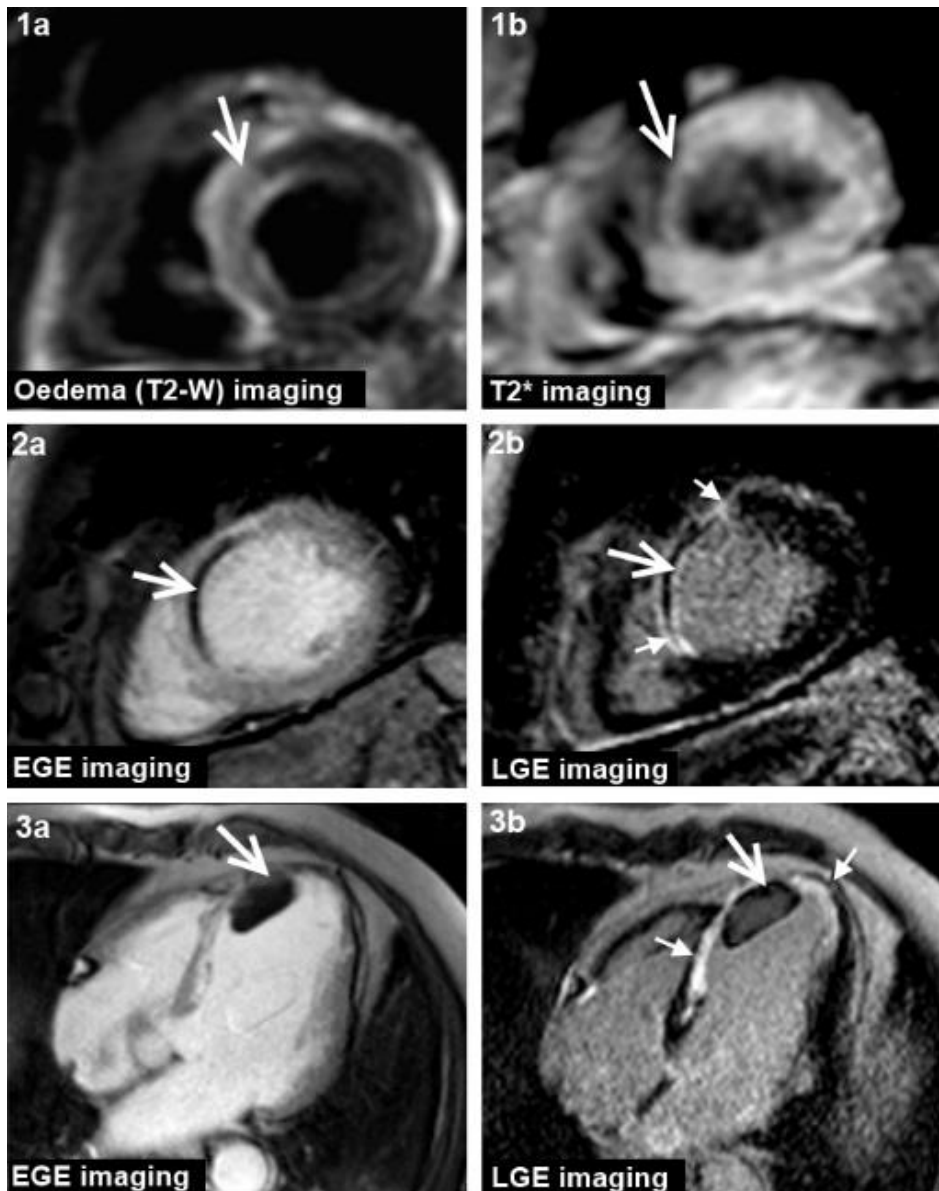
Following acute MI T2-weighted imaging can be used in acute coronary syndromes to identify myocardial oedema (inflammation), which occurs in reversibly ischemic injured myocardium[55]. Contrast agents are not required as the myocardial free water content affects paramagnetic properties of the tissue providing intrinsic image contrast, although with relatively low signal-to-noise ratio (SNR) and requires experience to interpret. T2-weighted oedema imaging is both sensitive [56] and specific

[57] to the timing of an event, thereby differentiating acute from chronic infarction (Figures 1.2 & 1.4). It therefore also allows delineation of the 'area-at-risk' (AAR) in acute infarction and the area of 'myocardial salvage' calculated by subtraction of the infarcted area determined by LGE[56]. The high signal on oedema imaging is persistent for up to 2 weeks after the reversible ischemic insult, the AAR can therefore be measured hours or days after a primary PCI, which makes it an ideal research tool for studies assessing novel antithrombotics and adjuvant techniques for mechanical revascularization.

#### **1.6.1.2 Microvascular obstruction**

In acute MI, despite successful revascularization therapy, perfusion is not completely restored in up to 30% of patients due to MO. This is seen angiographically as the 'no-reflow' phenomenon and is the consequence of capillary necrosis, clogging of small myocardial arterioles with embolic debris, acute inflammation, platelet aggregation and vasospasm.





**Figure 1.4 CMR in Acute Myocardial Infarction**

The top row shows mid-ventricular short-axis images from a patient on day 3 following an acute septal STEMI. Myocardial oedema i.e. the 'area-at risk' is seen as high-signal intensity on T2 weighted imaging (arrow, 1a) and a central core of reperfusion haemorrhage is seen as low signal intensity on T2\* imaging (arrow, 1b). The middle row shows mid-ventricular short-axis images from another patient with an occlusion of the proximal left anterior descending artery. Both EGE and LGE imaging show a core of non-contrast uptake i.e. microvascular obstruction (large arrows, 2a and 2b) within a transmural septal wall MI which is outlined by hyperenhancement on LGE imaging (small arrows, 2b). The bottom row shows 4-chamber images from a 55-year-old man with a recent LAD territory MI. EGE and LGE imaging show a non-enhancing (and therefore avascular) mass typical of LV thrombus. LGE imaging demonstrates that the thrombus overlies mid to apical antero-septum infarction seen as hyperenhancement (small arrows, 3b).

Contrast enhanced CMR allows accurate depiction of areas of microvascular damage within the core of the infarcted myocardium the extent of which correlates with biochemical markers of infarction[58]. In MO gadolinium penetration is impaired and limited to diffusion[59, 60] and results in contrast devoid low-signal intensity regions within the high-intensity infarcted areas (Figures 1.2 & 1.4). This may be imaged with several imaging techniques: first-pass perfusion, early gadolinium enhancement (EGE) imaging at 1 to 2 minutes after contrast injection (Figures 1.2 & 1.4) and LGE (10-15 mins after injection)[61]. Studies have shown that the presence and extent of MO (on EGE or LGE imaging) after acute MI is a strong predictor of adverse ventricular remodelling and clinical outcome, independent of infarct size or LV ejection fraction (LVEF) [62-66]. Notably, the presence and extent of MO imaged with LGE imaging (so called 'persistent' MO) is the strongest predictor of worse outcomes[67]. After acute MI, MO slowly shrinks over the following weeks (rarely persisting beyond 1 month) and is therefore not a feature of chronic infarction.

### **1.6.1.3 Intramyocardial haemorrhage**

Reperfusion of severely ischemic myocardium can lead to IMH within the infarct core caused by extravasation of red blood cells through large gaps in damaged endothelial walls. Deoxyhemoglobin is oxidised to methemoglobin, which causes shortening of the T2 relaxation time due to its paramagnetic properties and magnetic susceptibility effect and therefore, haemorrhage can be detected as areas of dark hypointense signal surrounded by oedema (bright signal) on T2-weighted imaging. Several studies have validated the

use of T2-weighted CMR imaging to identify IMH in acute MI against histopathological findings[68, 69]. Furthermore, T2\* CMR has also shown potential to detect IMH in the setting of acute MI, with the advantage of better distinction from MO (which is also seen as hypointensity on standard T2-weighted imaging)[70](Figure 1.4).

#### **1.6.1.4 Other sequelae of myocardial infarction**

CMR is superior to echocardiography for the identification of ventricular thrombi, which appear as dark filling defects on EGE or LGE imaging, typically on the endocardial surface of infarcts[71, 72](Figures 1.2 & 1.4). CMR is also able to detect other complications of MI including ventricular aneurysm, pseudoaneurysms, ventricular septal perforation and mitral regurgitation. Furthermore the high spatial resolution of CMR allows assessment of right ventricular involvement in acute myocardial infarction.

#### **1.6.2 Assessment of Myocardial Viability after Myocardial Infarction**

Ischemic myocardial injury is characterised by the presence of scar in predominantly a subendocardial distribution extending towards the epicardium reflecting the transmural gradient in the vulnerability of the myocardium. The transmural extent of hyperenhancement forms the basis upon which LGE can be used to assess tissue viability. The value of LGE CMR imaging for viability assessment in patients with a chronic CAD or a remote history of MI was established in the landmark study by Kim *et al* which demonstrated the relationship between transmural extent of hyper-

enhancement and the likelihood of functional recovery after revascularization[73]. They established that hyper-enhancement <25% of transmural extent was most likely to confer functional recovery, whilst those segments with hyperenhancement >75% of transmural extent were unlikely to benefit from revascularization - importantly this finding was consistent whether the affected segments were hypokinetic, akinetic or dyskinetic. These findings have subsequently been reproduced and a recent meta-analysis of eleven studies enrolling 331 patients using a 50% transmural cut off on LGE reported a sensitivity of 95% (95%CI: 93-97%) and specificity of 51% (40-62%) for predicting functional recovery[74]. In the acute phase after MI, interpretation of viability is more difficult as some of the hyperenhancement on LGE imaging may relate to myocardial oedema (due to increased extracellular volume) rather than non-viable 'scar'. Nonetheless, the transmural extent of hyperenhancement on LGE imaging has still been shown to accurately predict contractile recovery after MI and revascularisation even when imaging is performed acutely within the first 7 days[75].

#### **1.6.2.1 Transmurality of LGE**

Transmurality of LGE is a stronger predictor of both regional and global functional recovery after revascularization than myocardial wall thickness. Shah *et al* studied 201 consecutive patients with wall thinning undergoing revascularization observing increased myocardial wall thickness after revascularization in those segments where the LGE was limited to <25% (4.4mm increasing to 7.5mm after revascularization,  $p<0.001$ )[76].

Furthermore in patients with chronic LV systolic dysfunction due to CHD, the transmural extent of LGE has been shown to be the most sensitive technique for the assessment of viability compared to end diastolic wall thickness and wall thickening during low dose dobutamine stress[77]. Nevertheless myocardial viability can be assessed with low dose dobutamine (5-10 mcg/kg/min) with any segment considered viable if there is a 2mm or more demonstrable increase in systolic wall thickening.[78] Inotropic reserve assessed by low dose dobutamine has significantly higher specificity (91%)[74] suggesting a combination of the two techniques might improve diagnostic performance.

### **1.7 Prognostic Value of CMR in Coronary Heart Disease**

Currently SPECT remains the most widely performed non-invasive test for myocardial ischemia internationally and provides a wealth of prognostic information gained in over 30 years of experience with the technology. Emerging evidence suggests CMR will be as good, at prognostication, which is unsurprising since the technology assesses the same stage of the ischemic cascade but with higher spatial resolution allowing detection of more subendocardial ischemia and infarction. One recent large meta-analysis of 19 studies and over 11,000 patients showed a negative CMR was associated with only 0.8% annual event rate at 32 months follow-up (vs. 4.9% event rate in those with a positive test;  $p < 0.0001$ )[79] which is consistent with the reported annual event rate for a negative SPECT[80]. This benefit was observed equally whether undergoing vasodilatory stress or dobutamine stress. More recent data from a large prospective cohort of

consecutive patients undergoing adenosine stress perfusion have corroborated this prognostic value at an intermediate term follow-up period (4.2±2.1 years) showing that the presence of a reversible perfusion defects was associated with a threefold increase in cardiac death ( $p<0.0001$ ) and nonfatal myocardial infarctions ( $p=0.001$ )[81].

The presence of LGE has been demonstrated to be associated with an increased mortality risk in both symptomatic[82] and asymptomatic patients[77] without known previous myocardial infarction. In patients with chronic ischemic cardiomyopathy, LGE scar size independently predicts both death and sustained ventricular arrhythmia in those with preserved[83] and severely impaired LV function[84, 85]. One meta-analysis demonstrated the presence of LGE in CHD to be associated with a fourfold increase in the hazard ratio of both mortality and major adverse cardiovascular events (MACE), with each incremental gram of scar associated with a 4% increase in mortality and a 5% increase in MACE[86].

Infarct size by CMR similarly predicts sudden cardiac death (SCD) and arrhythmia after ST segment elevation MI independent of LVEF.[87] The authors of that study demonstrated that those with an LVEF of more than 30% with significant scarring (>5% of LV mass) had a similar risk of SCD and appropriate implantable cardiac defibrillator (ICD) discharge than a cohort with LVEF<30%, whilst those with LVEF>30% and minimal or no scarring had a more favourable prognosis, suggesting scar could be potentially used in risk stratification models for ICD implantation in the future.

Furthermore, after ST elevation myocardial infarction the presence of MO is recognised as an independent marker of subsequent adverse LV remodelling and a strong predictor of MACE[88]. Whilst recent studies have shown the presence of IMH identified by CMR is associated with other markers of adverse outcome such as larger infarct size, greater MO and lower LVEF, it may also be a strong independent marker of adverse remodelling and 6 month MACE.[70, 89, 90].

## **1.8 Conclusion**

CMR is a well-established non-invasive imaging technique with major applications in the evaluation of patients with coronary heart disease. In a single imaging session, CMR can assess cardiac anatomy, function, myocardial perfusion and tissue viability, without exposure to ionising radiation. Its use in both stable CHD and acute coronary syndromes is supported by a strong and rapidly expanding evidence-base. However the real challenge for any cardiovascular imaging modality is how it can change patient management and impact upon clinical outcomes. In this regard major on-going clinical trials are likely to raise the prominence of CMR in international guidelines and routine cardiological practice.

## **Chapter 2**

### **Individual Component Analysis of the Multi-Parametric Cardiovascular Magnetic Resonance Imaging Protocol in the CE-MARC Trial**

#### **2. 1 Abstract**

##### **2.1.1 Background**

The CE-MARC study assessed the diagnostic performance and investigated the use of cardiovascular magnetic resonance (CMR) in patients with suspected coronary artery disease (CAD). The study used a multi-parametric CMR protocol assessing 4 components: i) left ventricular function; ii) myocardial perfusion; iii) viability (late gadolinium enhancement (LGE)) and iv) coronary magnetic resonance angiography (MRA). In this pre-specified CE-MARC sub-study we assessed the diagnostic accuracy of the individual CMR components and their combinations.

##### **2.1.2 Methods**

All patients from the CE-MARC population (n=752) were included using data from the original blinded-read. The four individual core components of the CMR protocol were determined separately and then in paired and triplet combinations. Results were then compared to the full multi-parametric protocol.

##### **2.1.3 Results**

CMR and X-ray angiography results were available in 676 patients. The maximum sensitivity for the detection of significant CAD by CMR was achieved when all four components were used (86.5%). Specificity of



perfusion (91.8%), function (93.7%) and LGE (95.8%) on its own was significantly better than specificity of the multi-parametric protocol (83.4%)(all  $P < 0.0001$ ) but with the penalty of decreased sensitivity (86.5% vs. 76.9%, 47.4% and 40.8% respectively). The full multi-parametric protocol was the optimum to rule-out significant CAD (Likelihood Ratio negative (LR-) 0.16) and the LGE component alone was the best to rule-in CAD (LR+ 9.81). Overall diagnostic accuracy was similar with the full multi-parametric protocol (85.9%) compared to paired and triplet combinations. The use of coronary MRA within the full multi-parametric protocol had no additional diagnostic benefit compared to the perfusion/function/LGE combination (overall accuracy 84.6% vs. 84.2% ( $P=0.5316$ ); LR- 0.16 vs. 0.21; LR+ 5.21 vs. 5.77).

#### **2.1.4 Conclusions**

From this pre-specified sub-analysis of the CE-MARC study, the full multi-parametric protocol had the highest sensitivity and was the optimal approach to rule-out significant CAD. The LGE component alone was the optimal rule-in strategy. Finally the inclusion of coronary MRA provided no additional benefit when compared to the combination of perfusion/function/LGE.

## **2.2 Background**

Coronary artery disease (CAD) is a leading cause of death and disability worldwide. Cardiovascular magnetic resonance (CMR) is recognised in international guidelines as a non-invasive imaging option for the investigation of suspected CAD[1-3]. The CE-MARC study was the largest prospective evaluation of the diagnostic accuracy of CMR in stable CAD to date[4, 5]. The trial adopted a multi-parametric CMR protocol assessing left ventricular (LV) function, myocardial perfusion, viability and coronary artery anatomy in a single study. A rigorous study design avoided referral bias by mandating that all patients underwent X-ray coronary angiography (XRA) as the reference test independent of the result of the CMR or single-photon emission computed tomography (SPECT) scans. The results from CE-MARC and its sub-analyses have shown that CMR had high diagnostic accuracy for suspected CAD in males and females, in single and multi-vessel disease, had higher overall diagnostic accuracy and was also cost effective compared to SPECT[6, 7].

Previous studies designed to determine the diagnostic accuracy of the individual components of the CMR examination have been small and revealed contrasting results. Some have shown the full multi-parametric approach had higher diagnostic accuracy over the individual components of the combined examination, although these were performed in selected populations[8-11]. Furthermore the clinical utility of imaging coronary artery anatomy for the detection of stenosis by magnetic resonance angiography (MRA) within already lengthy protocols remains to be established. Klein *et al* demonstrated that MRA at 1.5 Tesla (T) did not add to the diagnostic

accuracy over perfusion and late gadolinium enhancement (LGE).[11] Other investigators have evaluated the effect of adding coronary MRA to stress perfusion and LGE on diagnostic performance in the intermediate to high risk group; when compared to invasive pressure-wire derived fractional flow reserve (FFR) at 1.5T there was no significant improvement in diagnostic accuracy[12].

This predefined sub-study of CE-MARC compared the diagnostic accuracy of the full multi-parametric CMR protocol with the individual components, and their paired and triplet combinations. The aim was to determine the diagnostic accuracy of the individual components and their combinations in a large, prospective, real-world population of patients with suspected CAD requiring further investigation.

## **2.3 Methods**

### **2.3.1 Study Design**

CE-MARC was a prospective study of 752 consecutive patients with a diagnosis of atypical or typical angina. They had at least one cardiovascular risk factor. Screening and recruitment occurred between March 2006 and August 2009.[5, 4] All patients were scheduled to undergo both SPECT and CMR (in randomized order). The protocol mandated all received XRA within 4 weeks irrespective of the CMR and SPECT result. Inclusion and exclusion criteria have been previously described.[5, 4] Patients provided informed written consent and the study was approved by the local Research Ethics Committee and complied with the Declaration of Helsinki (2000).

All patients from the CE-MARC population were included in this pre-specified sub-analysis. CMR results were from the original, blinded visual read. The diagnostic accuracy of each individual core component of the multi-parametric CMR protocol (perfusion, LV function, MRA and LGE) was determined separately and then in paired or triplet combinations. The results were compared with the full multi-parametric protocol.

### **2.3.2 CMR imaging and analysis**

The multi-parametric CMR (1.5-Tesla Intera CV, Philips, Best, The Netherlands) protocol and pulse sequence parameters have previously been described.[5, 4] The primary analysis used all four components of the multi-parametric CMR study. Criteria for a positive CMR result was any of the following: a) regional wall motion abnormality (RWMA) on cine imaging; b) hypoperfusion on stress/rest perfusion imaging; c) significant stenosis on MRA; d) infarct on LGE images (Table 2.1) following a 'believe the positive rule'. Individual component image quality scores for CMR (cines, perfusion, LGE, MRA) were graded 1 (unusable) to 4 (excellent).

### **2.3.3 X-Ray Angiography**

XRA images were analysed by two experienced cardiologists blinded to the CMR and SPECT results. Significant CAD was defined as  $\geq 70\%$  stenosis of a first order coronary artery measuring  $\geq 2$  mm in diameter, or left main stem stenosis  $\geq 50\%$  by quantitative coronary angiography (QCA) (QCAPlus, Sanders Data Systems, Palo Alto, California, USA).

**Table 2.1** Criteria for a Positive CMR result in the CE-MARC study[91, 92].

Parameter	Method	Positive Criteria
<b><i>RWMA</i></b>	Wall motion in each segment (17-segment model) was visually graded on post-stress cine imaging [0=normal, 1=mild-moderate hypokinesis, 2=severe hypokinesis, 3=akinesis, 4=dyskinesis]	Wall motion Score $\geq 1$ in two or more adjacent segments, or $\geq 2$ in one or more segments
<b><i>Ischemia</i></b>	Perfusion in each segment (17-segment model)* was visually graded at rest and then stress [0=normal, 1=equivocal, 2=subendocardial defect, 3=transmural defect, 4=transmural defect and wall thinned]	Decrease in perfusion score $\geq 2$ between rest and stress in any segment, or $\geq 1$ in each of two adjacent segments†
<b><i>Stenosis</i></b>	Percentage of coronary artery luminal narrowing visually assessed on MRA	$\geq 70\%$ stenosis or $\geq 50\%$ left main stem stenosis
<b><i>Infarction</i></b>	LGE images were visually assessed for hyper-enhancement in each segment (17-segment model) [0=none, 1=1–25%, 2=26–50%, 3=51–75%, 4=>75%]	Any score $\geq 1$ in a pattern consistent with myocardial infarction

\* 17-segment model excluding apical cap.

† With the exception of change between ‘normal’ and ‘equivocal’, which was coded as ‘normal’.

RWMA = regional wall motion abnormality; MRA = magnetic resonance coronary angiography; LGE = late-gadolinium enhancement

### **2.3.4 Statistical Analysis**

Statistical analyses were performed by the Clinical Trials Research Unit, University of Leeds. Confidence intervals for the sensitivity, specificity, overall accuracy and positive (PPV) and negative predictive values (NPV) were calculated with the Wilson score method. Sensitivities and specificities were compared by the McNemar's test, and predictive values were compared using the generalised score statistic. The positive (LR+) and negative likelihood ratios (LR-) were calculated using standard methods[13]. Assessment of the value of each component as "add on tests" were made with relative likelihood ratios.[13] Statistical analysis performed using with SAS software, version 9.2 at a two-sided 5% significance level.

## **2.4 Results**

### **2.4.1 Study Population**

Both CMR and XRA were available in 676 patients (mean 60±9.5 years, 62% male). For the individual components LGE was available in 674 (99.7%), perfusion in 661 (97.8%), ventricular function in 676 (100%) and MRA in 597 (88.3%). The prevalence of XRA defined significant CAD was 39% and further demographic details are shown in Table 2.2.

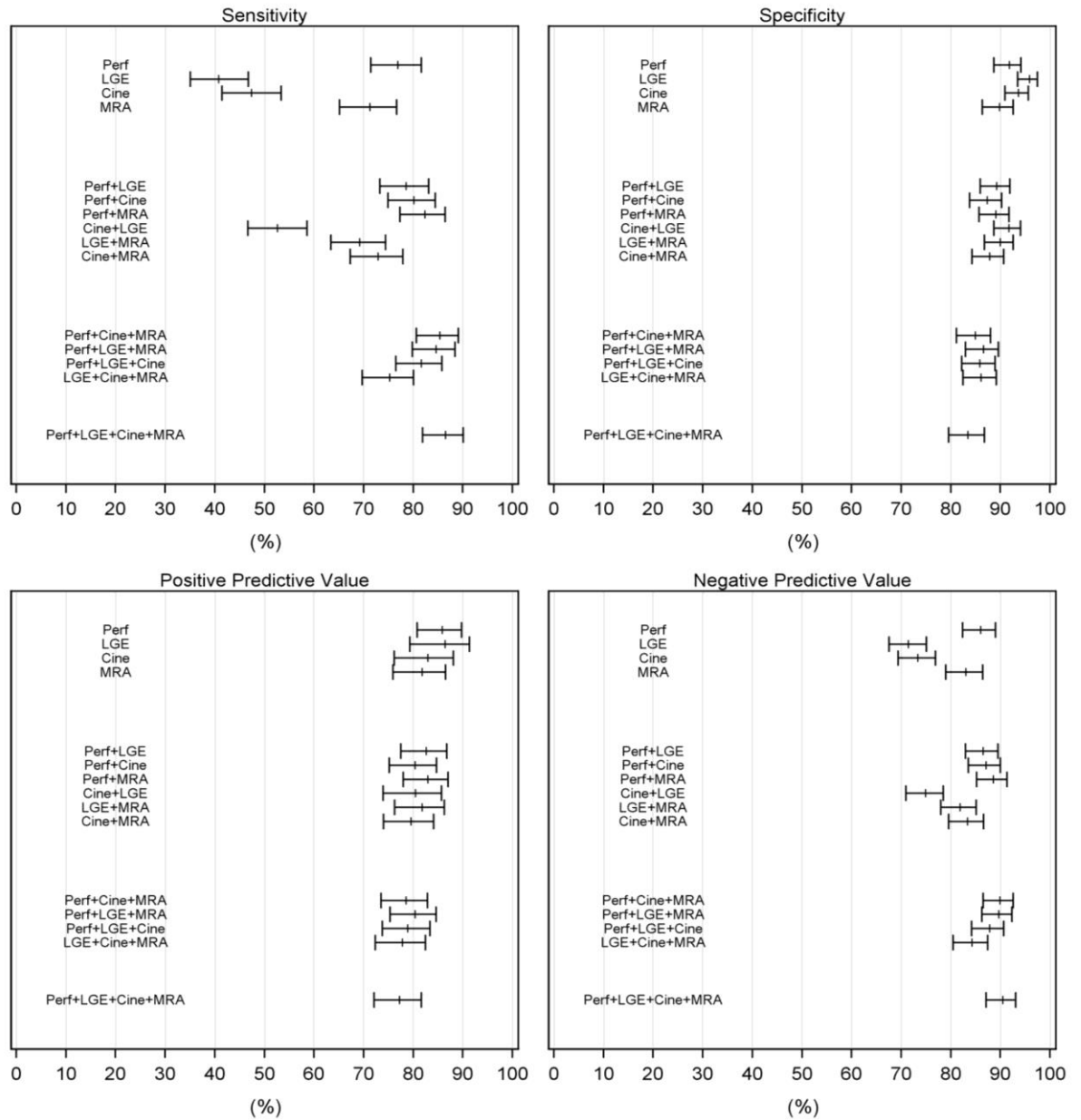
### **2.4.2 Diagnostic Accuracy**

The sensitivity of the combined CMR protocol was 86.5% (95%CI: 81.9-90.1), specificity 83.4% (79.5-86.7), PPV 77.2% (72.1-81.6%), NPV 90.5% (87.1-93.0) and overall diagnostic accuracy 84.6% (81.7-87.1). The diagnostic accuracy of the individual components, paired and triplet

combinations compared to the full multi-parametric protocol are presented in Table 2.3 and Figure 2.1.

We have shown that of the individual components, perfusion had numerically the highest sensitivity (76.9%), NPV (86.0%) and overall diagnostic accuracy (85.9%), whilst LGE had the highest specificity (95.8%) and PPV (86.4%) for the detection of significant CAD.

**Figure 2.1. Diagnostic accuracy of the individual components and their combinations compared to the full multi-parametric CMR examination.**



Cine – Cine imaging; LGE – late gadolinium enhancement; Perf –perfusion imaging; MRA – magnetic resonance coronary angiography [92]



#### **2.4.2.1 Sensitivity**

The maximum sensitivity (86.5%) and NPV (90.5%) for the detection of significant CAD by CMR was achieved when the full multi-parametric protocol was used, no individual component, paired or triplet combination outperformed the full multi-parametric protocol. However its lower specificity and PPV, meant that its overall diagnostic accuracy (84.6%) was broadly similar to the majority of paired and triplet combinations (Table 2.3).

#### **2.4.2.2 Specificity**

In terms of specificity, the individual components of perfusion (91.8%), ventricular function (93.7%) and LGE (95.8%) all performed significantly better than the multi-parametric protocol (83.4%)( $P < 0.0001$  for all). In addition, combining LGE with either ventricular function (91.7%) or MRA (90.0%) significantly improved the test specificity compared to the multi-parametric protocol ( $P < 0.0001$  for each).

#### **2.4.2.3 Overall Diagnostic Performance**

For overall diagnostic performance, no individual component or combination was better statistically than the full multi-parametric protocol (Table 2.3). The use of coronary MRA had no additional diagnostic benefit in terms of overall diagnostic accuracy when performed within a multi-parametric protocol (84.6% Vs. 84.2%)( $X^2 = 0.3913, 1df, P = 0.5316$ ).

**Table 2.2** Summary of demographic and angiographic characteristics.

		<b>n=676</b>
Age (years)		60.3 ± 9.5
Male gender		421 (62%)
Body Mass Index (kg/m <sup>2</sup> )		29.0 ± 4.3
Ethnicity	White	643 (95%)
	Black	5 (1%)
	Asian	24 (4%)
	Other	4 (1%)
Smoking Status	Never smoked	236 (35%)
	Ex-smoker	315 (47%)
	Current smoker	125 (18%)
Systolic Blood Pressure (mmHg)		138.1 ± 20.9
Diastolic Blood Pressure (mmHg)		79.0 ± 11.3
Previous admission for AMI or ACS		54 (8.0%)
Previous PCI		37 (5%)
Hypertension		347 (51%)
Diabetes mellitus		85 (13%)
	Type I	4 (5%)
	Type II	81 (95%)
Family history of premature CAD	Yes	392 (58%)
	No	237 (35%)
	Unknown	47 (7%)
Total cholesterol (mmol/L)		5.2 (1.2)
<b>Medication</b>		
Aspirin and/or Clopidogrel		404 (60%)
Statin		301 (45%)
ACEi / A2 Receptor Blockers		229 (37.2%)
Beta-blocker		203 (33.0%)
Patients undergoing X-ray angiography		
Any significant stenosis		266 (39%)
Triple Vessel Disease		40 (6%)
Double Vessel Disease		83 (12%)
Single Vessel Disease		143 (21%)
LMS Disease		22 (3%)
LAD Disease		169 (25%)
LCx Disease		126 (19%)
RCA Disease		105 (16%)

Mean±standard deviation. Number (percentage).

AMI = acute myocardial infarction; ACS – acute coronary syndrome; PCI – percutaneous coronary intervention; CAD – coronary artery disease; ACEi – angiotensin converting enzyme inhibitor; A2 – angiotensin 2; LMS – left main stem; LAD – left anterior descending; LCx – left circumflex; RCA – right coronary artery

**Table 2.3** Diagnostic accuracy of a multi-parametric CMR exam and its individual components, paired and triplet combinations compared to the reference test X-ray angiography.

	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)	Overall Accuracy (95% CI)
Overall multi-parametric CMR study (all components) (n= 676)	86.5 (81.8, 90.1)	83.4 (79.5, 86.7)	77.2 (72.1, 81.6)	90.5 (87.1, 93.0)	84.6 (81.7, 87.1)
<b>Individual CMR components</b>					
LGE (n= 674)	40.8 (35.0, 46.8)	95.8 (93.4, 97.4)	86.4 (79.3, 91.3)	71.4 (67.5, 75.0)	74.2 (70.7, 77.3)
Perfusion (n= 661)	76.9 (71.4, 81.6)	91.8 (88.7, 94.1)	85.8 (80.8, 89.7)	86.0 (82.4, 89.0)	85.9 (83.1, 88.4)
Ventricular function (n= 676)	47.4 (41.4, 53.4)	93.7 (90.9, 95.6)	82.9 (76.1, 88.1)	73.3 (69.3, 76.9)	75.4 (72.1, 78.5)
MRA (n= 597)	71.2 (65.1, 76.7)	89.8 (86.3, 92.5)	81.8 (75.9, 86.5)	83.0 (79.0, 86.4)	82.6 (79.3, 85.4)
<b>Paired combinations</b>					
Perfusion/LGE (n= 676)	78.6 (73.3, 83.1)	89.3 (85.9, 91.9)	82.6 (77.5, 86.8)	86.5 (82.9, 89.5)	85.1 (82.2, 87.5)
Perfusion/function (n= 676)	80.1 (74.9, 84.4)	87.3 (83.7, 90.2)	80.4 (75.2, 84.7)	87.1 (83.5, 90.0)	84.5 (81.5, 87.0)
Perfusion/MRA (n= 676)	82.3 (77.3, 86.4)	89.0 (85.6, 91.7)	83.0 (78.0, 87.0)	88.6 (85.2, 91.3)	86.4 (83.6, 88.8)
Function/LGE (n= 676)	52.6 (46.6, 58.6)	91.7 (88.6, 94.0)	80.5 (73.9, 85.7)	74.9 (70.9, 78.5)	76.3 (73.0, 79.4)
Function/MRA (n= 676)	72.9 (67.3, 77.9)	87.8 (84.3, 90.6)	79.5 (74.0, 84.1)	83.3 (79.5, 86.6)	82.0 (78.9, 84.7)
LGE/MRA (n= 676)	69.2 (63.4, 74.4)	90.0 (86.7, 92.5)	81.8 (76.2, 86.3)	81.8 (78.0, 85.1)	81.8 (78.7, 84.5)
<b>Triplet combinations</b>					
Perfusion/LGE/function (n= 676)	81.6 (76.5, 85.8)	85.9 (82.1, 88.9)	78.9 (73.7, 83.3)	87.8 (84.2, 90.6)	84.2 (81.2, 86.7)
Perfusion/LGE/MRA (n= 676)	84.6 (79.8, 88.4)	86.6 (82.9, 89.5)	80.4 (75.3, 84.6)	89.6 (86.3, 92.3)	85.8 (83.0, 88.2)
Perfusion/function/MRA (n= 676)	85.3 (80.6, 89.1)	84.9 (81.1, 88.0)	78.5 (73.5, 82.9)	89.9 (86.5, 92.5)	85.1 (82.2, 87.5)
LGE/function/MRA (n= 676)	75.2 (69.7, 80.0)	86.1 (82.4, 89.1)	77.8 (72.4, 82.5)	84.2 (80.5, 87.4)	81.8 (78.7, 84.5)

CMR – cardiovascular magnetic resonance; LGE – late gadolinium enhancement; LR- – Likelihood Ratio Negative; LR+ – Likelihood Ratio Positive; MRA – magnetic resonance coronary angiography.

### **2.4.3 The Value of Components as Individual and Add On Tests: Likelihood Ratios**

The highest likelihood ratio positive (LR+) was achieved when using LGE imaging alone (LR+ 9.81) signifying this individual component as the best approach for ruling in a diagnosis. All individual, paired and triplet combinations had higher LR+ than the full multi-parametric protocol (Table 2.4). However the full multi-parametric protocol had the lowest LR- (0.16) than all of the individual components and their combinations, signifying this as the best approach to rule out significant CAD. The absolute likelihood ratios for all of the components and their combinations are displayed in Table 2.4. Table 2.5 illustrates relative likelihood ratios using selected components as “add-on” tests to stress perfusion imaging alone, and the absolute number of new true and false positives cases produced with each combination.

## **2.5 Discussion**

This pre-specified sub-study of the CE-MARC study has demonstrated the diagnostic accuracy of the individual components and the paired and triplet combinations from the multi-parametric CMR examination. The three main findings were that i) no individual component or combination of components outperformed the full multi-parametric protocol to rule out significant coronary artery disease; ii) the LGE component has the best performance to rule-in significant CAD; and iii) the addition of MRA to function/perfusion/LGE does not offer any incremental benefit.

**Table 2.4** Likelihood ratios positive and negative for the multi-parametric CMR exam and its individual components, paired and triplet combinations compared to the reference test X-ray angiography.

	Likelihood Ratio +ve (95% CI)	Likelihood Ratio -ve (95% CI)
Overall multi-parametric CMR study (all components) (n= 676)	5.21 (4.17, 6.51)	0.16 (0.12, 0.22)
<b>Individual CMR components</b>		
LGE (n= 674)	9.81 (6.02, 15.97)	0.62 (0.56, 0.68)
Perfusion (n= 661)	9.35 (6.70, 13.05)	0.25 (0.20, 0.31)
Ventricular function (n= 676)	7.47 (5.04, 11.07)	0.56 (0.50, 0.63)
MRA (n= 597)	7.01 (5.11, 9.61)	0.32 (0.26, 0.39)
<b>Paired combinations</b>		
Perfusion/LGE (n= 676)	7.32 (5.50, 9.75)	0.24 (0.19, 0.30)
Perfusion/function (n= 676)	6.31 (4.86, 8.20)	0.23 (0.18, 0.29)
Perfusion/MRA (n= 676)	7.50 (5.66, 9.94)	0.20 (0.15, 0.26)
Function/LGE (n= 676)	6.35 (4.51, 8.93)	0.52 (0.45, 0.59)
Function/MRA (n= 676)	5.98 (4.57, 7.83)	0.31 (0.25, 0.38)
LGE/MRA (n= 676)	6.92 (5.12, 9.35)	0.34 (0.29, 0.41)
<b>Triplet combinations</b>		
Perfusion/LGE/function (n= 676)	5.77 (4.51, 7.37)	0.21 (0.17, 0.28)
Perfusion/LGE/MRA (n= 676)	6.31 (4.90, 8.11)	0.18 (0.13, 0.24)
Perfusion/function/MRA (n= 676)	5.64 (4.46, 7.14)	0.17 (0.13, 0.23)
LGE/function/MRA (n= 676)	5.41 (4.21, 6.95)	0.29 (0.23, 0.36)

LGE – late gadolinium enhancement; LR – likelihood ratio; MRA – magnetic resonance coronary angiography.

### **2.5.1 Likelihood Ratios**

We have shown the absolute likelihood ratio (LR) for each component and their combinations (Table 2.4) and demonstrated how many more (or less) times a particular component or combination result is likely in patients with CAD compared to those without the disease. LR is defined as the ratio of the expected test results in subjects with a certain disease to the subjects without disease, and they directly link the pre-test and post-test probability of the disease. A likelihood ratio of greater than 1 is associated with the presence of disease, whereas a ratio of less than 1 would indicate the test result is associated with the absence of disease. Importantly, as likelihood ratios are based on the ratio of sensitivity and specificity of an individual test, they are independent of disease prevalence, and can therefore be applied to different populations. The presented LRs can therefore be applied directly at the individual level and used to calculate how the probability of having CAD changes after the result of an individual component or combination of components of the CMR examination. Positive and negative likelihood ratios are therefore useful to understand the role of a test result in changing a clinician's estimate of the probability of disease in a patient.

The LR for positive tests (LR+) is the likelihood that a given test result would be expected in a patient with the disease (i.e. how much more likely the positive test result is to occur in subjects with the disease compared to those without the disease). LR+ is the best indicator for a rule-in diagnosis and the higher the LR+ the more indicative of disease. LR+ is calculated as follows:  $LR+ = \text{sensitivity} / (1 - \text{specificity})$ . Therefore high sensitivity and specificity result in high LR+. The individual components of LGE (LR+ 9.81) and

perfusion (9.35) had the highest LR+ amongst all the individual components and combinations with LGE benefitting from very high specificity to overcome poor sensitivity, and perfusion benefitting from both high sensitivity and specificity. For both components tested in isolation, a positive test finding increased the odds of the patient having CAD more than 9 fold. Therefore a positive LGE or perfusion test is a good test for ruling in the diagnosis of CAD.

**Table 2.5** Relative likelihood ratios and the numbers of new true positive and false positive cases produced by adding on further components sequentially to stress perfusion imaging in isolation.

	Relative LR+	Relative LR-	New True Positive Cases Produced	New False Positives Cases Produced
Perfusion (+LGE)	0.78	0.91	7	11
Perfusion (+function)	0.68	0.89	9	18
Perfusion (+MRA)	0.79	0.76	16	12
Perfusion +LGE (+function)	0.79	0.89	8	14
Perfusion +LGE (+MRA)	0.86	0.74	16	11
Perfusion +function (+MRA)	0.89	0.76	14	10
Perfusion +function (+LGE)	0.91	0.94	4	6

LGE – late gadolinium enhancement; LR – likelihood ratio; MRA – magnetic resonance coronary angiography.

Likelihood ratios for negative tests (LR-) demonstrate how much less likely the negative result will occur in subjects with the disease to the probability that the same result will occur without the disease. LR- is calculated as follows:  $LR- = (1 - \text{specificity}) / \text{sensitivity}$  and is a good indicator for ruling-out the diagnosis. For a single component, perfusion imaging produced the smallest likelihood ratio of disease for a negative finding (LR- 0.25): i.e. the odds of a patient having CAD were reduced by 75% to one quarter of the pre-test odds with a normal perfusion result. By comparison, the odds of having CAD were only reduced by around 40% with a negative LGE finding (LR- 0.62). Therefore for a single component, perfusion resulted in the greatest change in post-test odds of having coronary disease, and an overall diagnostic accuracy of 85.9%. In terms of both positive and negative likelihood ratios, no paired or triplet combination offered a significant benefit over the best performing component of perfusion alone.

When combining the information from the four components in the full multi-parametric protocol using the “believe the positive” rule, the consequent reductions in specificity were not met by similar increases in sensitivity, which resulted in a comparatively low LR+ of 5.21. The full multi-parametric CMR examination, however, with all 4 components combined had the lowest LR- (0.16) indicating that the combination of all 4 components was best for ruling out CAD.

The high LR+, low LR- and high overall diagnostic accuracy of the single perfusion component demonstrates that perfusion imaging ought to have most influence on a physician's risk stratification of the patients' likelihood of



having significant underlying CAD. We have therefore shown the relative likelihood ratios of the perfusion component as the starting point, and building on this using selected combinations as “add on” tests, highlighting the number of new true and false positive cases produced by each combination (Table 2.5). This analysis showed that no add on test to perfusion imaging is preferable for ruling in the diagnosis (since all add on tests reduce the relative LR+), but adding on components can improve the rule-out value of the CMR examination (all add on tests reduce the LR-).

### **2.5.2 Comparative Literature**

There have been a number of other studies analysing the diagnostic performance of the components of the CMR examination, although none of this magnitude and many of which being performed in highly selected populations.

One study analysed the diagnostic accuracy of CMR components in 100 patients preselected for X-ray coronary angiography ( $\geq 70\%$  stenosis as the reference standard).[8] The CMR protocol included wall motion, stress and rest perfusion and LGE. The analysis algorithm considered LGE images first with presence of severe CAD diagnosed if LGE was positive in an ischaemic pattern. If LGE was negative the perfusion images were analysed and a reversible defect used to diagnose CAD. This analysis algorithm had a sensitivity (89%) and specificity (87%) - which was similar to the CE-MARC study. In terms of individual components compared to CE-MARC, the perfusion component in this previous study had the highest sensitivity (84% vs. 77% in our population) although with a significantly lower specificity (58%

vs. 92%). Wall motion scoring was not considered in their analysis algorithm; cine images were acquired and had a similar sensitivity (49% vs. 47%) but lower specificity (73% vs. 94%) than in our study.

In patients with non ST-segment elevation myocardial infarction our group has previously evaluated the diagnostic accuracy of all 4 components of the CMR examination, performed within 72 hours of presentation, with an overall sensitivity of 96%, specificity 83%, PPV 96% and NPV 83%.[9] Once again the perfusion component of the examination yielded the highest sensitivity (88%), although in this study it was higher than when compared to our stable elective population (77%).

Cury *et al* studied a mixed cohort of 47 patients (14 with previous MI) and also demonstrated that stress perfusion imaging had the highest sensitivity (81%) and LGE the highest specificity (94%).[10] The maximum diagnostic accuracy was achieved with the combination of stress perfusion and LGE, and unsurprisingly this was again higher in the sub-group of patients with previous myocardial infarction than those with suspected CAD and no prior infarction (93% vs. 86%).

The clinical utility of imaging coronary artery anatomy with dedicated coronary MRA protocols in expert centres has been demonstrated to have good diagnostic accuracy for the detection of proximal CAD.[14] Technical advances at 3.0 Tesla and using a 32 channel coil have been shown to further improve signal to noise ratio and overall accuracy compared with initial reports, yielding sensitivities of 92-96%.[15, 16] However, the efficacy

of coronary imaging within a combined CMR protocol remains to be established. Klein *et al* performed coronary MRA, stress and rest perfusion and LGE imaging on 54 patients with suspected CAD, again showing the perfusion component was the most accurate alone (sensitivity 87%, specificity 88%). They showed that the addition of LGE to stress perfusion imaging did not improve the overall diagnostic accuracy (sensitivity 88%, specificity 88%). In terms of coronary imaging, 15% of overall MRA had non-diagnostic image quality; whole heart MRA had significantly inferior diagnostic accuracy due to poor specificity (sensitivity 92%, specificity 56%) unless only those with excellent MRA image quality (n=18, 33%) were analysed, whereupon it remained similar to the perfusion component alone (sensitivity 86%, specificity 91%).<sup>[11]</sup> Other investigators have evaluated the effect of adding coronary MRA to stress perfusion CMR on diagnostic performance; when compared to invasive pressure-wire derived fractional flow reserve (FFR) at 1.5T there was no significant improvement in diagnostic accuracy.<sup>[12]</sup>

Coronary MRA remains a time consuming acquisition, which often is non-diagnostic when performed within an already long multi-parametric protocol. In our study 79 patients (11.7%) had non-diagnostic coronary MRA images. Furthermore, in those with adequate or excellent image quality (n=597), the addition of the coronary MRA made no difference statistically on the overall diagnostic accuracy of the CMR examination. Equally, whilst some triplet combinations with MRA offer similar diagnostic accuracy, the components of cine, LGE and perfusion imaging offer clinical information above and beyond

detection of coronary disease (i.e. left ventricular volumes/ejection fraction, myocardial viability and ischaemic burden) which may have additional prognostic importance.

## **2.6 Conclusions**

From this pre-specified sub-analysis of the CE-MARC study, using the original blinded visual-read, we have demonstrated the diagnostic accuracy of the individual components and their combinations from the full multi-parametric CMR exam. In patients presenting with stable chest pain, the stress perfusion component of the multi-parametric CMR exam was the single most important component for overall diagnostic accuracy. However, the full combined multi-parametric protocol was the optimal approach for disease rule-out, and the LGE component best for rule-in. The inclusion of coronary MRA had no additional overall diagnostic benefit within a multi-parametric protocol.

## **Chapter 3**

### **Ischaemia and Scar Burden Measured by Cardiac Magnetic Resonance Imaging in Patients with Coronary Heart Disease - a CE-MARC Sub-study**

#### **3.1 Abstract**

##### **3.1.1 Background**

The prognostic importance of the ischaemia and scar burden is well established from single photon emission computed tomography (SPECT) studies. In the CE-MARC study, cardiovascular magnetic resonance (CMR), SPECT, and coronary angiography were performed in a large suspected coronary heart disease (CHD) population. The aim of this sub-study was to directly compare ischaemia and scar burden as quantified by CMR and SPECT.

##### **3.1.2 Methods**

From the 752 patients recruited to the CE-MARC study 241 with significant angiographic stenosis were identified. For each modality, the summed stress score (SSS), summed rest score (SRS) and summed difference score (SDS) were assessed on a 5-point scale for perfusion defects and/or scar in 16-segments.

##### **3.1.3 Results**

The overall SSS was slightly higher for CMR compared to SPECT (median (interquartile range): 11(3–16) vs. 9(3–20), $p=0.0447$ ). The SRS was significantly lower (0(0–0) vs. 4(1–10); $p<0.0001$ ) and the SDS greater by CMR than SPECT (10(3–15) vs. 3(0–10), $p<0.0001$ ). Overall, there was moderate positive correlation and agreement (SSS:  $r=0.36$ , Bland-Altman

limits (BA)=-22.0–21.7; SRS:  $r=0.42$ , BA=-7.9–15.1; SDS:  $r=0.30$ , BA=-21.1–15.4). Regression analysis fitting the CMR to SPECT SDS demonstrated a CMR SDS ischaemia burden of 15% would be the equivalent of an SPECT SDS of 10%.

### **3.1.4 Conclusions**

Measurements of overall CHD burden (SSS) moderately agree between both modalities. However, there are differences in the proportions of scar and ischaemia detected, likely due to the different approach to scar imaging (LGE vs. matched defect), attenuation with SPECT and differences in cardiac coverage for perfusion assessment.

### **3.2 Introduction**

Coronary heart disease (CHD) is a leading cause of death and disability and its optimal diagnostic and treatment strategy is an on-going challenge. It is an accepted paradigm that the haemodynamic relevance of a stenosis rather than the degree of obstruction alone should inform the decision between revascularization and optimal medical therapy (OMT)[93, 94]. Patients with significant ischaemia and without extensive scar are more likely to benefit from early revascularization, whereas patients with minimal or no ischaemia may be treated with OMT alone [95, 96]. In addition, scar in CHD patients confers unfavourable clinical and functional outcomes [82, 97]. Most prognostic data for ischaemia and scar burden, as well as their impact on treatment strategy, have been derived from single photon emission computed tomography (SPECT) myocardial perfusion imaging, one of the most frequently used tests for the assessment of CHD [98]. However, radiation exposure from SPECT perfusion tracers is of concern [99] and the technique can be limited by low spatial resolution and soft tissue attenuation artefacts.

Cardiovascular magnetic resonance (CMR) is an alternative non-invasive technique for the detection of ischaemia and scar. CE-MARC was the largest, prospective, real-world evaluation of CMR and showed that CMR had a higher sensitivity and negative predictive value compared to SPECT for the detection of CHD[29]. The rigorous design of the study minimised referral bias by mandating that all patients underwent coronary angiography as the reference test, independent of the preceding CMR or SPECT result

[30]. Furthermore CE-MARC five year follow-up has subsequently demonstrated the stronger prognostic value of CMR for the prediction of major adverse cardiovascular events over SPECT [100].

To date, measurements of ischaemia and scar burden by CMR and SPECT have not been directly compared. The CE-MARC study provides a unique patient population to undertake such a cross-modality comparison, such that our aims were to compare ischaemia and scar burden in 1) all patients with significant angiographic stenosis, and 2) all patients with angiographic stenosis and evidence of ischaemia on both CMR and SPECT (i.e. all three tests positive).

### **3.3 Methods**

#### **3.3.1 Patients**

CE-MARC was a prospective evaluation of 752 consecutive patients with suspected angina [29]. Between March 2006 and August 2009, patients were screened and enrolled if they had at least one major cardiovascular risk factor and a cardiologist considered them to have stable angina requiring further investigation. All patients were scheduled to undergo SPECT and CMR (in randomized order), followed by X-ray coronary angiography (XRA) within 4 weeks regardless of the treating physician's chosen clinical pathway. Exclusion criteria were as previously published [29, 30]. The study was conducted in accordance with the Declaration of Helsinki (2000) and approved by the local research ethics committee. Patients



provided informed written consent. For this pre-defined substudy, all patients recruited to CE-MARC who had diagnostic image quality and significant coronary artery stenosis ( $\geq 50\%$  left main stem (LMS) or  $\geq 70\%$  in a first order coronary artery  $\geq 2\text{mm}$ ) on quantitative invasive coronary angiography (QCA) were selected.

### **Investigational procedures and their analysis**

In the main CE-MARC analysis, SPECT, CMR and XRA were analysed blinded, by paired readers with at least 10 years' experience in their modalities.

#### **3.3.2 CMR imaging and analysis**

The multi-parametric CMR (1.5-Tesla Philips Intera; Best, The Netherlands) protocol comprised cine imaging, adenosine stress perfusion ( $140\mu\text{g}/\text{kg}/\text{min}$  for 4 minutes), rest perfusion, coronary MR angiography and late gadolinium enhancement (LGE). Specific imaging parameters have been previously described[30]. Image quality was visually graded on a scale from 0-3 as (0=non-diagnostic, 1=poor, 2=adequate and 3=high). For calculation of ischaemic burden perfusion images were scored according to a 5-point scoring scale: 0=normal (0% reduction in transmural extent of myocardial perfusion), 1=mild (0-49%), 2=moderate (50-74%), 3=severe (75-100%), 4=absent (thinned with persistent absence of contrast delivery)[101] and LGE images were graded by transmural extent of hyperenhancement (0=normal, 1=1-25%, 2=26-50%, 3=51-75%, 4=76-100%) for each segment in a 16-segment model according to the AHA/ACC classification, (excluding

the apical cap). The summed stress score (SSS) was calculated by adding the highest scores from either stress perfusion or LGE for each segment (i.e. an objective score of the area of hypoperfusion). The summed rest score (SRS) was considered as the sum of the LGE scores for each segment (area of myocardial infarction). The ischaemic burden was calculated as the summed difference score (SDS) by adding the differences between the stress and LGE scores for each segment (total area of hypoperfusion minus the area of infarction). The semiquantitative scores were graded according to their severity as previously described: SSS<4, 4 to 8, 9 to 13, and >13; SRS<2, 2 to 7, and >7 and SDS:<2, 2 to 7 and >7, respectively [102]. LV volumes were calculated by manually tracing endocardial and epicardial borders at end-diastole on short-axis cines (QMass 6.2.1, Medis, Leiden, The Netherlands)[103].

### **3.3.3 SPECT imaging and analysis**

SPECT used a dedicated cardiac gamma camera (MEDISO Cardio-C, Budapest, Hungary) and ECG-gating. Patients underwent a two-day protocol using a weight adjusted dose of <sup>99m</sup>Tc-tetrofosmin to a maximum 600MBq per examination. Rest and adenosine-stress images using an identical intravenous adenosine protocol to that in CMR were acquired. Full details have previously been described[30]. Image quality was visually graded in the same way as for CMR images, as non-diagnostic, poor, adequate and high. Evidence of ischaemia and scar were recorded by visual comparison of rest/stress SPECT scans, with reference to wall motion analysis. To allow for comparative analysis, this used the same 16-segment scoring system as for the CMR analysis. The SSS and SRS were calculated by adding the highest

scores for each segment from the stress and rest perfusion scans, respectively. The ischaemic burden was calculated as the SDS by adding the differences between the stress and rest scores for each segment. QGS software (Cedars-Sinai Medical Center, USA) was used to calculate end-diastolic and end-systolic volumes and wall-motion scores.

### **3.3.4 X-ray angiography**

X-ray angiograms were reported by two experienced cardiologists blinded to the other studies. Significant CAD was defined as LMS stenosis  $\geq 50\%$  or  $\geq 70\%$  stenosis of a first-order coronary artery measuring  $\geq 2\text{mm}$  in diameter by quantitative invasive coronary angiography (QCAPlus, Sanders Data Systems, Palo Alto, California, USA).

### **3.3.5 Statistical Analysis**

Baseline characteristics were summarised using descriptive statistics. The summed scores by CMR and by SPECT and image quality scores were compared using the Wilcoxon signed-rank test. In addition, the Pearson's correlation coefficient plots of difference between measures versus average of the two measures and the Bland–Altman limits of agreement were produced [104]. Image quality was compared between 2 measures using a chi-squared test. All statistical analysis undertaken used a 2-sided 5% significance level (SAS 9.2, SAS Institute, Cary, NC, USA).

## **3.4 Results**

### **3.4.1 Study Population**

Of the 752 CE-MARC patients, 241 patients had significant coronary artery stenosis on XRA, whilst 106 patients had significant coronary artery stenosis on XRA and evidence of ischaemia on both CMR and SPECT studies. Table 3.1 shows the clinical characteristics of these two sub-study populations.

### **3.4.2 Image Quality**

The image quality scores from the sub-population with both CMR and SPECT positive results are summarized in Table 3.2, showing a significant higher overall image quality for CMR than for SPECT studies.

### **3.4.3 Summed Scores**

#### **3.4.3.1 Primary Analysis: All Angiographic Positive Population**

The overall CHD burden, represented by the median SSS, was slightly higher for CMR compared to SPECT, (median (interquartile range) 11 (3–16) vs. 9 (3–20),  $p=0.0447$ ). In contrast, the median SRS was significantly lower by CMR than by SPECT (0 (0–0) vs. 4 (1–10);  $p<0.0001$ ) with SPECT showing more extensive rest perfusion defects than LGE CMR. Conversely, the ischaemic burden, represented by the median SDS was significantly greater by CMR than by SPECT (10 (3–15) vs. 3 (0–10),  $p<0.0001$ ) with more extensive ischemia measured by CMR.

**Table 3.1** Baseline characteristics

	All Tests +ve (n=106)	All XRA +ve patients (n=241)
Age (Years)	62 (8.8)	62 (8.4)
Men	88 (83%)	197 (82%)
Body Mass Index (kg/m <sup>2</sup> )	28.8 (3.7)	29.0 (3.9)
Smoking Status		
Never smoked	37 (35%)	70 (29%)
Ex-smoker	51 (48%)	128 (53%)
Current smoker	18 (17%)	43 (18%)
Systolic blood pressure (mmHg)	140 (20.0)	140 (20.0)
Diastolic blood pressure (mmHg)	78 (11.9)	78 (11.9)
Hypertension	48 (45%)	126 (52%)
Diabetes mellitus	14 (13%)	34 (14%)
Family history heart disease		
Yes	60 (57%)	135 (56%)
No	38 (36%)	86 (36%)
Unknown	8 (8%)	20 (8%)
Total Cholesterol (mmol/L)	5.4 (1.2)	5.2 (1.2)
Ejection Fraction (CMR)	54.1 (6.4)	54.1 (6.4)
Ejection Fraction (SPECT)	54.7 (7.5)	54.7 (7.5)
Pattern of Coronary Disease		
LMS	10 (9%)	22 (9%)
LAD	72 (68%)	159 (66%)
RCA	48 (45%)	91 (38%)
LCX	56 (53%)	118 (49%)

All Tests +ve = Positive Coronary Angiography (XRA), CMR and SPECT.

All XRA +ve = All positive coronary angiography patients.

Data are mean (SD) or n (%) unless otherwise stated. CMR= Cardiovascular Magnetic Resonance; SPECT – single photon emission computed tomography; LMS – left main stem; LAD – left anterior descending; RCA – right coronary artery; LCX – left circumflex.

**Table 3.2** Image Quality for CMR and SPECT

Image Quality	Poor (1)	Adequate (2)	High (3)	Overall	p
Stress Perfusion CMR	1 (1%)	29 (27%)	76 (72%)	2 (2,3)	p<0.01
Stress Perfusion SPECT	2 (2%)	69 (65%)	35 (33%)	2 (2,3)	
LGE Imaging	7 (7%)	33 (31%)	66 (62%)	3 (2,3)	p<0.01
Rest Perfusion SPECT	1 (1%)	65 (61%)	40 (38%)	3 (2,3)	

Data are presented as n (%) and median (first, third quartile).

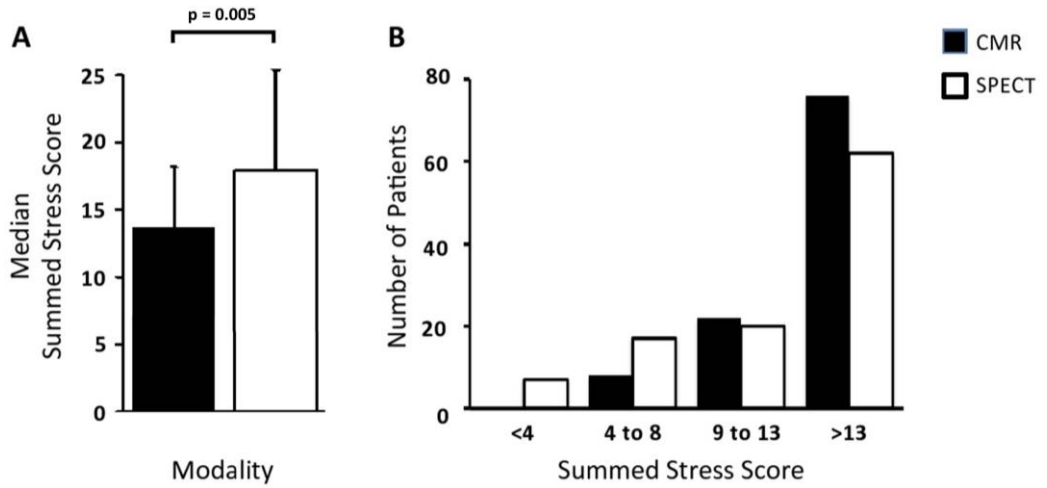
### 3.4.3.2 Secondary Analysis: All 3-Tests Positive Population

In this subgroup, the median (IQR) SSS was significantly lower with CMR than SPECT (14 (10–20) vs. 18 (10–27),  $P=0.0005$ ; Figure 3.1A). Again, SPECT demonstrated more extensive rest perfusion defects (SRS: 0 (0–0) vs. 5 (2–11),  $P<0.0001$ ; Figure 3.2A) whilst the ischaemic burden was significantly greater by CMR (SDS 13.5 (10–19) vs. 9 (5–18),  $P=0.0113$ ; Figure 3.3A).

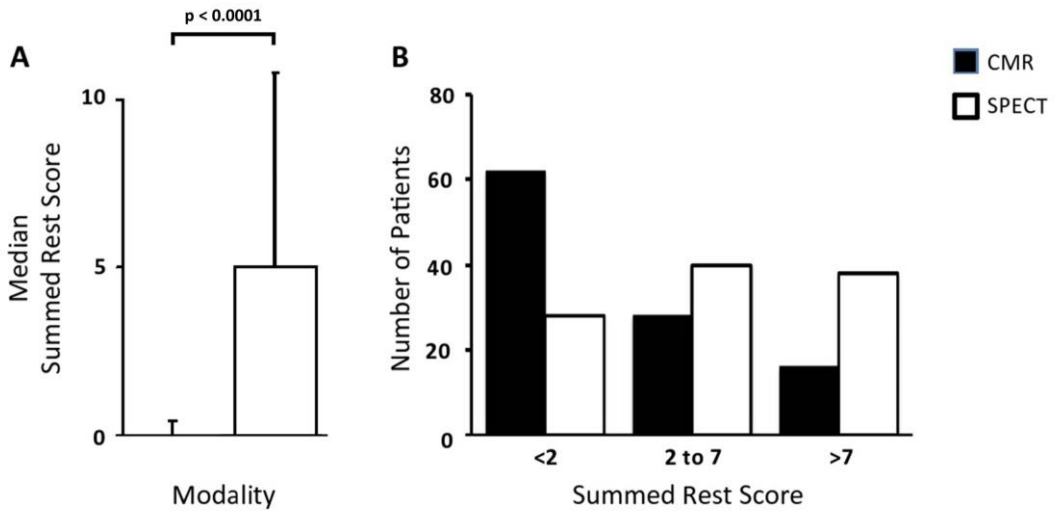
Figure 3.4 shows 2 case examples with similar overall SSS values by CMR and SPECT. In the first case scar and ischaemic burden are similar, while in the second case, SRS and SDS values are different between CMR and SPECT.

### 3.4.4 Correlation and Agreement of Summed Scores

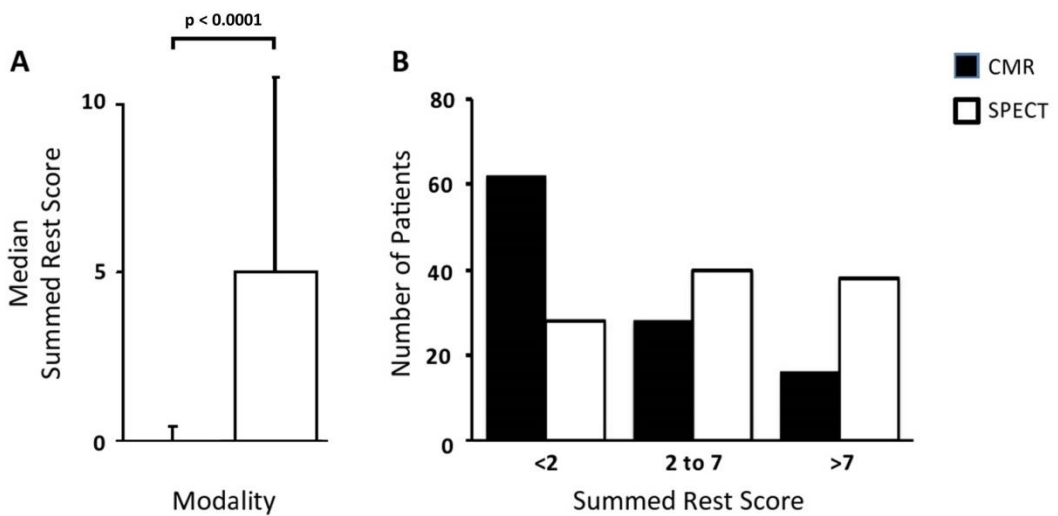
Overall in the secondary analysis population ( $n=106$ ), there was only moderate correlation and agreement of all summed scores between CMR and SPECT (SSS:  $r=0.36$ , BA= -22.0 to 21.7, bias=-0.1; SRS:  $r=0.42$ , BA= -7.9 to 15.1, bias=3.6; SDS:  $r=0.30$ , BA= -21.1 to 15.4, bias=-2.9; Figure 3.5).



**Figure 3.1** Median Summed Stress Score and Distribution

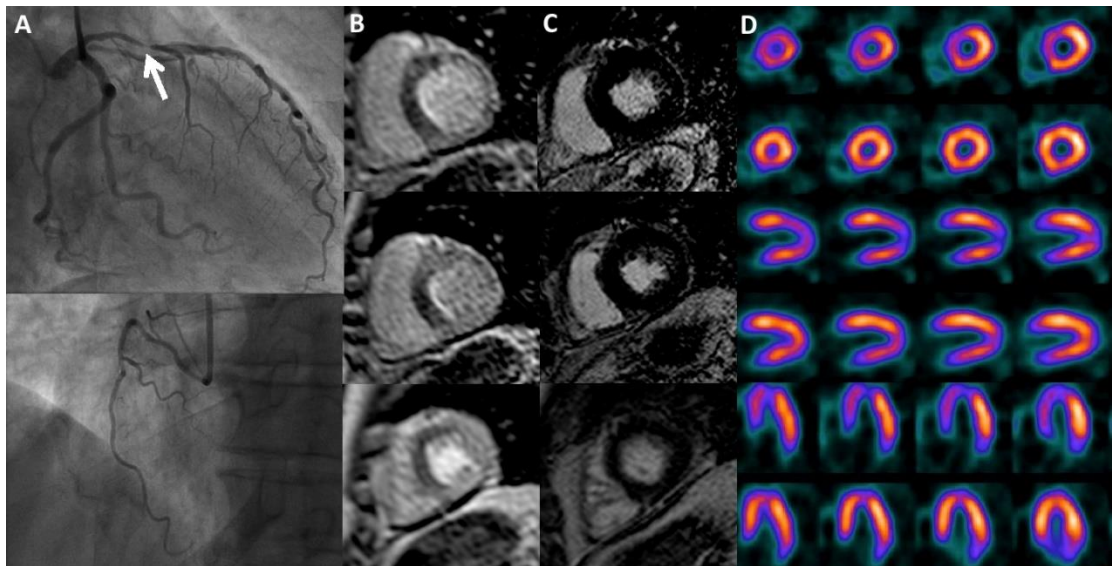


**Figure 3.2** Median Summed Rest Score and Distribution

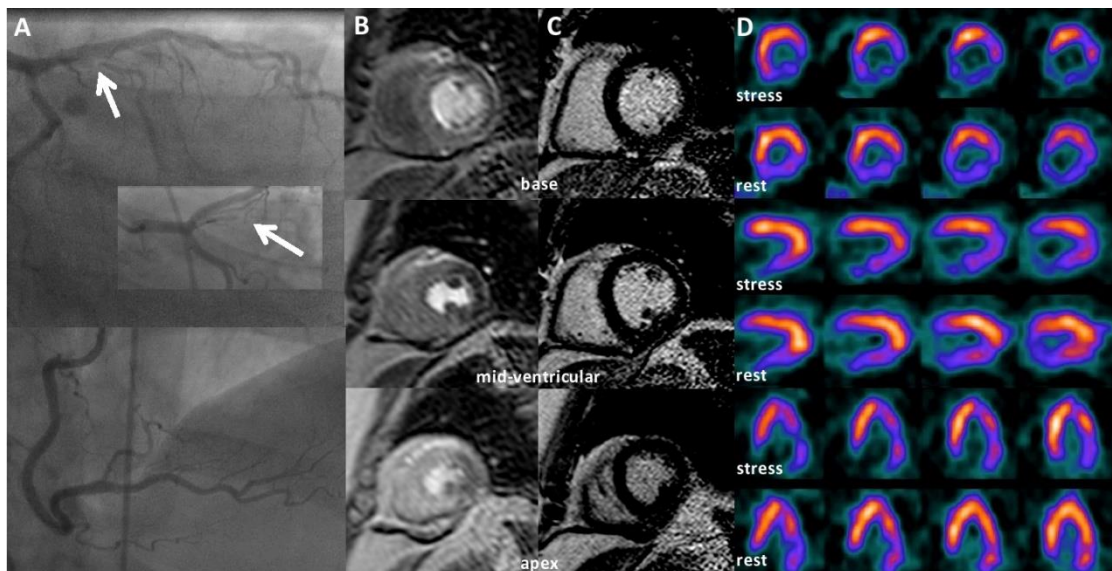


**Figure 3.3** Median Summed Difference Score and Distribution

Case1:



Case 2:

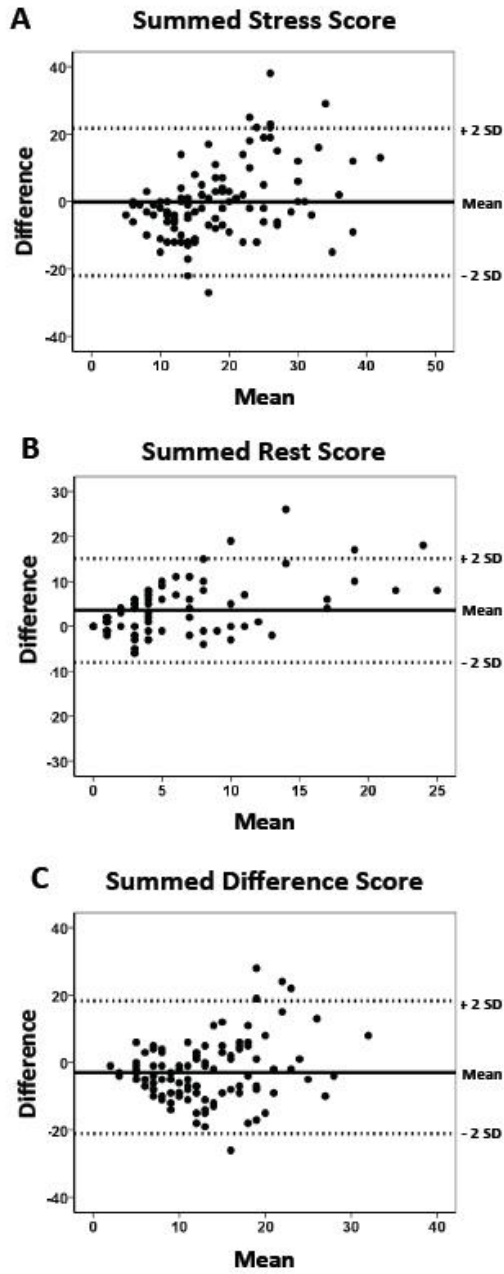


**Figure 3.4** Case examples of patients undergoing CMR and SPECT

**Case example 1:** A 70-year-old male patient with a BMI of 25.5 kg/m<sup>2</sup> presented with typical chest pain and was found to have a significant stenosis (95%; arrow) in the proximal left anterior descending artery (LAD) on invasive coronary angiography (A). The cardiovascular magnetic resonance (CMR) stress perfusion images were of high image quality and showed a large anterior and septal perfusion defect consistent with the LAD disease (B). The CMR late gadolinium enhancement images were of average image quality and did not demonstrate any evidence of myocardial scarring (C). Similar to CMR, the single photon emission computed tomography (SPECT) myocardial perfusion images were of high image quality and showed a large reversible defect in the LAD territory (D). The summed stress scores (SSS), the summed rest scores (SRS) and the summed difference scores (SDS) were similar between CMR and SPECT in this patient (SSS: 24 vs. 22; SRS: 0 vs. 0; SDS: 24 vs. 22).

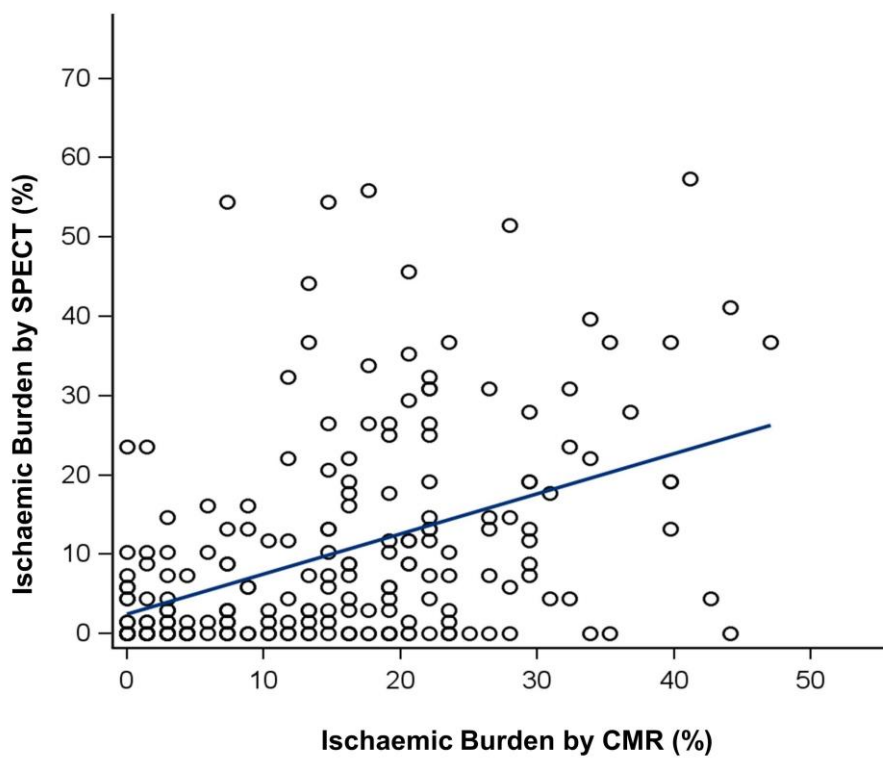


**Case example 2:** A 48-year-old male patient with a BMI of 39.0 kg/m<sup>2</sup> presented with typical chest pain and was found to have a significant stenosis (>90%; arrow) in the large intermediate coronary branch (IM) on invasive coronary angiography (A). The CMR stress perfusion images were of high image quality and showed an extensive perfusion defect in the infero-lateral and antero-lateral wall (B). The CMR late gadolinium enhancement images were also of high image quality and did not demonstrate any evidence of myocardial scarring (C). In contrast to CMR, the SPECT myocardial perfusion images showed only average image quality and a large fixed inferior and infero-lateral defect as well as a small reversible antero-lateral defect (D). The summed stress scores (SSS) were similar between both modalities (CMR vs. SPECT: 18 vs. 21). However, there were significant discrepancies between the summed rest scores (SRS) and the summed difference scores (SDS) between CMR and SPECT in this patient (SRS: 0 vs. 19, SDS: 16 vs. 2), most likely due to attenuation artefacts on the SPECT images.



**Figure 3.5** Bland-Altman limits of agreement for summed stress score, summed rest score and summed difference scores.

Regression analysis on the primary population (all XRA positive cases) fitting the CMR to the SPECT SDS, demonstrated a SPECT ischaemia burden of 10% would be equivalent to a CMR ischaemia burden of ~15%, whilst a 12.5% ischaemia burden by SPECT would be the equivalent of ~20% by CMR (Figure 3.6).



**Figure 3.6** Regression analysis fitting of cardiovascular magnetic resonance (CMR) ischaemic burden (%) to single photon emission computed tomography (SPECT) ischaemic burden (%)

### **3.5 Discussion**

CMR and SPECT are non-invasive imaging modalities that are both capable of assessing myocardial ischaemia and scar in patients with CHD; the severity and extent of which can have an important impact on risk stratification and patient outcome[39, 43, 105, 106]. However, it remains unknown how ischaemia and scar burden compare between the two modalities and whether thresholds defined by one technique can be applied to the other. Given that the two modalities use different techniques to visualize disease, in particular myocardial scar, and because the thresholds for the extent of clinically significant ischaemia have mostly been derived from SPECT studies, a comparison between the methods has considerable clinical relevance.

This is the first study that has directly compared measurements of overall CHD burden as well as ischaemia and scar burden by CMR and by SPECT. The study made use of the large prospective, well-defined CE-MARC population to identify a unique study population of patients with proven CHD confirmed by consensus of an invasive and two non-invasive assessments; this specifically minimised the impact of the different diagnostic performances of SPECT and CMR. For this sub-study, the overall extent of CHD burden and the proportions of scar and ischaemia for both modalities were measured using a consistent semi-quantitative scoring system.

The main findings of this study are that 1) the overall disease burden, represented by the SSS, and the number of patients with similar overall

disease severity are broadly comparable between CMR and SPECT. The SSS is the most powerful diagnostic and prognostic marker as shown in numerous SPECT studies [102, 105, 107] with superior prognostic impact compared with the SDS or SRS [108, 109]. As with SPECT, acquisition and analysis of perfusion and scar data are usually combined in CMR protocols, with improved detection of CHD [110]. The SSS can therefore be considered the most relevant marker of disease. 2) In terms of ischaemia and scar burden, there was only modest agreement between the two modalities, such that a 15% ischaemia burden by CMR was equivalent to the 10% threshold by SPECT, which is widely reported as the prognostic threshold [111].

However, despite the good agreement for overall disease burden, there was a statistically significant discrepancy between the scar and ischaemic burden measured by CMR and SPECT. The median SRS (scar) was significantly lower by CMR than by SPECT with SPECT tending to detect more patients with extensive defects. In contrast, the median SDS (ischaemia) was significantly greater by CMR than by SPECT with more patients with extensive ischaemia measured by CMR. This difference in proportions of ischaemia and scar burden between modalities may in part explain the stronger prediction for major adverse cardiovascular events with CMR vs SPECT [100].

There are several reasons which might in part explain the differences in ischaemia and scar burden: First, the two modalities use fundamentally different techniques to identify scar, while the detection of ischaemia is more

closely related, but not identical. CMR assessment of scar is based on LGE imaging and ischaemia is detected by dynamic first-pass stress perfusion. SPECT with  $^{99m}\text{Tc}$  uses the relative differences of tracer uptake in rest and stress studies to differentiate between fixed and reversible perfusion defects. Whilst a reversible perfusion defect represents ischaemia, a fixed perfusion defect may or may not be viable and does not necessarily represent myocardial scar as shown with LGE-CMR. Moreover, the lower spatial resolution of SPECT may lead to an underestimation of sub-endocardial scar in comparison to LGE-CMR [112].

Second, CMR LGE and SPECT cover the whole heart, whereas most CMR perfusion methods cover only three representative short axis slices. In CMR these slices are typically 10mm in thickness and thus around 60% of the myocardial mass is not evaluated. These differences in the cardiac coverage may lead to over- or underestimation of the severity and extent of ischaemia. In order to minimize these differences and to optimize the comparison between modalities, we chose a standard semi-quantitative scoring system, dividing the whole heart into segments and excluding the apical cap.

Third, although non-diagnostic scans had been excluded prior to final analysis, artefacts may impair image quality and at worst lead to false-positive or false-negative findings. These artefacts include mainly wrapping, motion, dark rim and metallic artefacts for CMR [113] and motion artefacts as well as soft-tissue attenuation for SPECT [98]. In particular, attenuation artefacts have remained an important issue in nuclear myocardial perfusion

imaging. Although the true prevalence of these artefacts is unknown, estimates have ranged from 20% to 50%[114].

As outlined above, CMR and SPECT have different strengths and limitations. Although this study provides new insights into the relative performance of both modalities, in the absence of a true reference test, it cannot determine which modality is more accurate in assessing the scar and ischaemic burden. It is widely accepted that LGE-CMR is superior to SPECT for the detection of myocardial scar [112] and that SPECT studies can be affected by attenuation artefacts mimicking fixed perfusion defects. This may lead to an overestimation of scar burden by SPECT and is the most likely cause for the observed discrepancies in the current study. The reasons for the differences in ischaemic burden between the two modalities in this study are less evident, but are most likely caused by the different imaging technique (dynamic vs. relative perfusion) and the different cardiac coverage. Recent developments in myocardial perfusion CMR that allow 3D whole heart coverage may overcome this limitation and should be compared with SPECT [50, 115, 116].

### **3.6 Study Limitations**

The limitations of CE-MARC have been previously discussed, and include its single-centre design and an anatomical reference standard i.e. QCA as opposed to invasive functional assessment (FFR). The latter is a limitation common to the majority of imaging studies prior to the FAME study, which was published after CE-MARC had recruited [93]. Whilst we acknowledge our single-centre design as a potential limitation it also had the advantage of

unifying pharmacological stress protocols and ensured consistency in both imaging modality protocols. Furthermore, we did not use attenuation correction for SPECT as this was not the technical standard in most nuclear institutions worldwide including ours at time of recruitment [117]. The semi-quantitative scores have been acquired using a modified 17-segment model without the apical cap for both modalities, as the apical cap is not visualized with CMR perfusion. This is a distinct advantage of SPECT over CMR, and we acknowledge that this might lead to an underestimation of disease burden, but in return it allows a more accurate comparison of the two modalities. Finally, this is a selected subpopulation from CE-MARC, which was analysed for the specific purpose of directly comparing scar and ischaemia burden between CMR and SPECT; no inference can be drawn as to the reasons for false positive and false negative studies.

### **3.7 Conclusion**

Measurements of overall CHD burden (SSS) show reasonable agreement between CMR and SPECT. Given that SSS is the most powerful prognostic marker this suggests that CMR may be comparable to SPECT in terms of risk prediction. However, there are differences in the estimates of scar and ischaemia burden between the two modalities, which are most likely related to the different approach to scar imaging (LGE vs. matched defect), soft-tissue attenuation with SPECT and different cardiac coverage for perfusion assessment. Further studies will have to evaluate the prognostic impact of these findings.



## **Chapter 4**

### **Patient Adaptive Maximal Resolution Magnetic Resonance Myocardial Stress Perfusion Imaging**

#### **4.1 Abstract**

##### **4.1.1 Background**

Magnetic resonance perfusion pulse sequences often leave potential acquisition time unused in patients with lower heart-rates (HR), and smaller body size. The aim of this study was to demonstrate the feasibility of an automatic adaptive acquisition sequence.

##### **4.1.2 Methods**

A perfusion technique was developed which automatically adapts to HR and field-of-view, by maximising in-plane spatial resolution whilst maintaining temporal resolution every cardiac cycle. Patients (n=10) and volunteers (n=10) were scanned with both a standard resolution and adaptive method. Image quality was scored, signal-to-noise ratio (SNR) calculated, and width of dark-rim artifact (DRA) measured.

##### **4.1.3 Results**

The acquired spatial resolution of the adaptive sequence ( $1.92 \times 1.92 \text{mm}^2 \pm 0.34$ ) was higher than the standard resolution ( $2.42 \times 2.42 \text{mm}^2$ ) ( $P < 0.0001$ ). Mean DRA width was reduced using the adaptive pulse sequence ( $1.94 \pm 0.60 \text{mm}$  vs.  $2.82 \pm 0.65 \text{mm}$ ,  $P < 0.0001$ ). SNR was higher with the standard pulse sequence ( $6.7 \pm 2.2$  vs.  $3.8 \pm 1.8$ ,  $P < 0.0001$ ). There was no difference in image quality score between

sequences in either volunteers ( $1.1 \pm 0.31$  vs.  $1.0 \pm 0.0$ ,  $P=0.34$ ), or patients ( $1.3 \pm 0.48$  vs.  $1.3 \pm 0.48$ ,  $P=1.0$ ) .

#### **4.1.4 Conclusion**

Optimising the use of available imaging time during first pass perfusion with a MR pulse sequence which adapts image acquisition duration to HR and patient size is feasible. Acquired in-plane spatial resolution is improved, the DRA is reduced, and whilst SNR is reduced with the adaptive sequence consistent with the lower voxel size used, image quality is maintained.

## 4.2 Introduction

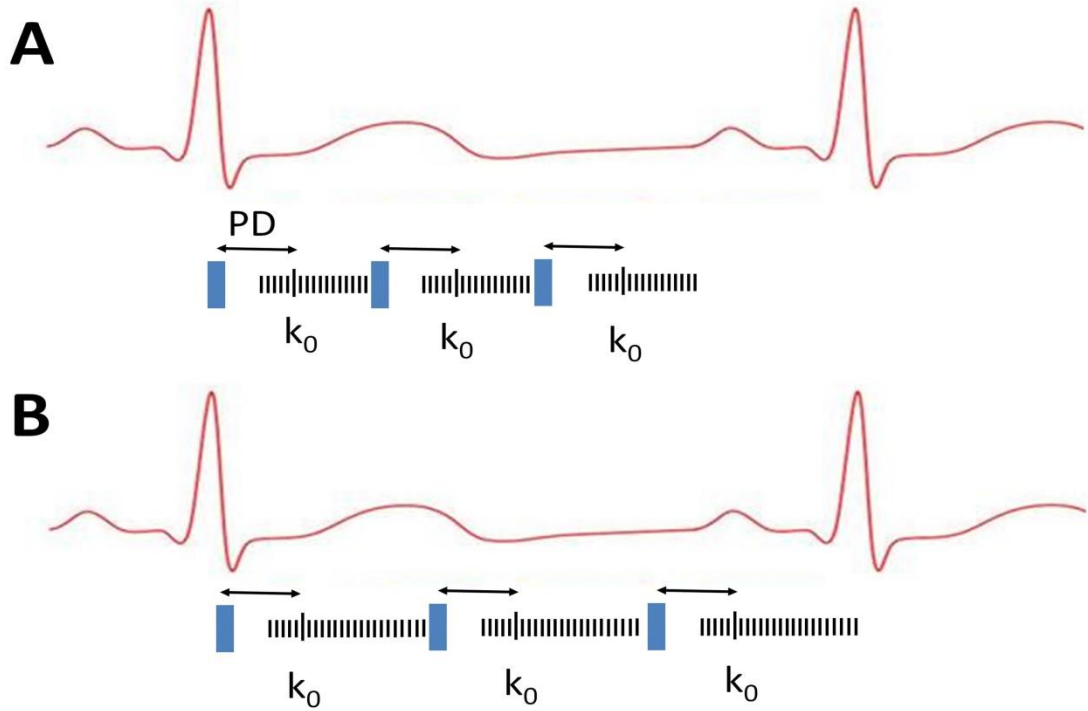
Myocardial perfusion magnetic resonance imaging with vasodilator stress has high diagnostic accuracy for the detection of coronary artery disease (CAD). A recent meta-analysis of 37 studies demonstrated a combined sensitivity of 89% (95%CI: 88%-91%) and specificity of 76% (95%CI: 73%-78%)[28].

Notable recent developments in acquisition techniques include highly accelerated pulse sequences based on spatio-temporal undersampling (for example *k-t* sensitivity encoding (*k-t* SENSE) and highly constrained back projection (HYPR))[118, 119], higher field strengths[120] and improved cardiac phase-array coils for higher signal-to-noise[47]. These advances allow improved acquired resolution and, in line with higher spatial resolution, a reduction of the width of dark rim artifact (DRA) enhancing visualization of sub-endocardial perfusion deficits. In small studies both spatio-temporal undersampling and perfusion at 3.0 Tesla (T) have led to even higher diagnostic accuracy for the detection of significant underlying CAD[47, 48].

Current MR perfusion pulse sequences are usually set to acquire at least three slices every heartbeat, optimised to accommodate heart rates that typically occur during pharmacological stress and large patient size. Therefore, the resolution of standard perfusion sequences is optimal only for subjects who are at the extremes of the patient characteristic ranges: the largest patient, with the highest heart rate that typically occurs during pharmacological stress. In patients with lower heart rates and/or of smaller

body habitus there can be a significant amount of unused potential imaging time with consequent unnecessary compromises in imaging parameters (Figure 4.1). Lower heart rates allow for more imaging time in each heart beat. Smaller body habitus necessitates smaller field-of-field (FOV) and thus a shorter image-readout duration for the same voxel size in the phase encoding direction. Both circumstances allow a potential image resolution increase. Whilst it is possible to manually adjust the sequence parameters and thus maximise the acquired resolution of an MRI scan, this is time consuming and could introduce uncertainty in potential image quality prior to the scan. Furthermore, in those with heart rates which are significantly higher during pharmacological stress than anticipated, acquisition with the fixed parameters of standard perfusion sequences is not possible at every heartbeat. This results in image acquisition every second R-R interval which may impact upon adequate characterisation of the signal changes effected during the first passage of gadolinium-based contrast agent through the heart[121].

A more flexible acquisition scheme could automatically optimise parameters specifically for each patient's size and heart rate. This would allow potential improvements in image quality (with artifact reduction, improved visualisation of the subendocardium), or maintenance of temporal resolution at very high heart rates (ensuring that time-intensity changes during the first-pass of contrast agent are always depicted) with the best available image resolution. An automated method would also reduce operator dependence of



**Figure 4.1 Schematic representing standard and adaptive resolution pulse sequences.**

A: Standard spatial resolution pulse sequence and B: Adaptive resolution pulse sequence with acquisition duration maximised for heart rate. A longer acquisition duration in the adaptive sequence makes better use of available imaging time within each heartbeat. Blue: Pre-pulse; PD - Preparation pulse Delay time;  $k_0$ : true centre of K space.[122]

acquisition parameters in those centers which manually adapt acquisition parameters to individual patients.

The aim of this study was to assess the feasibility of a patient-adaptive perfusion pulse sequence which automatically adapts to the heart rate, maximising imaging time and acquired in-plane spatial resolution, whilst maintaining single-beat temporal resolution. We hypothesised that maximising imaging time would improve the acquisition spatial resolution and reduce dark rim artifact whilst preserving image quality.

## **4.3 Methods**

### **4.3.1 Patient Selection**

Patients with stable angina (n=10) referred for clinically indicated myocardial ischaemia testing were prospectively recruited from a single tertiary centre from January 2013 until April 2014. Stable angina pectoris was defined as symptoms defined in current national and international standard[6, 123]. Exclusion criteria were contraindications to MR imaging (ferrous implants, claustrophobia or large abdominal girth), adenosine (atrioventricular nodal block II or III, asthma or severe hypertension) and presence of atrial fibrillation. Healthy volunteers (n=10) were recruited from staff and students of the University of Leeds. All volunteers and patients were requested to refrain from caffeine for 24 hours before the study. The study protocol was approved by the institutional research ethics committee and complied with the Declaration of Helsinki; all participants gave written informed consent.

### **4.3.2 Magnetic Resonance Imaging**

All patients and volunteers underwent adenosine stress and rest myocardial perfusion MR imaging tests on two separate visits. On the first occasion a conventional, fixed-parameter perfusion sequence was used and on the second the adaptive method was used. Scans were separate by at least 7 days (mean of 11 days).

Patients were examined using a clinical 3.0T whole-body scanner (Philips Achieva TX, Philips Healthcare, Best, The Netherlands) equipped with 80 mT/m maximum field gradients, 200 T/m/sec slew rate with a dedicated 32-channel cardiac phased array receiver coil with dual-source radiofrequency-field shimming. Imaging was performed with the subjects in the supine position and cardiac synchronisation was performed using a four-electrode vectorcardiogram and image acquisition triggered on the R wave.

Survey, receiver-coil sensitivity reference scans, and radiofrequency-field calibrations ( $B_1$  maps) were performed. A volume shim of both  $B_0$  and  $B_1$  was performed on all patients, with the shim volume encompassing the heart, and as much as possible also excluding lung. Short axis, vertical long axis and horizontal long axis cine images were then acquired with balanced steady-state free precession (bSSFP) pulse sequence (echo time (TE) 1.3 ms; repetition time (TR) 2.6 ms; flip angle  $40^\circ$ , spatial resolution  $1.6 \times 2.0 \times 10$  mm, 40 phases per cardiac cycle, FOV 300–420mm, sensitivity encoding factor 1.7). Stress perfusion imaging was performed with adenosine,

administered at 140µg/kg/min under continuous vectorcardiogram monitoring for at least 4 min.

Perfusion imaging was undertaken during the last minute of adenosine infusion with an intravenous bolus of 0.075mmol/kg of gadobutrol (Gadovist®, Bayer Schering Pharma, Berlin, Germany) administered at a rate of 4.0ml/s followed by a 20ml saline flush (Medrad Spectris Solaris power injector, Pittsburgh, Pennsylvania). Heart rate and blood pressure were recorded at rest and peak stress. Rest perfusion imaging was undertaken a minimum of 15 minutes after stress perfusion with a further injection of 0.075mmol/kg of gadobutrol in an identical geometry to the stress images. Rest images were acquired with the same FOV and acquisition duration as the stress scan for comparative purposes. The acquisition heart rate of the resting scan is lower than the stress heart rate, therefore a stress-then-rest order ensures that comparable scan geometry may be used without requiring further adjustment. Subjects received breath hold training and were instructed to hold their breath as long as possible during acquisition.

Standard resolution, fixed parameter perfusion image acquisition used a spoiled turbo gradient-echo sequence (TR 1.28 ms; TE 2.8 ms; flip angle 15°, acquired spatial resolution 2.42x2.42mm<sup>2</sup>) in three 10mm thick short axis slices with a FOV 300–420mm, variable matrix between 124x124 – 172x172 (dependent on FOV), sensitivity encoding factor 2.4, 0.65 partial Fourier acquisition and a saturation pre-pulse delay of 80ms. The “3-of-5”



technique was adopted to plan the sequences in a reproducible and consistent manner by acquiring the central 3 slices of 5 parallel short-axis slices spaced equally from mitral valve annulus to LV apical cap[23].

Adaptive perfusion used a new acquisition method, which automatically adapts the acquisition duration to maximize spatial resolution whilst maintaining 3 slice acquisition during every heart beat. In-plane voxel size was automatically minimised in order to fill the time available for data acquisition, according to the user's preference of (i) maximum image acquisition duration, and (ii) maximum acceptable acquired voxel size. Both these preferences are entered into the system as scan parameters. The system reduces the voxel size by a small amount and checks whether the protocol remains valid and ready to scan, if it does, a further voxel size reduction is made and the check repeated. Thus the minimum allowed voxel size allowed is found in an iterative manner, within the user-defined boundary conditions. Acquisition duration was limited to 150ms to minimise the blurring effect of cardiac motion[124], and acquired voxels were square (maximum allowed  $3.0 \times 3.0 \text{mm}^2$ ). All other protocol parameters are taken into account as normal by the system and were the same as for the standard method. Acquired resolution ( $\text{mm}^2$ ), mean shot acquisition time (ms) and image acquisition time (ms) were recorded for both sequences.

### **4.3.3 Image Analysis**

Images were evaluated independently by two readers, both with over 3 years MR experience, who were blinded to the acquisition sequence used.

Overall image quality was recorded as follows: 1=high, 2=adequate, 3=poor, 4=unusable. The occurrence of dark rim artifact was scored as 1=none/minor, 2=mild, 3=moderate and 4=severe; when present the maximum width of dark rim artifact was measured with electronic callipers at window settings as recommended in international guidelines [125], and assessed in the dynamic which it appeared most prominent. In plane acquired spatial resolution of perfusion images was recorded.

#### **4.3.3.1 Quantitative measurements of SNR**

Quantitative measurements of SNR were taken from the interventricular septum at the mid-systolic slice. SNR was determined by measuring the mean signal from two identical regions of interest of consecutive time frame images and calculated using the difference method [126, 127]. A subtraction image from the two time frames was used for the noise estimate. Whilst the use of parallel imaging produces variable noise across the field of view, reproducible coil and scan geometry, and a consistent acceleration factor, allows a comparison of the SNR difference between different scans at the same geometry and position in the heart. The use of images from consecutive time frames assumes an absence of gross patient motion between the time frames, and minimal contrast change in the myocardium; this was verified by visual assessment of the noise (subtraction) image.

#### **4.3.4 Statistical Analysis**

Continuous variables were confirmed to be normally distributed and expressed as a mean  $\pm$  standard deviation, whereas categorical variables

are expressed as proportions. Normal distribution of continuous variables was confirmed with a Shapiro-Wilk test of normality. Within group variables were compared with a two sided paired t-test. All statistical tests were 2-tailed; p values <0.05 were considered significant. Statistical analysis was performed using IBM SPSS® Statistics 21.0.

## 4.4 Results

Healthy volunteers (n=10, 8 male, mean age 22 years, range 21-23) and patients (n=10, all male, mean age 58, range 48-72) were scanned on two separate occasions, between 7 and 28 days apart (mean 11 days). Demographics and haemodynamic data are displayed in Table 4.1. No differences in stress haemodynamic data between the two different perfusion pulse sequences were observed ( $P>0.1$  for all)(Table 4.2).

### 4.4.1 Scan Parameters and Image Attributes

The acquired resolution of the standard perfusion pulse sequence was  $2.42 \times 2.42 \text{mm}^2$  in-plane. The mean acquired resolution of the adaptive pulse sequence was higher in the whole population ( $1.92 \times 1.92 \text{mm}^2 \pm 0.34$ , range 1.53-2.89,  $P<0.0001$ ); in volunteers ( $1.88 \times 1.88 \text{mm}^2 \pm 0.44$ , range 1.53-2.89,  $P=0.004$ ) and in patients ( $1.96 \times 1.96 \text{mm}^2 \pm 0.21$ , range 1.73-2.37,  $P<0.0001$ ). Mean shot acquisition was longer with the adaptive sequence ( $106 \text{ms} \pm 9$  vs.  $129 \text{ms} \pm 23$ ,  $P=0.019$ ) (Table 4.3).

No significant differences in mean perfusion image quality scores between the standard and adaptive perfusion pulse sequences were detected in either the volunteer or patient group by either reader or in consensus read. Mean perfusion image scores in volunteers were as follows: Reader 1, standard resolution  $1.2 \pm 0.42$ , adaptive resolution  $1.1 \pm 0.32$ ,  $P=0.59$ ; Reader 2  $1.1 \pm 0.32$  Vs.  $1.0 \pm 0.0$ ,  $P=0.34$ ; Consensus read  $1.1 \pm 0.31$  Vs.  $1.1 \pm 0.0$ ,  $P=0.34$ . Whilst in the patient group image score was: Reader 1, standard

1.2±0.42, adaptive 1.2±0.42, P=1.0; Reader 2 1.4±0.51 Vs.1.3±0.48, P=0.34; Consensus read 1.3±0.48, Vs. 1.3±0.48, P=1.0.

There was no difference in artifact scoring in volunteers. Mean artifact score was as follow: Reader 1, standard resolution 1.6±0.52, adaptive resolution 1.7±0.95, P=0.76; Reader 2 2.0±0.67 Vs. 2.1±0.88, P=0.73; Consensus Read 1.9±0.74 Vs. 2.1±0.88, P=0.34. In patients, however, the mean artifact score was higher with the standard pulse sequence by both readers and in consensus (1.8 Vs. 1.2, P=0.05; 2.2 Vs. 1.7, P=0.015 ; 2.1 Vs. 1.6, P=0.05).

The mean DRA width using the standard acquisition sequence was 2.82±0.65mm and adaptive resolution 1.94±0.60mm (P<0.0001), which was lower in both the volunteers and patient groups (Table 4.3).

In two volunteers, the heart rate at stress exceeded the maximum heart rate for which the standard resolution pulse sequence can maintain every-heartbeat temporal resolution (116 and 120 bpm) and data were acquired at two-heartbeat temporal resolution. This did not occur in the HR adaptive acquisition since the spatial resolution was adapted (to 2.84x2.84mm<sup>2</sup> and 2.89x2.89mm<sup>2</sup> respectively), and every-heartbeat temporal resolution was maintained.

**Table 4.1** Demographic and Haemodynamic Data

Parameters	Volunteers (n=10)	Patients (n=10)
<b>Clinical Factors</b>		
Gender, male, n (%)	8 (80%)	10 (100%)
Age, y	22 ± 1.3	58 ± 8.8
Range	19 – 23	48 – 72
Body mass index, kg/m <sup>2</sup>	21.8 ± 2.5	28.1 ± 4.5
Body surface area, m <sup>2</sup>	1.88 ± 0.11	2.06 ± 0.11
Current Smoker	0	2 (20%)
Hypertension	0	5 (50%)
Diabetes Mellitus	0	2 (20%)
Hypercholesterolaemia	0	3 (30%)
Previous Revascularisation	0	1 (10%)
<b>Baseline Haemodynamics</b>		
Mean SBP, mmHg	112±12	127±14
Mean DBP, mmHg	59±6	70±4
Mean HR, 1.min <sup>-1</sup>	67±9	62±7
Mean HR-SBP product, mmHg.min <sup>-1</sup>	7495±1332	7794±1134
<b>Stress Haemodynamics – Standard Resolution Sequence</b>		
Mean SBP, mmHg	111±11	120±15
Mean DBP, mmHg	57±10	67±4
Mean HR, 1.min <sup>-1</sup>	90±12	80±10
Mean HR-SBP product, mmHg.min <sup>-1</sup>	10026±1954	9565±1672
<b>Stress Haemodynamics – Adaptive Resolution Sequence</b>		
Mean SBP, mmHg	106±8	115±13
Mean DBP, mmHg	56±6	69±6
Mean HR, 1.min <sup>-1</sup>	90 ± 20	81 ± 6
Mean HR-SBP product, mmHg.min <sup>-1</sup>	9549 ± 2118	9549 ± 2118

Data are mean ± SD.HR, heart rate; BP, blood pressure.

**Table 4.2** Comparison of Stress Haemodynamic Data

<b>Parameters</b>	<b>Standard Resolution Pulse Sequence</b>	<b>Adaptive Resolution Pulse Sequence</b>	<b>P</b>
<b>Volunteers (n=10)</b>			
Mean SBP, mmHg	111±11	106±8	0.13
Mean DBP, mmHg	57±10	56±6	0.63
Mean HR, 1.min <sup>-1</sup>	90±12	90 ± 20	0.93
Mean HR-SBP product, mmHg.min <sup>-1</sup>	10026±1954	9549 ± 2118	0.53
<b>Patients (n=10)</b>			
Mean SBP, mmHg	120±15	115±13	0.24
Mean DBP, mmHg	67±4	69±6	0.66
Mean HR, 1.min <sup>-1</sup>	80±10	81 ± 6	0.55
Mean HR-SBP product, mmHg.min <sup>-1</sup>	9565±1672	9549 ± 2118	0.73

Data are mean ± SD.HR, heart rate; BP, blood pressure.

**Table 4.3** Comparison of Scan Parameters and Image Scores

<b>Parameters</b>	<b>Standard Resolution Pulse Sequence</b>	<b>Adaptive Resolution Pulse Sequence</b>	<b>P</b>
<b>Volunteers (n=10)</b>			
Acquired Resolution (mm <sup>2</sup> )	2.42x2.42	1.88x1.88±0.44	0.004
Range (mm)	–	1.53 – 2.89	–
Shot Duration (ms)	171±7	189±17	0.016
Image Acquisition (ms)	106±9	129±23	0.019
Image Quality Score	1.1	1.0	0.34
Artifact Score	2.1	1.9	0.34
Width of Dark Rim Artifact (mm)	3.0±0.7	2.1±0.6	<0.0001
Relative Signal-to-Noise Ratio	7.3±2.2	4.2±2.1	0.002
<b>Patients (n=10)</b>			
Acquired Resolution (mm <sup>2</sup> )	2.42x2.42	1.96x1.96±0.21	<0.0001
Range (mm)	–	1.73 – 2.37	–
Shot Duration (ms)	184±4	210±12	<0.0001
Image Acquisition (ms)	110±4	142±12	<0.0001
Image Quality Score	1.3	1.3	1.0
Artifact Score	2.1	1.6	0.05
Width of Dark Rim Artifact (mm)	2.6±0.6	1.8±.5	0.005
Mean Signal-to-Noise Ratio	6.1±2.1	3.4±1.4	<0.0001

Data are mean ± SD.



#### **4.4.2 Signal-to-Noise Ratio**

The mean baseline (before arrival of contrast agent) SNR of the standard acquisition was higher than the adaptive acquisition in the whole population ( $6.7\pm 2.2$  vs.  $3.8\pm 1.8$ ,  $P<0.0001$ ); in volunteers ( $7.3\pm 2.2$  vs.  $4.2\pm 2.1$ ,  $P<0.002$ ) and in patients ( $6.1\pm 2.1$  vs.  $3.4\pm 1.4$ ,  $P<0.0001$ ). This difference was consistent with the smaller voxel size in the adaptive perfusion group.

#### **4.5 Discussion**

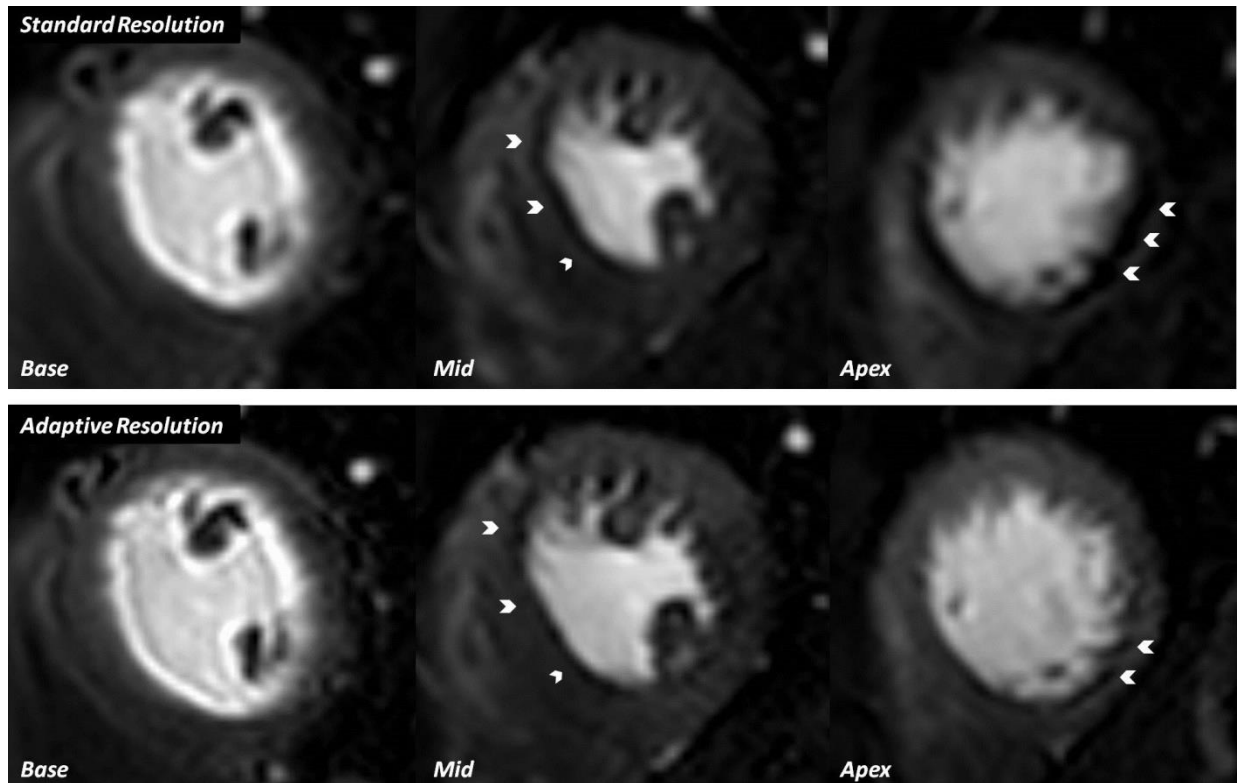
This study has shown that optimising the use of available imaging time during MR myocardial first pass perfusion by adapting the acquisition duration to the heart rate and patient size is feasible, improves the acquired in-plane spatial resolution and reduces dark rim artifact. Whilst the SNR was reduced with the adaptive pulse sequence, in line with the improved spatial resolution, overall image quality is maintained.

MR stress perfusion imaging is an established technique with high diagnostic accuracy for the detection of underlying coronary artery disease which outperforms SPECT [29, 128], partly due to the improved spatial resolution of the test. The Society for Cardiovascular Magnetic Resonance (SCMR) 2013 standardization guidelines recommends a minimum in-plane resolution of  $3\times 3\text{mm}^2$  for first pass perfusion[129]. Recent improvements in both acquisition techniques and hardware, which may be utilised to improve the acquired spatial resolution, have been demonstrated to enhance the diagnostic accuracy of stress perfusion MR. In one single centre study of

100 patients high resolution myocardial perfusion MR using k-space and time sensitivity encoding (*k-t* SENSE) acceleration to achieve an in-plane spatial resolution of  $1.6\text{mm}^2$  had greater overall diagnostic accuracy than standard resolution acquisition ( $2.5\text{mm}^2$ ) for identifying angiographically defined CAD, with an area under the curve (AUC) of 0.93 vs. 0.83;  $p < 0.001$ [47]. Equally imaging at higher field strength produces greater tissue magnetization and therefore higher SNR and increased contrast enhancement which may be utilized to improve spatial/temporal resolution whilst preserving image quality. However, many data acceleration techniques currently are more susceptible to motion artifact, require post acquisition reconstruction, and are not routinely available in all centres[49]. Here, we have demonstrated a conceptually straightforward and effective method of obtaining spatial resolution increases in most MR perfusion patients, allowing access to the benefits of improved resolution[130] in many patients, applicable to any perfusion pulse sequence, on any MR system.

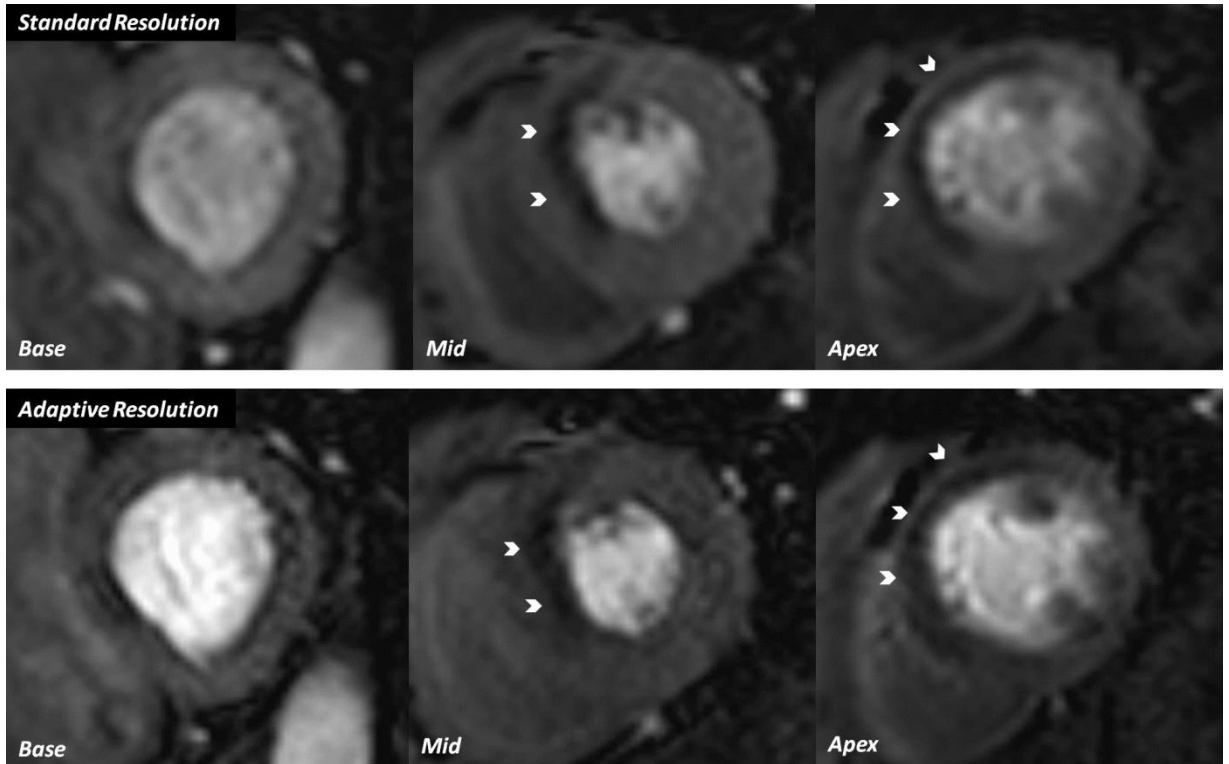
SCMR standardization guidelines [129] also recommend at least three short axis slices to be imaged every heartbeat. The standard (fixed) resolution first pass perfusion pulse sequence used in this study is designed to allow 3 slice imaging every heart beat at heart rates typically achieved during pharmacological stress. In those with even higher heart rates, acquisition with fixed parameters may not be possible at every heartbeat, leading on most commercial scanners to acquire data every second R-R interval. We demonstrated this in two volunteers in whom the heart rate was too high for

every heart beat imaging (116 and 120 bpm) with the standard resolution pulse sequence and therefore data were acquired in alternate R-R intervals.



**Figure 4.2 Stress perfusion imaging in a health volunteer: standard imaging vs. adaptive resolution pulse sequence.**

Adenosine stress perfusion in a healthy volunteer. The top row shows an acquisition with a standard (fixed) resolution pulse sequence ( $2.42 \times 2.42 \text{mm}^2$  in-plane resolution) and the bottom row with a pulse sequence which adapts the acquisition duration to the heart rate ( $1.97 \times 1.97 \text{mm}^2$ ) demonstrating a significant reduction in dark rim artefact thickness and extent (arrows) with the adaptive resolution scan.



**Figure 4.3 Stress perfusion imaging in a patient: standard imaging vs. adaptive resolution pulse sequence.**

Adenosine stress perfusion in a 60 year-old gentleman with typical anginal symptoms. The top row shows an acquisition with a standard (fixed) spatial resolution pulse sequence ( $2.42 \times 2.42 \text{mm}^2$  in-plane) and the bottom row with a pulse sequence which adapts the acquisition duration to the heart rate ( $1.94 \times 1.94 \text{mm}^2$ ) demonstrating a large perfusion defect in the mid to apical septum and apical segment of the anterior wall.

This did not occur with the adaptive pulse sequence as the spatial resolution was automatically adapted prior to imaging (to  $2.84 \times 2.84 \text{mm}^2$  and  $2.89 \times 2.89 \text{mm}^2$  respectively) to maintain the temporal resolution. The effect of missing dynamic images during first pass perfusion can affect the diagnostic accuracy of quantitative perfusion analysis[121]. Whilst in such cases, an expert user would appreciate that the perfusion sequence requires adjustment before contrast-agent injection, because they note the particularly high heart rate, the method described here automatically performs this action up to the maximum allowed voxel size saved in the protocol. This reduces the potential for operator-dependent error or operator-dependent variability in scan setup.

The signal-to-noise ratio may be used as a measurement to assess the performance of the magnetic resonance images and potential clinical usefulness of the images. Too much noise may render the images clinically uninterpretable. SNR is proportional to the voxel volume and therefore the adaptive acquisition, with improved spatial resolution and lower voxel size, is expected to have a lower SNR. We demonstrated that the reduction in SNR is proportional to the spatial resolution with this pulse sequence.

The adaptive perfusion method used a longer acquisition duration of up to 150ms per slice. This is longer than recommended by current guidelines, which propose a maximum of 125ms. Motion artifact is however related to heart rate and is much more likely at higher heart rates. In this study, the longer acquisition duration at lower heart rates had no adverse effect on

image quality scoring. Furthermore, given the SNR is proportional to the change in spatial resolution, this would suggest that cardiac motion due to increased imaging time has little effect on SNR measurement.

Adapting pulse sequence parameters between stress and rest perfusion can make comparisons in the same individual challenging. Therefore in this study, when acquiring rest perfusion data with the adaptive method, we matched the acquisition parameters of the stress perfusion scan. The MR system acquires each slice consecutively immediately following the R-wave of the vectorcardiogram. This results in images acquired at earlier cardiac phases for the rest perfusion sequence (due to the slower heart rate) and makes clinical comparison between rest and stress sequences more challenging. Although not used here, this may be mitigated by a method of trigger delay matching, in which the trigger delays of the rest scan may be adjusted to match the timing within the cardiac cycle of the stress scan.

#### **4.5.1 Limitations**

This is a small proof of concept study with a limited number of subjects designed to assess the feasibility of an adaptive pulse sequence. Dark rim artefact was measured in a method consistent with international guidelines for clinical reporting perfusion MRI. Whilst this is open to the application of different window settings, this reflects what occurs in clinical practice for the reading of perfusion imaging. Furthermore whilst every attempt was made to blind the image interpretation to the reader, the higher resolution would have been apparent in visualisation which may result in reader bias. Finally further

research is required to assess the diagnostic accuracy of an adaptive perfusion sequence for the detection of underlying coronary artery disease.

#### **4.5.2 Conclusions**

This study demonstrated the feasibility of patient-adaptive perfusion imaging in order to maximize the potential spatial resolution. We show that using a standard SENSE accelerated pulse sequence without spatiotemporal undersampling, which adapts image acquisition duration up to 150ms to maximize available imaging time, improves the resolution and reduces DRA, and therefore has potential to improve the diagnostic accuracy for the detection of underlying CAD. This flexible, automated method may also reduce operator dependence in those centers which manually adapt acquisition parameters to individual patients.

## **Chapter 5**

### **Rationale and design of the Clinical Evaluation of MAgnetic Resonance imaging in Coronary heart disease 2 trial (CE-MARC 2): A prospective, multi-centre, randomized controlled trial of diagnostic strategies for suspected coronary heart disease**

#### **5.1 Abstract**

##### **5.1.1 Background**

A number of investigative strategies exist for the diagnosis of coronary heart disease (CHD). Despite the widespread availability of non-invasive imaging, invasive angiography is commonly used early in the diagnostic pathway. Consequently, approximately 60% of angiograms reveal no evidence of obstructive coronary disease. Reducing unnecessary angiography has potential financial savings and avoids exposing the patient to unnecessary risk. There were no large scale comparative effectiveness trials of the different diagnostic strategies recommended in international guidelines and none that have evaluated the safety and efficacy of cardiovascular magnetic resonance (CMR).

##### **5.1.2 Trial Design**

CE-MARC 2 was a prospective, multi-centre, 3-arm parallel group, randomized controlled trial of patients with suspected CHD (pre-test likelihood 10-90%) requiring further investigation. 1200 patients were randomized on a 2:2:1 basis to receive 3.0 Tesla CMR-guided care, single photon emission computed tomography (SPECT) guided care (according to ACC/AHA appropriate-use criteria) or National Institute for Health and Care



Excellence guidelines-based management. The primary (efficacy) endpoint was the occurrence of unnecessary angiography as defined by a normal ( $>0.8$ ) invasive fractional flow reserve. Safety of each strategy was assessed by 3-year major adverse cardiovascular event rates.

## **5.2 Background**

Coronary heart disease (CHD) is a leading cause of death and disability worldwide. In a typical hospital setting a variety of investigations may be used to diagnose CHD, risk-stratify and determine the need for coronary revascularization. Myocardial perfusion scintigraphy by single-photon emission computed tomography (SPECT) is the most commonly used test world-wide for the assessment of myocardial ischaemia and there is a large body of evidence to support its prognostic value. Whilst cardiovascular magnetic resonance (CMR) has high diagnostic accuracy for the detection of CHD and the CE-MARC study demonstrated CMR's superiority over SPECT[29]. Despite the widespread availability and recommendation of these non-invasive imaging investigations in national and international guidelines[4-6], invasive coronary angiography is commonly used early in the diagnostic pathway. Evidence from large populations of patients presenting with chest pain have confirmed that the majority will not have significant obstructive coronary disease[131, 132]. In the US, the American College of Cardiology National Cardiovascular Data Registry identified almost 400,000 patients without known CHD that underwent elective catheterisation from January 2004 through April 2008, and only 38% had obstructive CHD[132].

Avoiding unnecessary angiography has potential financial savings and avoids exposing the patient to unnecessary risk. Invasive coronary angiography has a risk of major complications of 1.7%. Furthermore the dose and stochastic effects of X-ray radiation are frequently misjudged[133]

with the risk of developing a solid tumour estimated at 1:2500 diagnostic coronary angiographic procedures[134]. Paradoxically, the implementation of UK national guidelines for the assessment and diagnosis of recent onset chest pain has been demonstrated to increase invasive coronary angiography rates between 20-28%[135].

A previous single centre trial (CECaT) indicated that invasive angiography could be avoided in 20-25% of patients using functional testing as an initial gate-keeper[136]. To date, there are no large scale comparative effectiveness trials of the different diagnostic strategies recommended in international guidelines and none that have evaluated the safety and efficacy of CMR.

### **5.3 Study Objectives**

The primary objectives were to determine if 3.0Tesla (T) CMR-guided management was superior to a) National Institute for Health and Care Excellence (NICE) guidelines-based management (CG95)[6], and b) SPECT-guided management[137], in terms of reducing the rates of unnecessary invasive angiography occurring within 12 months in patients with a pre-test likelihood (PTL) of CHD of 10-90%.

Secondary objectives were to determine a) if in patients with a high PTL of CHD (61-90%), non-invasive imaging (CMR or SPECT) was superior to NICE guidelines-based management, in terms of reducing the occurrence of

unnecessary invasive angiography; b) safety in terms of major adverse cardiovascular events (MACE) at 3 years between the CMR-guided care group and those receiving NICE guidelines-based management; c) safety in terms of MACE at 3 years between the CMR-guided care group and those receiving SPECT-guided management and d) cost-effectiveness and impact on health-related quality-of-life measures (HRQoL) of a CMR-guided care strategy compared to NICE guidelines-based management and to SPECT-guided management.

## **5.4 Methods**

### **5.4.1 Study Design**

CE-MARC 2 (clinicaltrials.gov: NCT01664858) was a prospective, multi-centre, multi-vendor, 3-arm parallel group, randomized controlled trial of patients who were referred to cardiology care for further evaluation of symptoms thought to be angina pectoris. A total of 1200 patients with suspected CHD were be randomized on a 2:2:1 basis to receive CMR-guided care, SPECT-guided care or NICE guidelines based management [Figure 5.1 & 5.2].

Statistical analysis was carried out by the Clinical Trials Research Unit (CTRU), University of Leeds and the Centre for Health Economics, University of York. The study population was followed-up prospectively for a minimum of 3 years to establish long-term MACE in each investigation arm. The study was conducted in accordance with the Declaration of Helsinki and has been approved by the National Research Ethics Service.

#### **5.4.2 Patient Population, Recruitment & Randomisation**

Subjects were considered for inclusion if they were age  $\geq 30$  yrs and presented to participating hospitals (Appendix 1) with suspected cardiac chest pain (angina) with a defined CHD PTL of 10-90%[6]. Full inclusion and exclusion criteria are listed in Table 5.1. An anonymized log of all patients screened for eligibility who are not recruited either because they are ineligible or because they declined to participate was kept.

The treating clinician made a clinical diagnosis of typical angina if the patient had all three salient features of angina (constricting discomfort in the front of the chest, or in the neck, shoulders, jaw or arms; precipitated by physical exertion; and relieved by rest or GTN within ~5min) or atypical angina if they had two out of three[6, 123]. Those with one or none of the features were defined as non-anginal chest pain[6, 123] and were ineligible for the study. The patients' risk factors (age, gender, ethnicity, abdominal & hip circumference, lipid profile, blood pressure, smoking and diabetic status), past medical history (including rheumatoid arthritis, hypertension, hyperlipidemia, peripheral vascular disease, cerebrovascular disease) and family history of premature CHD were recorded.

Patients underwent risk stratification with their PTL of having CHD calculated [6, 138] and categorised as low (10-29%), intermediate (30-60%) or high (61-90%). Randomisation was achieved using minimisation, incorporating a random element through a computer-generated program accessed via a 24h telephone service. This allocated patients in a 2:2:1 ratio between

CMR:SPECT:NICE and took account of the following stratification factors: randomising site; age (30-64,≥65); PTL (10-29%,30-60%,61-90%) and gender. Those with low PTL of underlying CHD (10-29%) randomized to NICE guidelines will undergo cardiac CT (CCT); intermediate PTL (30-60%) SPECT and high PTL (61-90%) coronary angiography.

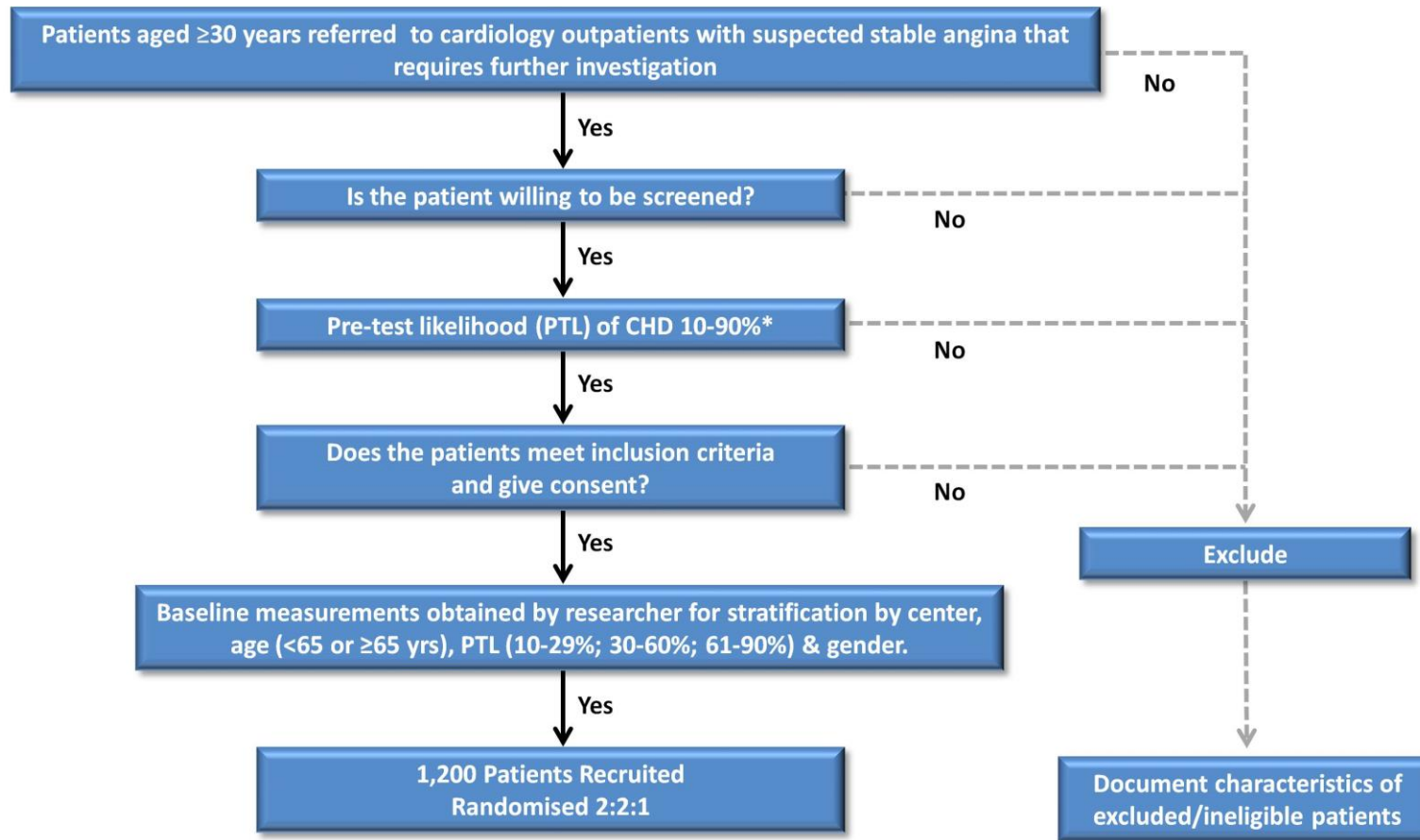


Figure 5.1 CE MARC 2 study flow diagram illustrating the recruitment process.

\* Pre-test likelihood as defined by NICE (CG95) guidelines(3).

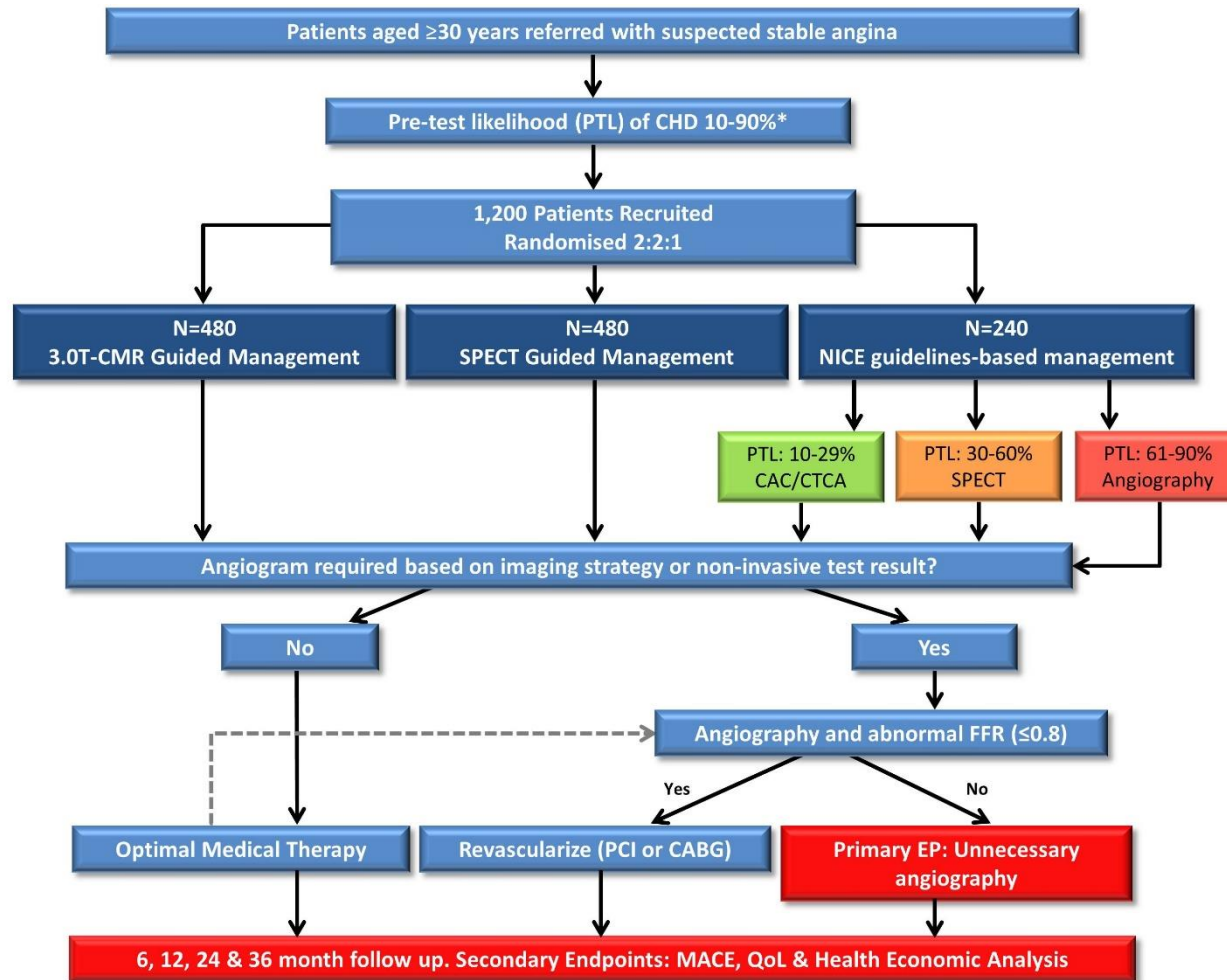


Figure 5.2 CE-MARC 2 study flow diagram illustrating randomization, investigative strategy and study end-points[139].



**Table 5.1** Inclusion and Exclusion Criteria into the CE-MARC2 Study

<b>Inclusion Criteria</b>	<b>Exclusion Criteria</b>
Age $\geq 30$ yrs	Non-anginal chest pain
Suspected stable angina (CHD) that requires further investigation	Normal SPECT/CCT within the last 2- years
A defined pre-test likelihood of 10-90%	Clinically unstable
Suitable for revascularization if required	Previous MI or biomarker positive ACS
	Previous revascularization with coronary artery bypass surgery or PCI
	Contraindication to CMR imaging
	Known adverse reaction to Adenosine or Gadolinium/iodinated contrast agents
	Obesity (where body girth exceeds scanner diameter)
	Pregnancy and/or breast feeding
	Known chronic renal failure (eGFR $< 30$ mL/min/1.73m <sup>2</sup> )
	Inability to give informed consent

### **5.4.3 Funding**

The trial was funded by the British Heart Foundation (SP/12/1/29062). Additional support was received from the Leeds Teaching Hospital Charitable Foundation and the National Institute for Health Research, through the Local Clinical Research Networks.

### **5.4.4 Investigation Details**

#### **5.4.4.1 CMR**

CMR was carried out on a clinical 3.0T scanner using protocols that conformed to international standards[140]. A cardiac imaging receiver coil configuration was used and ECG gating was performed. The scan comprised of:

1. Survey and reference scans prior to defining the short, vertical long and horizontal long axes acquired with a balanced steady state free precession (bSSFP), single slice breathhold sequence. bSSFP pulse sequence parameters dependent on scanner manufacturer and site. Typical parameters: echo time (TE) 1.3ms, repetition time (TR) 2.6ms, flip angle (FA)  $40^{\circ}$ , field of view 320–420mm according to patient size, SENSE or GRAPPA acceleration, slice thickness 10mm and 30 phases per cardiac cycle.
2. Stress perfusion imaging performed with adenosine administered initially at  $140\mu\text{g}/\text{kg}/\text{min}$ . Adequate hemodynamic response was assessed by either  $\geq 10\%$  HR increase,  $\geq 10\text{mmHg}$  decrease in systolic blood pressure. If there was inadequate hemodynamic response then the dose was increased incrementally to  $170\mu\text{g}/\text{kg}/\text{min}$

and then 210µg/kg/min for a further 2 minutes until hemodynamic response was achieved.

Perfusion image acquisition used a two dimensional, T1-weighted saturation-recovery-prepared gradient echo pulse sequence in 3 short axis slices, planned using the 3/5 technique[23], using either parallel imaging acceleration (SENSE or GRAPPA), or spatio-temporal undersampling (5x *kt*-BLAST). First-pass contrast-enhanced study was performed using a dual-bolus technique(0.075mmol/kg of gadobutrol (Gadovist®, Bayer Schering Pharma, Berlin, Germany)) for the main bolus preceded by the same volume of a 10% dilute contrast agent dose for the pre-bolus, both administered at a rate of 4.0ml/s followed by a 20ml saline flush.

3. Resting wall motion and LV function was assessed with a contiguous stack of multiphase ventricular short axis bSSFP cines (10-12 slices; 30 phases; 10mm slice thickness, 0mm gap, same cine pulse sequence as above).
4. The rest myocardial perfusion study used identical pulse sequence, slice positioning and injection characteristics to the stress perfusion scan. If the stress perfusion scan was not of adequate quality (e.g. ectopics, failure to trigger) a repeat stress was performed as alternative to the rest study.

5. Late gadolinium enhancement (LGE) was performed in 10-12 short axis slices 10-15mins after step 4 with an inversion recovery-prepared T1-weighted gradient echo pulse sequence. Typical parameters: TE 2.0ms, TR 3.7ms, FA  $25^{\circ}$ , acquired spatial resolution  $0.70 \times 0.70 \times 10 \text{mm}^3$ , Inversion time (TI) individually adjusted according to TI scout. LGE was acquired with alternate heart beat acquisition (with single shot or navigated LGE an option for poor breath holders) and long axis and modified views acquired if clinically indicated.

#### **5.4.4.2 SPECT**

Radionuclide imaging was performed according to local standard departmental practice conforming to both national and international guidelines[141-143]. Patients underwent either a one or two-day scanning protocol with a radioisotope tracer  $^{99\text{m}}\text{Tc}$ -tetrofosmin or  $^{99\text{m}}\text{Tc}$ -sestamibi (MYOVUE™; CARDIOLITE™). A weight-adjusted dose up to a maximum of 1000MBq per examination was used for stress and rest imaging, carried out within 5 days of each other.

Stress examination was performed with either treadmill or bicycle exercise, pharmacological vasodilator stress (with adenosine or regadenoson), or a combination. Treadmill involved exercise using the BRUCE or modified BRUCE protocol or bicycle ergometer typically commencing at 25 watts increasing workload by 25 watts every two minutes. Radioisotope tracer was injected at peak stress.

If pharmacological stress with adenosine was used the administration regime was comparable to the CMR protocol. If Regadenoson was used,

0.4mg was delivered by rapid intravenous injection. Radioisotope tracer was injected after at least 4min of adequate hemodynamic/symptom response. Vasodilator stress could be combined with sub-maximal exercise.

Images were acquired on either a dual headed gamma camera or solid state cadmium zinc telluride camera. Stress and rest images were gated to the ECG and attenuation correction was used where routinely available.

#### **5.4.4.3 Cardiac CT**

Cardiac CT (CCT) was performed on a minimum 64-slice multi-detector CT and follow international guidelines[144]. Coronary artery calcium (CAC) scoring scan protocol involved:

1. Scout Scans
2. Unenhanced scan with prospective gating and inspiratory breathhold.  
A minimum scan length (z-axis distance) from tracheal bifurcation to the inferior border of the heart.
3. Agatston CAC score was calculated and NICE-guidance followed[6]. If CAC was 0 no further imaging was performed; if CAC score was 1-400 proceeded to CT coronary angiography (CTCA) ; and if CAC score was >400 referred for invasive coronary angiography.

For CTCA heart rate control was achieved with beta-blockade (intravenous or oral) and short acting sublingual nitrates were routinely given. CTCA was performed where possible with a prospective gating technique using the minimum scan range planned from the unenhanced scan. Typical scan parameters: 0.625mm collimation, pitch 0.2-0.4, 100-120kVp and 400-

830mAs (adjusted according to body mass index). If retrospective gating was required ECG dose modulation was used to minimize radiation dose. The acquisition window was typically centred at end-diastole (however end-systole could be used at the discretion of the attending physician). In those with variable heart rates time interval padding was used to allow reconstruction of both the systolic and diastolic phase datasets. The exact scan parameters and radiation reduction algorithms used were dependent on the hardware vendor. 60–120ml of iodinated contrast agent was administered at a flow rate of 4.5-6.5 ml/s followed by a bolus of normal saline (e.g.50ml, 5ml/s) during an acquisition with inspiratory breath-hold. Either a test bolus or a bolus tracking technique was used.

#### **5.4.4.4 X-ray angiography and FFR**

Angiography was performed using a standard technique (radial or femoral approach). FFR (PressureWire<sup>TM</sup>, St Jude Medical, Minneapolis, USA) was performed in all vessels  $\geq 2.5$ mm with stenosis  $\geq 40\%$  and  $\leq 90\%$ , following intra-coronary nitrates with adenosine at 140-210mcg/kg/min to achieve maximal hyperemia and hemodynamic steady state; pull back assessment of diffuse disease or serial stenoses may have been performed. Adenosine was administered as per CMR protocol. Totally occluded coronary arteries were recorded to have a default FFR value of 0.50; for lesions  $>90\%$  FFR was also considered to be positive (0.50) and lesions  $<40\%$  FFR were considered normal (0.90)[145]. All sites had an FFR quality assurance core laboratory assessment of the FFR recordings using vendor software (RADVIEW 2.2, St Jude Medical Corp.).

### **5.4.5 Investigation Reporting**

All test results were reported by independent cardiology/radiology consultants with a minimum 5yr experience in the imaging modality.

#### **5.4.5.1 CMR**

CMR analysis was by both visual and quantitative following international recommendations[146]. Local on-site reporting included regional wall motion abnormalities (by visual analysis using the 17-segment American Heart Association (AHA)/American College of Cardiology (ACC) model). Each segment was scored as 0:normal, 1:mild hypokinesia, 2:severe hypokinesia, 3:akinesia, or 4:dyskinesia. Quantitative analysis included: end diastolic volume (ml), end systolic volume (ml), stroke volume (ml) and ejection fraction (%).

Detection of hypoperfusion (ischemia), by visual comparison of stress, rest and LGE scans, was scored as 0:normal, 1:equivocal, 2:non-transmural ischemia <50%, 3:non-transmural ischemia ≥50%, 4:transmural ischemia in 16 segments of the 17 segment AHA/ACC model (excluding the apical cap).

Any infarct (scar) was reported based on the LGE images (17 segment model) with scores of 0: no hyperenhancement, 1: 1–25% mural thickness, 2: 26–50%, 3: 51–75%, or 4: >75% allocated to each segment.

A positive result ( $\geq 2$  adjacent segments (or 60 degree arc-equivalent if the defect crosses segmental boundaries) with  $\geq 50\%$  transmural extent of ischemia, scar, or ischemia-scar combination) by protocol necessitated referral for invasive angiography +/- FFR

#### **5.4.5.2 SPECT**

SPECT analysis was both visual and quantitative. Local on-site reporting included any regional wall motion abnormality (by visual analysis using the 17-segment model). Each segment was scored as 0 (normal), 1 (mild hypokinesia), 2 (severe hypokinesia), 3 (akinesia), or 4 (dyskinesia).

Evidence of ischemia, by visual comparison of rest and stress scans, was scored as 0 (normal), 1 (mild 51-70%), 2 (moderate 31-50%), 3 (severe 10-30%), 4 (absent <10%) in each segment. Quantitative analysis included summed rest score (SRS) and summed stress scores (SSS); quantitative perfusion SPECT (QPS) defect extent (%); QPS total perfusion deficit (%); end systolic volume (ml); end diastolic volume (ml); stroke volume (ml) and ejection fraction (%).

The presence of artefacts including sub-diaphragmatic activity affecting the inferior wall, significant patient movement anterior attenuation, inferior attenuation and LBBB artefact were recorded.



A positive result ( $SSS \geq 4$ ), unless believed by the reporting clinician to represent attenuation artefact, by protocol necessitated referral for invasive angiography +/- FFR.

#### **5.4.5.3 Cardiac CT**

The total Agatston CAC score from the unenhanced scan was determined. If the CAC score was  $>0$  and  $<400$  a contrast enhanced scan was performed.

Coronary stenosis were graded as 0: normal, 1: minimal  $<25\%$  stenosis, 2: mild 25-49%, 3: moderate 50-69%, 4: severe 70-99%, 5: occluded 100%. A positive result (either  $CAC > 400$  or any luminal stenosis  $\geq 50\%$  in an epicardial coronary artery  $\geq 2.5\text{mm}$  diameter) by protocol necessitated invasive angiography  $\pm$  FFR.

#### **5.4.5.4 X-ray angiography and FFR**

Invasive X-ray angiography was interpreted visually by the performing clinician recording the coronary artery dominance, location and visual degree (%) of all coronary stenoses in all major epicardial coronary arteries (with luminal diameter  $\geq 2.5\text{mm}$ ). FFR measurement was recorded in all arteries  $\geq 2.5\text{mm}$  with a visually recorded diameter stenosis  $\geq 40\%$  and  $\leq 90\%$ . Where FFR could not be performed due to clinical/safety reasons quantitative coronary angiography (QCA) was performed using validated commercial vendor software. In this instance QCA measurements were made during off-line analysis by a single independent blinded observer at the Glasgow Angiographic core-lab. Lesions were considered significant if a coronary artery segment (luminal diameter  $\geq 2.5\text{mm}$ ) analysed by QCA had a

percentage diameter stenosis of  $\geq 70\%$  in one view or  $\geq 50\%$  in two orthogonal views.

In accordance with usual clinical practice all clinical data from all imaging modalities was made available for the reporting physician to make an overall clinical judgement.

#### **5.4.6 Protocol deviations**

On occasion where the attending cardiologist over-ruled the protocol requirement to proceed to invasive coronary angiography, this was recorded as a protocol violation.

#### **5.4.7 Annual Follow-up**

Annual follow-up over the subsequent 3 years was undertaken to record death (including cause), other MACE and withdrawal. For alive patients, medical history since randomization, including details and dates of: acute coronary syndrome (ACS), emergency or elective revascularization procedure, any admission for cardiovascular cause was obtained and verified from hospital or family practitioner records. Details of any recent cardiovascular investigations was be taken. In addition, Office for National Statistics monitoring was sought for deceased patients to determine the certified causes of death.

## **5.4.8 Primary Endpoint**

### **5.4.8.1 Unnecessary invasive coronary angiography occurring within 12 months in each arm.**

This was defined at the time of coronary angiography by a FFR measurement of  $>0.80$  in all vessels  $\geq 2.5\text{mm}$  in a patient-based analysis (i.e. at least one vessel with a FFR measurement of  $<0.8$  was required to define a patient with disease).

An “Unnecessary angiogram” was defined as one of the following:

- A negative FFR and positive non-invasive test (i.e. a False Positive test result)
- A negative FFR in a high PTL (61-90%) patient that proceeds directly to invasive angiography in the NICE guidelines-based strategy arm (i.e. a False Positive for the strategy).
- A negative FFR and a negative non-invasive test (i.e. a True Negative strategy result in which the imaging result was ‘not believed’ by the treating cardiologist – based on intention-to-treat (ITT) principles).
- A negative FFR and an inconclusive non-invasive test result (CMR, SPECT, or CCT) in which angiography had to be performed to make the diagnosis (i.e. failure of the strategy to produce a diagnosis).

## **5.4.9 Secondary Endpoints**

### **5.4.9.1 Major adverse cardiovascular events**

For all patients MACE at 12 months and a minimum of 3 years was reported. MACE was defined as death due to cardiovascular cause, MI (defined by the Third universal definition[147]), unplanned coronary revascularization and hospital admission for cardiovascular cause. Hospitalisation for cardiovascular cause were defined as: troponin negative ACS, spontaneous MI (Type 1), MI secondary to ischemic imbalance (Type 2), MI related to stent thrombosis (Type 4b), arrhythmia, stroke and heart failure.

### **5.4.9.2 Positive coronary angiogram**

The proportion of patients who underwent an invasive coronary angiogram yielding a positive finding by FFR within 12 months of randomisation

### **5.4.9.3 Economic Evaluation**

To assess the long term cost-effectiveness of the alternate diagnostic testing strategies, information from the trial will be used to update the economic model developed as part of the CE-MARC trial[36]. The model will use information from the trial, including resource use, costs, HRQoL and other clinical outcomes (e.g. on unnecessary tests and MACE events), together with epidemiological, clinical and economic data from other sources to calculate costs and quality-adjusted life-years for patients. The economic evaluation will use methods consistent with those recommended by NICE[148]. Given the potential difference between diagnostic strategies in

terms of mortality, the modelling will adopt a lifetime time horizon to capture any difference.

#### **5.4.9.4 Quality of Life**

Health-related quality-of-life (HRQoL) was measured by

- Seattle Angina Questionnaire–UK Version (SAQ-UK);
- Medical Outcomes Survey-Short Form 12 (SF12v2)
- EuroQol 5-Dimensions (EQ-5D).

#### **5.4.9.5 Complications**

Complications directly related to investigational or procedural aspects of the study resulting in prolonged hospital stay/specific treatment that would otherwise have not been required were reported. These were established and adjudicated by the Trial Steering Committee (TSC) and Trial Management Group (TMG) and reported to the Data Monitoring and Ethics Committee (DMEC).

#### **5.4.10 Statistical Considerations**

##### **5.4.10.1 Sample Size**

Sample size calculations were performed using nQuery 7.0. For the primary endpoint analyses a sample size of 1200 (allowing for 20% non-completion) was estimate to provide 99% power to detect a difference of unnecessary angiography rates between CMR and NICE-guidelines based management - accounting for the 2:1 allocation ratio - and 94% power between CMR and SPECT-guided care (2-sided test 5% significance level for a continuity-

corrected chi-squared test[149]). This was based on projected unnecessary angiography rates of 4.5%, 11.7% and 30% in the CMR, SPECT and NICE arms respectively, arrived at by estimating the PTL profile of CEMARC patients (we estimated the PTL distribution to be 10%:33%;57% for low:moderate:high PTL, for those patients with PTL 10-90%) and the false positive rates of CMR and SPECT in these subgroups to compute a weighted average false positive rate as the expected unnecessary angiogram rate. For the NICE arm, we noted that in patients with 61-90% PTL, nearly 60% of angiograms were negative, and so would drive high rates for this strategy, despite CT and SPECT patients (10-60% PTL) undergoing fewer unnecessary angiograms.

#### **5.4.10.2 Analysis Plan**

Statistical analysis were performed as agreed in the pre-specified statistical analysis plan. All analyses were performed on intention-to-treat basis. The primary endpoint was performed after the 12-month assessment has been completed by the last patient entered into the study and a complete and exhaustive data chase has been performed. Analyses of primary and secondary endpoints were performed separately for the CMR-guided vs. NICE-guided care; CMR-guided vs. SPECT-guided care and SPECT-guided vs. NICE-guided care comparisons.

#### **5.4.10.3 Primary Endpoint Analysis**

The difference in proportions of patients randomised to each arm with a study-defined unnecessary angiogram and 95%CI for this difference was presented for summary purposes. A binary logistic regression was used to model the relative odds of receiving an unnecessary angiogram for CMR-guided care vs. the group of interest (either NICE or SPECT-guided care pathways) when controlling for the minimisation factors. The estimated odds ratios, 95%CI and P-values was presented. An unadjusted analysis compared the difference in the proportions between the two groups using a chi-squared test.

#### **5.4.10.3 Secondary Endpoint Analysis**

##### *1. Major Adverse Cardiovascular Events*

The proportions of patients in the three groups with a MACE at twelve and thirty-six months and absolute differences in these MACE rates is presented. This analysis was performed both on the ITT and per-protocol basis. Peri-procedural MI - type 4a (related to percutaneous coronary intervention) and type 5 (related to coronary artery bypass grafting) and planned revascularization (PCI or CABG) based on the index FFR results was censored.

##### *2. Quality of Life*

The scores will be presented for the groups at 6, 12, 24 and 36 months. The scores for the dimensions of the SAQ and SF12 will be summarised by

randomised group at each time point. Multi-level repeated measures modelling will be used to estimate differences between the groups at all post-baseline time points (allowing for time, trial group, trial group by time interaction, and adjusting for baseline QoL and minimisation factors [all fixed effects], and for patient and patient by time interaction [random effects]). Residuals and predicted values produced from the multivariate models will be examined to assess the assumptions of the statistical model.

#### **5.4.11 Data monitoring**

Data was monitored for completeness and quality by the CTRU. A full monitoring schedule including Serious Adverse Events and Adverse Reactions was established and agreed by the TSC and TMG. Ethical and Safety considerations was monitored by the DMEC. A quality assurance process was undertaken centrally by independent modality-specific imaging experts, to monitor the quality of image acquisition and interpretation of each imaging modality at all recruiting centres. This involved an initial review of the first 15 imaging studies followed by an ongoing review of a random 10% of each imaging modality at each participating site. Clinical interpretation of the individual components of each imaging modality and overall study recommendation was scored as 1 (agreement), 2 (minor disagreement) or 3 (major disagreement) and reported to the DMEC for independent consideration/action.



#### **5.4.11 Conclusion**

The CE-MARC 2 trial was a prospective, multi-centre, 3-arm parallel group, randomized controlled trial; it provides comparative efficacy and safety evidence for three different strategies of investigating patients with suspected CHD, with the intention of reducing unnecessary invasive angiography rates. Evaluation of these management strategies has the potential to improve patient care, HRQoL and the cost effectiveness of CHD investigation.

## **Chapter 6**

### **Results from the Clinical Evaluation of MAgnetic Resonance imaging in Coronary heart disease 2 trial (CE-MARC 2): A prospective, multi-centre, randomized controlled trial of diagnostic strategies for suspected coronary heart disease**

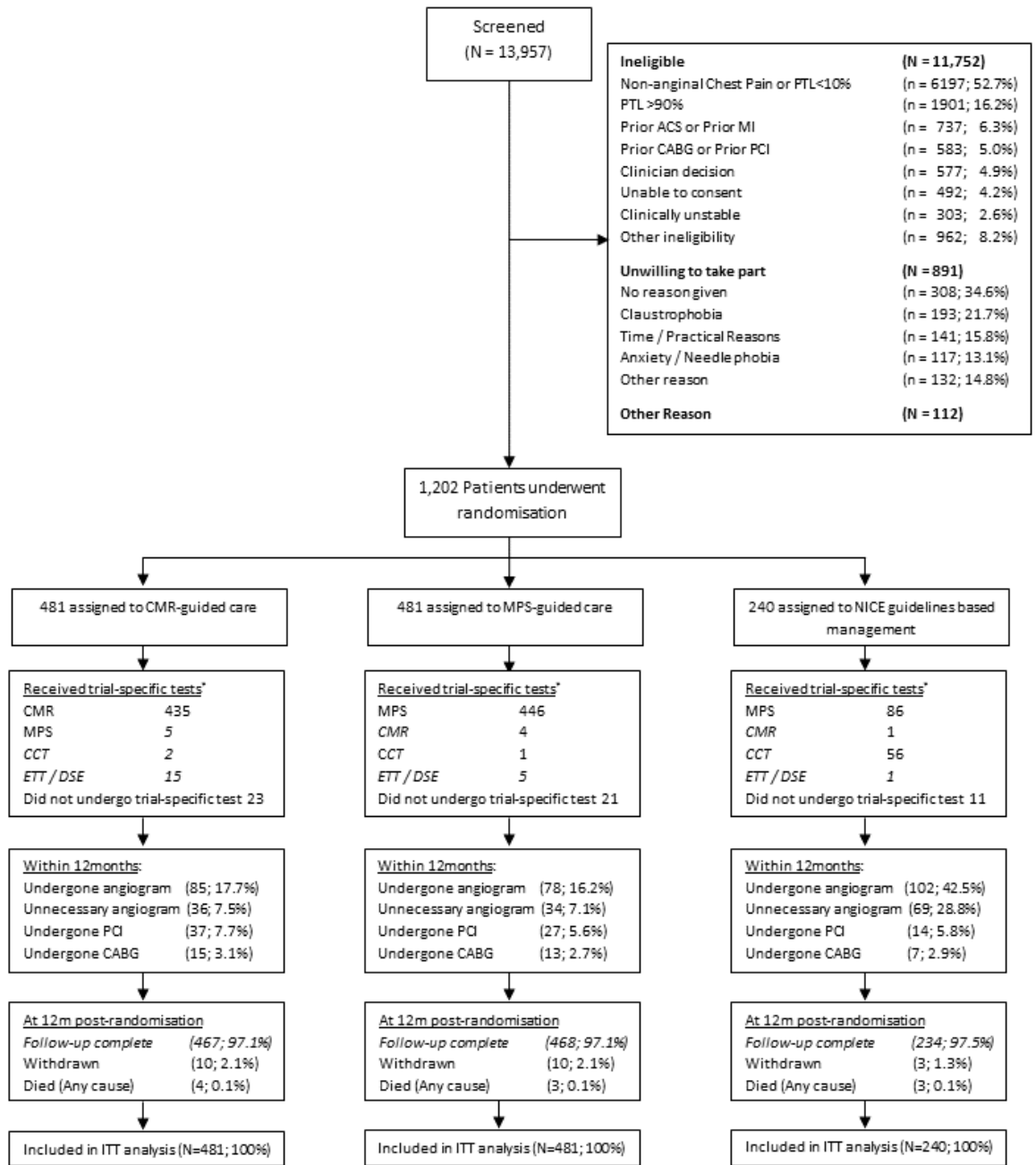
#### **6.1 Results**

##### **6.1.1 Trial Population**

Between November 2012 and March 2015, 13 957 patients were screened of whom 2205 were eligible (Figure 6.1 lists reasons for noneligibility and nonconsent). From 6 UK centers (Leeds, Glasgow, Leicester, Bristol, Oxford, London [St Georges]), 1202 patients (55% of eligible) were recruited and allocated to NICE guidelines-directed care (n = 240) or management by CMR (n = 481) or MPS (n = 481) (Figure 6.1).

##### **6.1.2 Baseline Characteristics**

The mean age of patients was 56.3 years (SD, 9.0), 638 patients (53%) were men, the mean body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) was 29.1 (SD, 5.2), and 1107 patients (92%) were classified ethnically as white (Table 6.1). The study population had a substantial burden of cardiovascular risk factors: 150 patients (12.5%) had diabetes, 458 patients (38.1%) had hypertension, 702 patients (58.4%) were past or current tobacco users, 483 patients (40.2%) had dyslipidemia, and 651 patients (54.2%) had a family history of premature CHD. Patients had a median of 2 of these 5 risk factors. All



**Figure 6.1 Flow of Patients Through the Study of Noninvasive Imaging and Angiography Rates.**

ACS indicates acute coronary syndrome; CABG, coronary artery bypass grafting; CHD, coronary heart disease; NICE, National Institute for Health and Care Excellence; PCI, percutaneous coronary intervention.[150]

\* Patients may have received more than 1 test, in addition to or as an alternative to their strategy.

**Table 6.1** Baseline Characteristics of Participants With Suspected Coronary Heart Disease (CHD) by Study Group

Characteristic	CMR-guided care (N=481)	MPS-guided care (N=481)	NICE-guided Care (N=240)	Total (N=1,202)
Age, Mean (SD)	56.5 (9.10)	55.9 (8.87)	56.5 (9.21)	56.3 (9.03)
Female sex, no. (%)	227 (47.2%)	225 (46.8%)	112 (46.7%)	564 (46.9%)
Non-white Ethnicity, no. (%)	38 (7.9%)	38 (7.9%)	19 (7.9%)	95 (7.9%)
<b>Cardiac risk factors</b>				
Body Mass Index, Mean (SD)	29.2 (5.36)	29.1 (5.12)	29.0 (5.24)	29.1 (5.23)
Hypertension, no. (%)	177 (36.8%)	182 (37.8%)	99 (41.3%)	458 (38.1%)
Diabetes, no. (%)	53 (11.0%)	73 (15.2%)	24 (10.0%)	150 (12.5%)
Dyslipidemia, no. (%)	186 (38.7%)	198 (41.2%)	99 (41.3%)	483 (40.2%)
Current or past Smoking, no. (%)	284 (59.0%)	271 (56.3%)	147 (61.3%)	702 (58.4%)
Family history of premature CHD*	252 (52.4%)	259 (53.8%)	140 (58.3%)	651 (54.2%)
Peripheral Vascular Disease, no. (%)	8 (1.7%)	9 (1.9%)	10 (4.2%)	27 (2.2%)
Cerebrovascular disease, no. (%)	17 (3.5%)	17 (3.5%)	8 (3.3%)	42 (3.5%)
<b>Nature of Angina, no. (%)</b>				
Atypical	318 (66.1%)	325 (67.6%)	158 (65.8%)	801 (66.6%)
Typical	163 (33.9%)	156 (32.4%)	82 (34.2%)	401 (33.4%)
<b>Risk Burden</b>				
PTL %, Mean (SD)†	49.9% (24.25%)	48.6% (23.57%)	50.7% (23.28%)	49.5% (23.78%)
No. risk factors/patient, Mean (SD)	2.0 (1.18)	2.0 (1.11)	2.1 (1.05)	2.0 (1.13)
10yr ASCVD risk >7.5%‡	175/377 (46.4%)	173/367 (47.1%)	93/179 (52.0%)	441/923 (47.8%)
<b>Medications, no. (%)</b>				
Antiplatelet therapy	271 (56.3%)	268 (55.7%)	150 (62.5%)	689 (57.3%)
Beta Blocker	150 (31.2%)	157 (32.6%)	74 (30.8%)	381 (31.7%)
Statin or other lipid lowering therapy	191 (39.7%)	201 (41.8%)	108 (45.0%)	500 (41.6%)
ACE inhibitor or ARB	115 (23.9%)	122 (25.4%)	66 (27.5%)	303 (25.2%)
Other anti-anginal medication	283 (58.8%)	276 (57.4%)	142 (59.2%)	701 (58.3%)

\* Family history of premature CHD defined as diagnosis of the disease in a male first-degree relative before 55 years of age or in a female first-degree relative before 65 years of age.

† According to Pryor et al.[138]

‡ According to Goff et al.[151] ASCVD, atherosclerotic cardiovascular disease; ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker.

patients were symptomatic, with 401 patients (33.4%) reporting typical chest pain and 801 patients (66.6%) reporting atypical chest pain as their primary symptom. The assessment of cardiac risk, calculated according to the 2013 atherosclerotic cardiovascular disease risk score from the American College of Cardiology Foundation and American Heart Association guidelines, showed that 441 of 923 patients (47.8%) had a 10-year risk of events of 7.5% or higher[151]. The mean pretest likelihood of obstructive CHD according to the Duke score was 49.5% (SD, 23.8%)[138].

### **6.1.3 Test Conduct**

Of 481 patients assigned to the CMR group, 435 patients (90.4%) had CMR as the initial test (median time from randomization, 20 days [interquartile range, 13-34]), 5 patients (1.0%) had MPS, 5 patients (1.0%) went directly to angiography, and 23 patients (4.8%) had no test. Of 481 patients assigned to the MPS group, 446 patients (92.7%) had MPS as the initial test (median time from randomization, 28 days [interquartile range, 22-39]), 4 patients (0.8%) had CMR, 5 patients (1.0%) went directly to angiography, and 21 patients (4.4%) had no test. Of 240 patients assigned to the NICE guidelines group, 56 patients (23.3%) had CCT (median time from randomization, 34 days [interquartile range, 14-44]), 86 patients (35.8%) had MPS, 85 patients (35.4%) went directly to angiography, and 11 patients (4.6%) had no test. The numbers of patients adherent to receiving both their initial randomized test and per-protocol compliance with their test result were 200 patients (83.3%) in the NICE guidelines group, 414 patients (86.1%) in the CMR group, and 368 patients (76.5%) in the MPS group.

Study sites reported their interpretation of the initial test as positive for CHD in 54 of 435 patients (12.4%) in the CMR group, in 81 of 446 patients (18.2%) in the MPS group, and in 19 of 142 patients (13.4%) in the NICE guidelines group. There was no difference in revascularization rates (Figure 6.1) between the 3 groups ( $P = .47$ ). The rate of patients with incomplete data required for analysis of the primary end point was low: 18 of 240 patients (7.5%) in the NICE guidelines group, 50 of 481 patients (10.4%) in the CMR group, and 33 of 481 patients (6.9%) in the MPS group. Of these, 11 of 240 patients (4.6%) in the NICE guidelines group, 23 of 481 patients (4.8%) in the CMR group, and 21 of 481 patients (4.4%) in the MPS group were related to missing test results.

#### **6.1.4 Primary End Point**

Overall, 265 patients (22.0%) underwent at least 1 coronary angiogram (10 patients underwent 2 angiograms) within 12 months of randomization: 102 of 240 patients (42.5%) in the NICE guidelines group, 85 of 481 patients (17.7%) in the CMR group, and 78 of 481 patients (16.2%) in the MPS group. The primary end point of unnecessary angiography occurred in 69 patients (28.8%) in the NICE guidelines group, 36 patients (7.5%) in the CMR group, and 34 patients (7.1%) in the MPS group. Of these angiograms, 98 angiograms (70.5%) had no visual stenosis and were not assessed further, 40 angiograms (28.8%) reached the conclusion by FFR measurement and 1 angiogram (0.7%) involved QCA only. The adjusted

**Table 6.2** Summary of the CE-MARC 2 Trial Endpoints.

	Total Patients (N = 1202)	Guided Care			Absolute Differences, % (95% CI)	
		NICE Guidelines (n = 240)	CMR (n = 481)	MPS (n = 481)	CMR vs NICE	CMR vs MPS
<b>Primary End Point</b>						
Unnecessary invasive angiography, No. (%)	139 (11.6)	69 (28.8)	36 (7.5)	34 (7.1)	-21.3 (-28.7 to -13.6)	0.4 (-6.0 to 6.8)
Components of the primary end point						
False-positive noninvasive test	35	5	18	12		
Direct to angiography (by strategy)	59	59				
Negative test, not per-protocol	41	5	15	21		
Inconclusive test/result	4	-	3	1		
<b>Secondary End Points</b>						
Positive angiography occurrence, No. (%)	118 (9.8)	29 (12.1)	47 (9.8)	42 (8.7)	-2.3 (-10.0 to 5.4)	1.0 (-5.4 to 7.5)
False-positive noninvasive test	73	4	38	31		
Direct to angiography (by strategy)	23	23				
Negative noninvasive test, not per-protocol	9	1	2	6		
Inconclusive noninvasive test/result	2		2			
Acute/urgent angiography indication	9	1	4	4		
Angiography as alternative initial investigation	2	-	1	1		
Major adverse cardiovascular events, No. (No. of patients)	44 (36)	7 (6)	20 (15)	17 (15)	1.0 (-6.7 to 8.8)	0.0 (-6.4 to 6.4)
Cardiovascular death	5	1	1	3		
Myocardial infarction	9	2	5	2		
Revascularization						
Unplanned PCI	12	2	6	4		
Unplanned CABG	1		1			
Arrhythmia	9	2	4	3		
Heart failure	4			4		
Stroke/TIA	4		3	1		

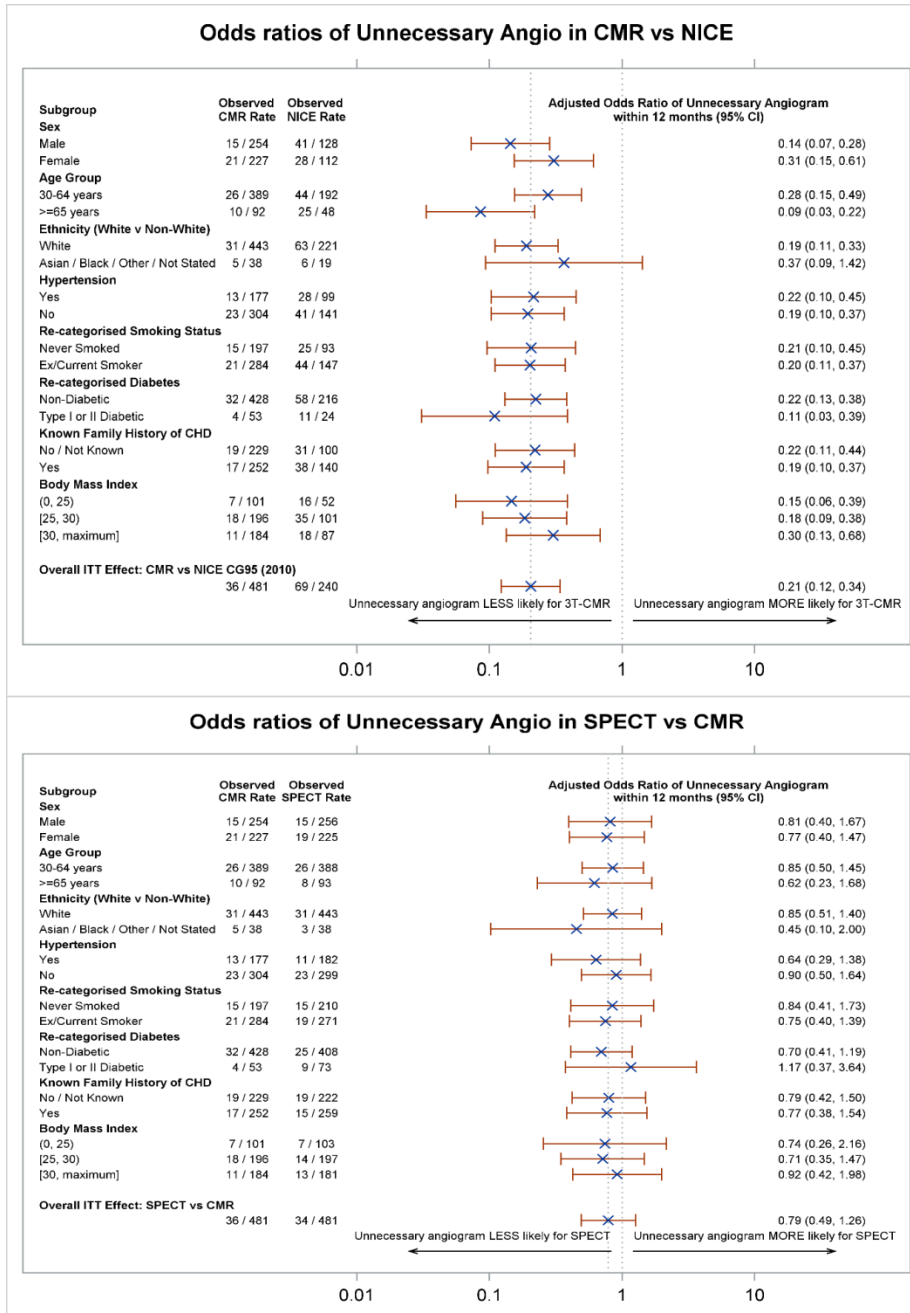
Abbreviations: CABG, coronary artery bypass graft; CMR, cardiovascular magnetic resonance; MACE, major adverse cardiovascular events; MPS, myocardial perfusion.

odds ratio of unnecessary angiography for the CMR group vs the NICE guidelines group was 0.21 (95% CI, 0.12-0.34;  $P < .001$ ) and 1.27 (95% CI, 0.79-2.03;  $P = .32$ ) for the CMR group vs the MPS group. Table 6.2 shows individual components of the primary end point. For both comparisons, the primary analysis was repeated in the per-protocol population, with no effect on the trial results. Sensitivity analyses using random center effects or adjusting for further risk factors (hypertension, ethnicity, smoking status) or using the per-protocol population did not change overall trial conclusions. Exploratory subgroup analyses showed consistent results across subgroups (Figure 6.2).

### **6.1.5 Secondary End Points**

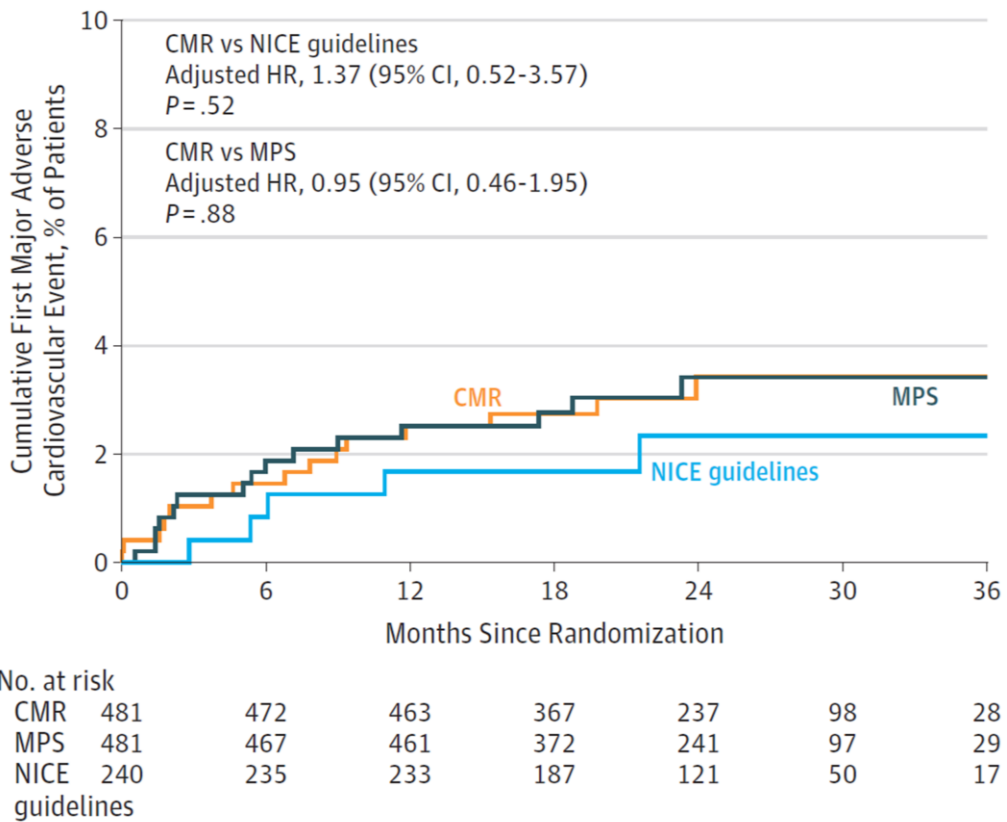
Positive angiography was observed in 29 patients (12.1% [95% CI, 8.2%-16.9%]) in the NICE guidelines group, 47 patients (9.8% [95% CI, 7.3%-12.8%]) in the CMR group, and 42 patients (8.7% [95% CI, 6.4%-11.6%]) in the MPS group ( $P = .36$ ). During the minimum 1-year follow-up (median, 15.8 months [interquartile range, 12.1-24.2]), 36 patients (3.0%) had at least 1 MACE: NICE guidelines group, 6 patients (2.5%); CMR group, 15 patients (3.1%); MPS group, 15 patients (3.1%) (Table 6.2). Annualized MACE rates were 1.6% for the NICE guidelines group, 2.0% for the CMR group, and 2.0% for the MPS group. Adjusted hazard ratios for MACE were 1.37 (95% CI, 0.52-3.57;  $P = .52$ ) for the CMR group vs the NICE guidelines group and 0.95 (95% CI, 0.46-1.95;  $P = .88$ ) for the CMR group vs the MPS group. Hard events (cardiovascular death and myocardial infarction) occurred in 3





**Figure 6.2 Effect of Specific Patient Characteristics on Results for CMR-Guided Care vs NICE Guidelines-Directed Care and MPS-Guided Care Among Patients With Suspected Coronary Heart Disease**

CMR indicates cardiovascular magnetic resonance; ITT, intention to treat; NICE, National Institute for Health and Care Excellence; MPS, myocardial perfusion scintigraphy.



**Figure 6.3 Time to First Major Adverse Cardiovascular Event After a Minimum of 12-Month Follow-Up From Randomization Among Patients With Suspected Coronary Heart Disease (Median, 16 Months)[150]**

CMR indicates cardiovascular magnetic resonance; NICE, National Institute for Health and Care Excellence; MPS, myocardial perfusion scintigraphy.

patients (1.3%) in the NICE guidelines group, 5 patients (1.0%) in the CMR group, and 4 patients (0.8%) in the MPS group ( $P = .93$ ). Figure 6.3 shows the Kaplan-Meier cumulative incidence estimate of first MACE. In the study, five test-related medical complications were reported: CMR (1 case: mild urticarial reaction), MPS (0 cases), cardiac CT (1 case: vasovagal episode) and angiography (3 cases: ventricular tachycardia; pseudo-aneurysm & popliteal DVT; right coronary artery spasm & transient ST elevation).

### **6.1.6 Functional Imaging Assessment**

Using functional imaging as a first-line strategy (CMR or MPS) in patients with a 61% to 90% (high,  $n=389$ ) CHD pretest likelihood resulted in substantially reduced odds of unnecessary angiography compared with the NICE guidelines group; 29/307 (9.4%) vs 51/82 (62.2%), odds ratio (OR) 0.048 (95% CI, 0.02-0.10),  $P < .001$ . Among those with less than 30% (low,  $n=330$ ) CHD pretest likelihood, the odds of unnecessary angiography were also numerically lower by a functional imaging approach compared with anatomical (CCT) assessment; 13/269 (4.8%) vs 7/61 (11.5%), odds ratio, 0.44 (95% CI, 0.17-1.17);  $P = .099$ ).

## **6.2 Discussion**

CE-MARC 2 was a multicenter, randomized clinical trial in a large community-based population of symptomatic patients undergoing assessment for suspected CHD, in whom further investigation was appropriate according to international guidelines. A CMR-guided strategy

significantly reduced unnecessary angiography occurrence compared with NICE guidelines-guided care, but was not significantly different from an MPS-guided strategy (following US appropriate use criteria)[137]. Between the 3 strategies, there was no difference in short-term MACE rates or disease detection (positive angiography) rates.

There is concern that coronary angiography is overused in the diagnostic pathway of suspected CHD, and that the majority of patients investigated will not have significant obstructive coronary disease[131, 132]. Avoiding unnecessary invasive angiography could have significant financial benefits, avoids exposing patients to unnecessary risk, and is also a strong patient desire[152]. For this reason, we chose this as our patient-focused primary end point.

Current international guidelines for investigation and management of suspected CHD all suggest risk stratification based on pretest likelihood estimation[138, 153, 154]. The Duke score, used in NICE guidelines, is based upon the original Diamond Forrester model, but includes additional demographic factors to further stratify risk[138]. These models, derived more than 3 decades ago, tend to overestimate CHD risk because patient demographics, risk factors, and treatment have changed considerably over time[155]. In the CE-MARC 2 trial, the reduction in unnecessary angiography by a CMR or MPS strategy appears largely driven by the overestimation of disease probability from using the Duke score. Current NICE guidelines categorize a pretest likelihood of 60% to 90% as being at high-risk of CHD,

and recommend direct referral for angiography. In the CE-MARC 2 trial, this explained the majority of patients in the NICE-guidelines group who got referred for angiography (82 of 102 patients; 80.4%), and the majority of unnecessary angiograms (59 of 69 patients; 85.5%). This was further emphasized by the preplanned, subanalysis of any functional imaging (CMR or MPS) in the 60% to 90% (high risk) pretest likelihood population, which showed substantially reduced odds of unnecessary angiography in this combined subgroup compared with the NICE guideline group.

Overall, rates of disease detection (positive angiography) were comparable for the 3 strategies, suggesting no penalty for using functional imaging as a gatekeeper for angiography, even in high-risk subgroups. Consistent with published studies, the CE-MARC 2 trial showed a low overall rate of MACE in a stable chest pain population, with no early difference between strategies.

It remains a point of debate as to whether all of our protocol-defined unnecessary angiograms are truly clinically unnecessary; some would argue that negative tests are the “price to pay” for not missing important disease in others. This assumes a population perspective, and our trial primary end point was derived after close consultation with patient and public representatives: from an individual patient perspective, an angiogram that does not change their treatment or their clinical outcome is considered by patients to have been unnecessary. Certainly guidelines are clear that

physicians do not need to undertake angiography to either diagnose angina or offer primary prevention and symptom control.

To our knowledge, there have been no randomized clinical trials comparing the performance of current management guidelines and a broad functional imaging approach in terms of important clinical end points. Although cross-sectional imaging (CMR and CCT) has improved diagnostic ability, benefits in terms of health outcomes are harder to demonstrate, partly due to complexity of subsequent treatment effects. Functional vs anatomical assessment as a potential gatekeeper to the catheterization laboratory is a topic of ongoing debate[156, 157]. The Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) trial showed no improvement in clinical outcomes using CCT vs a variety of functional tests in patients investigated for suspected CHD; whereas the CCT strategy increased rates of cardiac catheterization (12.2% vs 8.1%,  $P = .02$ ) and 90 day coronary revascularization (6.2% vs 3.2%,  $P < .001$ )[156]. This may be important following a recent observational study of 544 US centers showing higher rates of inappropriate percutaneous coronary intervention at sites performing the highest rates of angiography, suggesting anatomical assessment could predispose patients to unnecessary therapy[158]. Although numbers are small, in the CE-MARC 2 trial an increased rate of unnecessary angiography was suggested in the low-risk subgroup of the NICE guidelines group, the majority of whom underwent CCT.

### **6.2.1 Limitations**

The false-positive and false-negative rates are often quantities of interest in evaluating diagnostic methods. The CE-MARC 2 trial only angiographically verified a subset of patients, contingent on strategy findings, and so cannot provide accurate estimates. The original CE-MARC trial defined the false-positive and false-negative rates for CMR and MPS, and showed CMR-guided strategy as being superior to the MPS-guided strategy[30]. In the current study, there was no statistical difference between the CMR and MPS strategies for reduction in unnecessary angiography, despite the finding from the CE-MARC trial. However, the CE-MARC trial was able to detect small differences due to its paired design (all patients underwent all tests), whereas the current study compared independent groups, which confers lower power.

The study population was predominantly white northern European, therefore findings may not translate to other populations; geographic heterogeneity of CHD incidence is well known[153]. At trial initiation, contemporary guidelines used the Duke score[4, 6], with the NICE guidelines classifying high risk for CHD as 60% to 90% pretest likelihood. It is now recognized that this may overestimate CHD risk, such that recent guidelines[5] have adopted a recalibrated risk model[153]. The primary end point was objective (using FFR measurement), although performance was not clinically possible in all cases; blinded core laboratory analysis of QCA data avoided subjective visual angiography interpretation. Overall full adherence to the protocol was high, with some unavoidable variation due to individual clinical practice,

which could have introduced bias (eg, abnormal imaging results not proceeding to angiography). To mitigate this, analysis was by intention-to-treat principles and the primary end point was purposely all inclusive (ie, false-positives, true-negatives when not believed by clinicians, and also test failures). The slightly different rates of incomplete data (not statistically significant) between study groups was not of concern, as the data completeness rate was high overall. Per-protocol and sensitivity analyses did not alter the trial conclusions. Although clinically robust, a MACE is not a proxy for a missed diagnosis or treatment (eg, missed opportunity for revascularization by not having angiography [due to a false-negative result]). However, it remains debatable whether revascularization for stable angina has prognostic benefit over optimal medical therapy, which will be answered by the ongoing International Study of Comparative Health Effectiveness With Medical and Invasive Approaches (ISCHEMIA) trial. Finally quality of life and cost-effectiveness analyses will be important for understanding the patient-centered perspectives and payer/policy implications of these findings; these data are currently being collected/analyzed.

### **6.2.2 Conclusions**

In patients with suspected angina, investigation by CMR produced a lower probability of unnecessary angiography within 12 months than NICE guideline-directed care, with no statistically significant difference between CMR and MPS strategies. There were no statistically significant differences in MACE rates at 12 months after randomization.





## **Chapter 7**

### **Final Conclusions**

The evidence for the use of CMR in the assessment of coronary artery disease is growing rapidly. There have been significant technological advances, it is established in both national and international guidelines and now in main stream use in the clinical arena. The focus of this thesis was on the diagnostic accuracy of the components of the multi-parametric CMR examination, the comparison of the ischaemic burden with SPECT and technical advances with perfusion sequences. Finally the utility of a CMR-guided strategy was demonstrated for the investigation of stable coronary artery disease in a prospective, multi-centre, randomised controlled trial.

The main findings were:

#### **7.1 Diagnostic Accuracy of Cardiovascular Magnetic Resonance**

- i) The full multi-parametric CMR protocol using : i) left ventricular function; ii) myocardial perfusion; iii) viability (late gadolinium enhancement (LGE)) and iv) coronary magnetic resonance angiography (MRA) had the highest sensitivity and was the optimal approach to rule-out significant CAD.

- ii) The LGE component alone was the optimal rule-in strategy to detect significant CAD.
- iii) The inclusion of coronary MRA provided no additional benefit when compared to the combination of perfusion/function/LGE

## **7.2 Comparison of Ischaemic Burden between CMR and SPECT.**

- i) Measurements of overall CHD burden (SSS) show reasonable agreement between CMR and SPECT.
- ii) SSS is the most powerful prognostic marker. This therefore suggests that CMR may be comparable to SPECT in terms of predicting future cardiovascular events.
- iii) There are differences in the estimates of scar and ischaemia burden between the two modalities. This may be due to the different approach to scar imaging (LGE vs. matched defect), soft-tissue attenuation with SPECT and different cardiac coverage for perfusion assessment.

## **7.3 Developing a new perfusion pulse technique to maximise spatial resolution.**

- i) Using a pulse sequence which automatically adapts the acquisition sequence to the available scanning time spatial resolution improves in both patients and healthy volunteers.

- ii) The adaptive acquisition sequence also reduces dark rim artefact in both patients and healthy volunteers.
  
- iii) There was no difference in both image quality scoring in patients and volunteers and in artefact scoring in volunteers. There was a significantly better artefact score in patients with the adaptive pulse sequence.
  
- iv) The improvement in spatial resolution with the adaptive pulse sequence lead to a reduction in signal-to-noise ratio.
  
- v) This proof of concept study suggests there may be benefits from using an automotive adaptive resolution sequence and further research is required.

## **7.4 The Use of CMR as a Gate keeper to Invasive Coronary Angiography**

- i) In patients with suspected angina using CMR as an initial investigative strategy produced a significantly lower probability of unnecessary angiography compared to NICE guidance.
  
- ii) There was no statistically significant difference in CMR vs MPS guided strategy in relation to unnecessary angiography.
  
- iii) There was no statistically significant difference in MACE rates at 12 months between NICE guideline-directed care; CMR-directed strategy of SPECT-guided strategy.

- iv) The rates of CAD detection were comparable for the 3 strategies, suggesting no penalty for using functional imaging as a gatekeeper for angiography.

## **7.5 Future Directions**

Technological advances in acquisition techniques (software) and hardware (scanners with higher field strengths and improved cardiac phased-array coils) have allowed the development of advanced perfusion techniques. These use highly accelerated pulse sequences based on spatio-temporal undersampling which allow the acquisition of high resolution images (in-plane  $<1.5\text{mm}^2$ )[130] permitting the detection of sub-endocardial myocardial ischaemia and 3D whole heart myocardial perfusion imaging with full left ventricular coverage[159, 160]. Other techniques such as blood oxygen level dependent (BOLD) imaging[161] and arterial spin labelling (ASL)[162] are able to detect myocardial ischaemia without the use of contrast agents. BOLD uses the inherent magnetic differences between oxygenated and deoxygenated blood to detect differences in signal intensity in ischaemic vs. non-ischaemic myocardium, and is able to detect 'ischaemic' myocardium through the use of vasodilator stress techniques'[161, 163]. More work is required to assess the use of these new technologies in the clinical setting.

## List of References

1. Heidenreich, P.A., et al., *Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association*. *Circulation*, 2011. **123**(8): p. 933-44.
2. Go, A.S., et al., *Heart disease and stroke statistics--2013 update: a report from the American Heart Association*. *Circulation*, 2013. **127**(1): p. e6-e245.
3. Bradshaw, P.J., et al., *Trends in the incidence and prevalence of cardiac pacemaker insertions in an ageing population*. *Open Heart*, 2014. **1**(1): p. <xocs:firstpage xmlns:xocs=""/>.
4. Fihn, S.D., et al., *2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons*. *Circulation*, 2012. **126**(25): p. e354-471.
5. Montalescot, G., 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): p. 2949-3003.
6. *Assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin (CG95)*. London: National Institute for Health and Care Excellence. 2010.
7. Petersen, S.E., et al., *Update of the European Association of Cardiovascular Imaging (EACVI) Core Syllabus for the European Cardiovascular Magnetic Resonance Certification Exam*. *Eur Heart J Cardiovasc Imaging*, 2014. **15**(7): p. 728-9.
8. Pohost, G.M., et al., *Task Force 12: training in advanced cardiovascular imaging (cardiovascular magnetic resonance [CMR]): endorsed by the Society for Cardiovascular Magnetic Resonance*. *J Am Coll Cardiol*, 2006. **47**(4): p. 910-4.
9. Kim, R.J., et al., *Guidelines for training in Cardiovascular Magnetic Resonance (CMR)*. *J Cardiovasc Magn Reson*, 2007. **9**(1): p. 3-4.
10. Steg, P.G., et al., *ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation*. *Eur Heart J*, 2012. **33**(20): p. 2569-619.
11. Pennell, D.J., et al., *Clinical indications for cardiovascular magnetic resonance (CMR): Consensus Panel report*. *Eur Heart J*, 2004. **25**(21): p. 1940-65.
12. Ridgway, J.P., *Cardiovascular magnetic resonance physics for clinicians: part I*. *J Cardiovasc Magn Reson*, 2010. **12**: p. 71.
13. Herfkens, R.J., et al., *Nuclear magnetic resonance imaging of the cardiovascular system: normal and pathologic findings*. *Radiology*, 1983. **147**(3): p. 749-59.

14. Bradley, W.G., Jr., et al., *The appearance of rapidly flowing blood on magnetic resonance images*. AJR Am J Roentgenol, 1984. **143**(6): p. 1167-74.
15. Axel, L. and L. Dougherty, *MR imaging of motion with spatial modulation of magnetization*. Radiology, 1989. **171**(3): p. 841-5.
16. Swoboda, P.P., et al., *Reproducibility of myocardial strain and left ventricular twist measured using complementary spatial modulation of magnetization*. J Magn Reson Imaging, 2014. **39**(4): p. 887-94.
17. Myerson, S.G., et al., *Aortic regurgitation quantification using cardiovascular magnetic resonance: association with clinical outcome*. Circulation, 2012. **126**(12): p. 1452-60.
18. Lanzer, P., et al., *ECG-synchronized cardiac MR imaging: method and evaluation*. Radiology, 1985. **155**(3): p. 681-6.
19. Lenz, G.W., E.M. Haacke, and R.D. White, *Retrospective cardiac gating: a review of technical aspects and future directions*. Magn Reson Imaging, 1989. **7**(5): p. 445-55.
20. Raj, V. and S.K. Agrawal, *Ischaemic heart disease assessment by cardiovascular magnetic resonance imaging*. Postgrad Med J, 2010. **86**(1019): p. 532-40.
21. Ferreira, P.F., et al., *Cardiovascular magnetic resonance artefacts*. J Cardiovasc Magn Reson, 2013. **15**: p. 41.
22. Kanal, E., et al., *ACR guidance document for safe MR practices: 2007*. AJR Am J Roentgenol, 2007. **188**(6): p. 1447-74.
23. Messroghli, D.R., et al., *Assessment of regional left ventricular function: accuracy and reproducibility of positioning standard short-axis sections in cardiac MR imaging*. Radiology, 2005. **235**(1): p. 229-36.
24. Strich, G., et al., *Tissue distribution and magnetic resonance spin lattice relaxation effects of gadolinium-DTPA*. Radiology, 1985. **154**(3): p. 723-6.
25. Caro, J.J., E. Trindade, and M. McGregor, *The risks of death and of severe nonfatal reactions with high- vs low-osmolality contrast media: a meta-analysis*. AJR Am J Roentgenol, 1991. **156**(4): p. 825-32.
26. Marckmann, P., et al., *Nephrogenic systemic fibrosis: suspected causative role of gadodiamide used for contrast-enhanced magnetic resonance imaging*. J Am Soc Nephrol, 2006. **17**(9): p. 2359-62.
27. Bellenger, N.G., et al., *Comparison of left ventricular ejection fraction and volumes in heart failure by echocardiography, radionuclide ventriculography and cardiovascular magnetic resonance; are they interchangeable?* Eur Heart J, 2000. **21**(16): p. 1387-96.
28. Jaarsma, C., 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**(19): p. 1719-28.
29. Greenwood, J.P., 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): p. 453-60.

30. Greenwood, J.P., et al., *Clinical evaluation of magnetic resonance imaging in coronary heart disease: the CE-MARC study*. *Trials*, 2009. **10**: p. 62.
31. Greenwood, J.P., et al., *Comparison of Cardiovascular Magnetic Resonance and Single-Photon Emission Computed Tomography in Women with Suspected Coronary Artery Disease from the CE-MARC Trial*. *Circulation*, 2013.
32. Schwitter, J., et al., *MR-IMPACT II: Magnetic Resonance Imaging for Myocardial Perfusion Assessment in Coronary artery disease Trial: perfusion-cardiac magnetic resonance vs. single-photon emission computed tomography for the detection of coronary artery disease: a comparative multicentre, multivendor trial*. *Eur Heart J*, 2013. **34**(10): p. 775-81.
33. Klein, C., et al., *Combined magnetic resonance coronary artery imaging, myocardial perfusion and late gadolinium enhancement in patients with suspected coronary artery disease*. *J Cardiovasc Magn Reson*, 2008. **10**: p. 45.
34. Bettencourt, N., et al., *Additive value of magnetic resonance coronary angiography in a comprehensive cardiac magnetic resonance stress-rest protocol for detection of functionally significant coronary artery disease: a pilot study*. *Circ Cardiovasc Imaging*, 2013. **6**(5): p. 730-8.
35. Bonow, R.O., *What's past is prologue: advances in cardiovascular imaging*. *Lancet*, 2012. **379**(9814): p. 393-5.
36. Walker, S., 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): p. 873-81.
37. Boldt, J., et al., *Cost-effectiveness of cardiovascular magnetic resonance and single-photon emission computed tomography for diagnosis of coronary artery disease in Germany*. *J Cardiovasc Magn Reson*, 2013. **15**: p. 30.
38. Moschetti, K., et al., *Cost evaluation of cardiovascular magnetic resonance versus coronary angiography for the diagnostic work-up of coronary artery disease: application of the European Cardiovascular Magnetic Resonance registry data to the German, United Kingdom, Swiss, and United States health care systems*. *J Cardiovasc Magn Reson*, 2012. **14**: p. 35.
39. Nandalur, K.R., et al., *Diagnostic performance of stress cardiac magnetic resonance imaging in the detection of coronary artery disease: a meta-analysis*. *J Am Coll Cardiol*, 2007. **50**(14): p. 1343-53.
40. Nagel, E., et al., *Noninvasive diagnosis of ischemia-induced wall motion abnormalities with the use of high-dose dobutamine stress MRI: comparison with dobutamine stress echocardiography*. *Circulation*, 1999. **99**(6): p. 763-70.
41. Korosoglou, G., et al., *Prognostic value of high-dose dobutamine stress magnetic resonance imaging in 1,493 consecutive patients: assessment of myocardial wall motion and perfusion*. *J Am Coll Cardiol*, 2010. **56**(15): p. 1225-34.
42. Hundley, W.G., et al., *Magnetic resonance imaging determination of cardiac prognosis*. *Circulation*, 2002. **106**(18): p. 2328-33.



43. Jahnke, C., et al., *Prognostic value of cardiac magnetic resonance stress tests: adenosine stress perfusion and dobutamine stress wall motion imaging*. *Circulation*, 2007. **115**(13): p. 1769-76.
44. Poldermans, D., et al., *Long-term prognostic value of dobutamine-atropine stress echocardiography in 1737 patients with known or suspected coronary artery disease: A single-center experience*. *Circulation*, 1999. **99**(6): p. 757-62.
45. Wahl, A., et al., *Safety and feasibility of high-dose dobutamine-atropine stress cardiovascular magnetic resonance for diagnosis of myocardial ischaemia: experience in 1000 consecutive cases*. *Eur Heart J*, 2004. **25**(14): p. 1230-6.
46. Kuijpers, D., et al., *Dobutamine stress MRI. Part I. Safety and feasibility of dobutamine cardiovascular magnetic resonance in patients suspected of myocardial ischemia*. *Eur Radiol*, 2004. **14**(10): p. 1823-8.
47. Motwani, M., et al., *High-resolution versus standard-resolution cardiovascular MR myocardial perfusion imaging for the detection of coronary artery disease*. *Circ Cardiovasc Imaging*, 2012. **5**(3): p. 306-13.
48. Cheng, A.S., et al., *Cardiovascular magnetic resonance perfusion imaging at 3-tesla for the detection of coronary artery disease: a comparison with 1.5-tesla*. *J Am Coll Cardiol*, 2007. **49**(25): p. 2440-9.
49. Plein, S., et al., *k-Space and time sensitivity encoding-accelerated myocardial perfusion MR imaging at 3.0 T: comparison with 1.5 T*. *Radiology*, 2008. **249**(2): p. 493-500.
50. Manka, R., et al., *Whole-heart dynamic three-dimensional magnetic resonance perfusion imaging for the detection of coronary artery disease defined by fractional flow reserve: determination of volumetric myocardial ischaemic burden and coronary lesion location*. *Eur Heart J*, 2012. **33**(16): p. 2016-24.
51. Jogiya, R., et al., *Validation of dynamic 3-dimensional whole heart magnetic resonance myocardial perfusion imaging against fractional flow reserve for the detection of significant coronary artery disease*. *J Am Coll Cardiol*, 2012. **60**(8): p. 756-65.
52. Ripley, D.P., et al., *The distribution and prognosis of anomalous coronary arteries identified by cardiovascular magnetic resonance: 15 year experience from two tertiary centres*. *J Cardiovasc Magn Reson*, 2014. **16**: p. 34.
53. Plein, S., et al., *Assessment of non-ST-segment elevation acute coronary syndromes with cardiac magnetic resonance imaging*. *J Am Coll Cardiol*, 2004. **44**(11): p. 2173-81.
54. Greenwood, J.P., et al., *Safety and diagnostic accuracy of stress cardiac magnetic resonance imaging vs exercise tolerance testing early after acute ST elevation myocardial infarction*. *Heart*, 2007. **93**(11): p. 1363-8.
55. Aletras, A.H., et al., *Retrospective determination of the area at risk for reperfused acute myocardial infarction with T2-weighted cardiac magnetic resonance imaging: histopathological and displacement encoding with stimulated echoes (DENSE) functional validations*. *Circulation*, 2006. **113**(15): p. 1865-70.

56. Friedrich, M.G., et al., *The salvaged area at risk in reperfused acute myocardial infarction as visualized by cardiovascular magnetic resonance*. J Am Coll Cardiol, 2008. **51**(16): p. 1581-7.
57. Abdel-Aty, H., et al., *Delayed enhancement and T2-weighted cardiovascular magnetic resonance imaging differentiate acute from chronic myocardial infarction*. Circulation, 2004. **109**(20): p. 2411-6.
58. Younger, J.F., et al., *Troponin-I concentration 72 h after myocardial infarction correlates with infarct size and presence of microvascular obstruction*. Heart, 2007. **93**(12): p. 1547-51.
59. Kim, R.J., et al., *Myocardial Gd-DTPA kinetics determine MRI contrast enhancement and reflect the extent and severity of myocardial injury after acute reperfused infarction*. Circulation, 1996. **94**(12): p. 3318-26.
60. Hirsch, A., et al., *Intracoronary infusion of mononuclear cells from bone marrow or peripheral blood compared with standard therapy in patients after acute myocardial infarction treated by primary percutaneous coronary intervention: results of the randomized controlled HEBE trial*. Eur Heart J, 2011. **32**(14): p. 1736-47.
61. Mather, A.N., et al., *Appearance of microvascular obstruction on high resolution first-pass perfusion, early and late gadolinium enhancement CMR in patients with acute myocardial infarction*. J Cardiovasc Magn Reson, 2009. **11**: p. 33.
62. Gerber, B.L., et al., *Microvascular obstruction and left ventricular remodeling early after acute myocardial infarction*. Circulation, 2000. **101**(23): p. 2734-41.
63. Wu, K.C., et al., *Prognostic significance of microvascular obstruction by magnetic resonance imaging in patients with acute myocardial infarction*. Circulation, 1998. **97**(8): p. 765-72.
64. Hombach, V., et al., *Sequelae of acute myocardial infarction regarding cardiac structure and function and their prognostic significance as assessed by magnetic resonance imaging*. Eur Heart J, 2005. **26**(6): p. 549-57.
65. Choi, C.J., et al., *Infarct involution and improved function during healing of acute myocardial infarction: the role of microvascular obstruction*. J Cardiovasc Magn Reson, 2004. **6**(4): p. 917-25.
66. Nijveldt, R., et al., *Functional recovery after acute myocardial infarction: comparison between angiography, electrocardiography, and cardiovascular magnetic resonance measures of microvascular injury*. J Am Coll Cardiol, 2008. **52**(3): p. 181-9.
67. de Waha, S., et al., *Impact of early vs. late microvascular obstruction assessed by magnetic resonance imaging on long-term outcome after ST-elevation myocardial infarction: a comparison with traditional prognostic markers*. Eur Heart J, 2010. **31**(21): p. 2660-8.
68. Basso, C., et al., *Morphologic validation of reperfused hemorrhagic myocardial infarction by cardiovascular magnetic resonance*. Am J Cardiol, 2007. **100**(8): p. 1322-7.
69. van den Bos, E.J., et al., *Magnetic resonance imaging of haemorrhage within reperfused myocardial infarcts: possible interference with iron oxide-labelled cell tracking?* Eur Heart J, 2006. **27**(13): p. 1620-6.

70. Mather, A.N., et al., *Reperfusion haemorrhage as determined by cardiovascular MRI is a predictor of adverse left ventricular remodelling and markers of late arrhythmic risk*. Heart, 2011. **97**(6): p. 453-9.
71. Mollet, N.R., et al., *Visualization of ventricular thrombi with contrast-enhanced magnetic resonance imaging in patients with ischemic heart disease*. Circulation, 2002. **106**(23): p. 2873-6.
72. Bulluck, H., et al., *Incidence and predictors of left ventricular thrombus by cardiovascular magnetic resonance in acute ST-segment elevation myocardial infarction treated by primary percutaneous coronary intervention: a meta-analysis*. J Cardiovasc Magn Reson, 2018. **20**(1): p. 72.
73. Kim, R.J., et al., *The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction*. N Engl J Med, 2000. **343**(20): p. 1445-53.
74. Romero, J., et al., *CMR imaging assessing viability in patients with chronic ventricular dysfunction due to coronary artery disease: a meta-analysis of prospective trials*. JACC Cardiovasc Imaging, 2012. **5**(5): p. 494-508.
75. Choi, K.M., et al., *Transmural extent of acute myocardial infarction predicts long-term improvement in contractile function*. Circulation, 2001. **104**(10): p. 1101-7.
76. Shah, D.J., et al., *Prevalence of regional myocardial thinning and relationship with myocardial scarring in patients with coronary artery disease*. JAMA, 2013. **309**(9): p. 909-18.
77. Schelbert, E.B., et al., *Prevalence and prognosis of unrecognized myocardial infarction determined by cardiac magnetic resonance in older adults*. JAMA, 2012. **308**(9): p. 890-6.
78. Baer, F.M., et al., *Dobutamine magnetic resonance imaging predicts contractile recovery of chronically dysfunctional myocardium after successful revascularization*. J Am Coll Cardiol, 1998. **31**(5): p. 1040-8.
79. Lipinski, M.J., et al., *Prognostic value of stress cardiac magnetic resonance imaging in patients with known or suspected coronary artery disease: a systematic review and meta-analysis*. J Am Coll Cardiol, 2013. **62**(9): p. 826-38.
80. Metz, L.D., et al., *The prognostic value of normal exercise myocardial perfusion imaging and exercise echocardiography: a meta-analysis*. J Am Coll Cardiol, 2007. **49**(2): p. 227-37.
81. Buckert, D., et al., *Intermediate-term prognostic value of reversible perfusion deficit diagnosed by adenosine CMR: a prospective follow-up study in a consecutive patient population*. JACC Cardiovasc Imaging, 2013. **6**(1): p. 56-63.
82. Kwong, R.Y., et al., *Impact of unrecognized myocardial scar detected by cardiac magnetic resonance imaging on event-free survival in patients presenting with signs or symptoms of coronary artery disease*. Circulation, 2006. **113**(23): p. 2733-43.
83. Klem, I., et al., *Assessment of myocardial scarring improves risk stratification in patients evaluated for cardiac defibrillator implantation*. J Am Coll Cardiol, 2012. **60**(5): p. 408-20.

84. Kwon, D.H., et al., *Extent of left ventricular scar predicts outcomes in ischemic cardiomyopathy patients with significantly reduced systolic function: a delayed hyperenhancement cardiac magnetic resonance study*. JACC Cardiovasc Imaging, 2009. **2**(1): p. 34-44.
85. Yokota, H., et al., *Quantitative characterization of myocardial infarction by cardiovascular magnetic resonance predicts future cardiovascular events in patients with ischemic cardiomyopathy*. J Cardiovasc Magn Reson, 2008. **10**: p. 17.
86. Zemrak, F. and S.E. Petersen, *Late gadolinium enhancement CMR predicts adverse cardiovascular outcomes and mortality in patients with coronary artery disease: systematic review and meta-analysis*. Prog Cardiovasc Dis, 2011. **54**(3): p. 215-29.
87. Izquierdo, M., et al., *Value of Early Cardiovascular Magnetic Resonance for the Prediction of Adverse Arrhythmic Cardiac Events After a First Non-complicated ST Segment Elevation Myocardial Infarction*. Circ Cardiovasc Imaging, 2013.
88. Cochet, A.A., et al., *Major prognostic impact of persistent microvascular obstruction as assessed by contrast-enhanced cardiac magnetic resonance in reperfused acute myocardial infarction*. Eur Radiol, 2009. **19**(9): p. 2117-26.
89. Ganame, J., et al., *Impact of myocardial haemorrhage on left ventricular function and remodelling in patients with reperfused acute myocardial infarction*. Eur Heart J, 2009. **30**(12): p. 1440-9.
90. Eitel, I., et al., *Prognostic value and determinants of a hypointense infarct core in T2-weighted cardiac magnetic resonance in acute reperfused ST-elevation-myocardial infarction*. Circ Cardiovasc Imaging, 2011. **4**(4): p. 354-62.
91. Greenwood, J.P., et al., *Comparison of cardiovascular magnetic resonance and single-photon emission computed tomography in women with suspected coronary artery disease from the Clinical Evaluation of Magnetic Resonance Imaging in Coronary Heart Disease (CE-MARC) Trial*. Circulation, 2014. **129**(10): p. 1129-38.
92. Ripley, D.P., et al., *Individual component analysis of the multi-parametric cardiovascular magnetic resonance protocol in the CE-MARC trial*. J Cardiovasc Magn Reson, 2015. **17**: p. 59.
93. Tonino, P.A., et al., *Fractional flow reserve versus angiography for guiding percutaneous coronary intervention*. N Engl J Med, 2009. **360**(3): p. 213-24.
94. Boden, W.E., et al., *Optimal medical therapy with or without PCI for stable coronary disease*. N Engl J Med, 2007. **356**(15): p. 1503-16.
95. Hachamovitch, R., et al., *Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography*. Circulation, 2003. **107**(23): p. 2900-7.
96. Hachamovitch, R., et al., *Impact of ischaemia and scar on the therapeutic benefit derived from myocardial revascularization vs. medical therapy among patients undergoing stress-rest myocardial perfusion scintigraphy*. Eur Heart J, 2011. **32**(8): p. 1012-24.
97. Steel, K., et al., *Complementary prognostic values of stress myocardial perfusion and late gadolinium enhancement imaging by*

- cardiac magnetic resonance in patients with known or suspected coronary artery disease. Circulation, 2009. 120(14): p. 1390-400.*
98. Hansen, C.L., et al., *Myocardial perfusion and function: single photon emission computed tomography. J Nucl Cardiol, 2007. 14(6): p. e39-60.*
  99. Einstein, A.J., *Effects of radiation exposure from cardiac imaging: how good are the data? J Am Coll Cardiol, 2012. 59(6): p. 553-65.*
  100. Greenwood, J.P., et al., *Prognostic Value of Cardiovascular Magnetic Resonance and Single-Photon Emission Computed Tomography in Suspected Coronary Heart Disease: Long-Term Follow-up of a Prospective, Diagnostic Accuracy Cohort Study. Ann Intern Med, 2016. 165(1): p. 1-9.*
  101. Jogiya, R., et al., *Ischemic burden by 3-dimensional myocardial perfusion cardiovascular magnetic resonance: comparison with myocardial perfusion scintigraphy. Circ Cardiovasc Imaging, 2014. 7(4): p. 647-54.*
  102. Berman, D.S., et al., *Adenosine myocardial perfusion single-photon emission computed tomography in women compared with men. Impact of diabetes mellitus on incremental prognostic value and effect on patient management. J Am Coll Cardiol, 2003. 41(7): p. 1125-33.*
  103. Kramer, C.M., et al., *Standardized cardiovascular magnetic resonance imaging (CMR) protocols, society for cardiovascular magnetic resonance: board of trustees task force on standardized protocols. J Cardiovasc Magn Reson, 2008. 10: p. 35.*
  104. Bland, J.M. and D.G. Altman, *Statistical methods for assessing agreement between two methods of clinical measurement. Lancet, 1986. 1(8476): p. 307-10.*
  105. Hachamovitch, R., et al., *Incremental prognostic value of myocardial perfusion single photon emission computed tomography for the prediction of cardiac death: differential stratification for risk of cardiac death and myocardial infarction. Circulation, 1998. 97(6): p. 535-43.*
  106. Heller, G.V., et al., *Independent prognostic value of intravenous dipyridamole with technetium-99m sestamibi tomographic imaging in predicting cardiac events and cardiac-related hospital admissions. J Am Coll Cardiol, 1995. 26(5): p. 1202-8.*
  107. Travin, M.I., et al., *The prognostic value of ECG-gated SPECT imaging in patients undergoing stress Tc-99m sestamibi myocardial perfusion imaging. J Nucl Cardiol, 2004. 11(3): p. 253-62.*
  108. Piccini, J.P., et al., *Single-photon emission computed tomography myocardial perfusion imaging and the risk of sudden cardiac death in patients with coronary disease and left ventricular ejection fraction>35%. J Am Coll Cardiol, 2010. 56(3): p. 206-14.*
  109. Zellweger, M.J., et al., *When to stress patients after coronary artery bypass surgery? Risk stratification in patients early and late post-CABG using stress myocardial perfusion SPECT: implications of appropriate clinical strategies. J Am Coll Cardiol, 2001. 37(1): p. 144-52.*
  110. Klem, I., et al., *Improved detection of coronary artery disease by stress perfusion cardiovascular magnetic resonance with the use of delayed enhancement infarction imaging. J Am Coll Cardiol, 2006. 47(8): p. 1630-8.*

111. Shaw, L.J., et al., *Comparative definitions for moderate-severe ischemia in stress nuclear, echocardiography, and magnetic resonance imaging*. JACC Cardiovasc Imaging, 2014. **7**(6): p. 593-604.
112. Wagner, A., et al., *Contrast-enhanced MRI and routine single photon emission computed tomography (SPECT) perfusion imaging for detection of subendocardial myocardial infarcts: an imaging study*. Lancet, 2003. **361**(9355): p. 374-9.
113. Pennell, D.J., et al., *Clinical indications for cardiovascular magnetic resonance (CMR): Consensus Panel report*. J Cardiovasc Magn Reson, 2004. **6**(4): p. 727-65.
114. Hendel, R.C., et al., *Multicenter clinical trial to evaluate the efficacy of correction for photon attenuation and scatter in SPECT myocardial perfusion imaging*. Circulation, 1999. **99**(21): p. 2742-9.
115. Vitanis, V., et al., *High resolution three-dimensional cardiac perfusion imaging using compartment-based k-t principal component analysis*. Magn Reson Med, 2011. **65**(2): p. 575-87.
116. McDiarmid, A.K., et al., *Three-dimensional whole-heart vs. two-dimensional high-resolution perfusion-CMR: a pilot study comparing myocardial ischaemic burden*. Eur Heart J Cardiovasc Imaging, 2016. **17**(8): p. 900-8.
117. Germano, G., P.J. Slomka, and D.S. Berman, *Attenuation correction in cardiac SPECT: the boy who cried wolf?* J Nucl Cardiol, 2007. **14**(1): p. 25-35.
118. Tsao, J. and S. Kozerke, *MRI temporal acceleration techniques*. J Magn Reson Imaging, 2012. **36**(3): p. 543-60.
119. Kozerke, S. and S. Plein, *Accelerated CMR using zonal, parallel and prior knowledge driven imaging methods*. J Cardiovasc Magn Reson, 2008. **10**: p. 29.
120. Wieben, O., C. Francois, and S.B. Reeder, *Cardiac MRI of ischemic heart disease at 3 T: potential and challenges*. Eur J Radiol, 2008. **65**(1): p. 15-28.
121. Thiele, H., et al., *Effects of missing dynamic images on myocardial perfusion reserve index calculation: comparison between an every heartbeat and an alternate heartbeat acquisition*. J Cardiovasc Magn Reson, 2003. **5**(2): p. 343-52.
122. Ripley, D.P., et al., *Patient adaptive maximal resolution magnetic resonance myocardial stress perfusion imaging*. J Magn Reson Imaging, 2015. **42**(4): p. 946-53.
123. Diamond, G.A., et al., *Computer-assisted diagnosis in the noninvasive evaluation of patients with suspected coronary artery disease*. J Am Coll Cardiol, 1983. **1**(2 Pt 1): p. 444-55.
124. Tong, C.Y. and F.S. Prato, *A novel fast T1-mapping method*. J Magn Reson Imaging, 1994. **4**(5): p. 701-8.
125. Schulz-Menger, J., et al., *Standardized image interpretation and post processing in cardiovascular magnetic resonance: Society for Cardiovascular Magnetic Resonance (SCMR) board of trustees task force on standardized post processing*. J Cardiovasc Magn Reson, 2013. **15**: p. 35.

126. Plein, S., et al., *Dynamic contrast-enhanced myocardial perfusion MRI accelerated with k-t sense*. Magn Reson Med, 2007. **58**(4): p. 777-85.
127. Reeder, S.B., et al., *Practical approaches to the evaluation of signal-to-noise ratio performance with parallel imaging: application with cardiac imaging and a 32-channel cardiac coil*. Magn Reson Med, 2005. **54**(3): p. 748-54.
128. Schwitter, J., et al., *Superior diagnostic performance of perfusion-cardiovascular magnetic resonance versus SPECT to detect coronary artery disease: The secondary endpoints of the multicenter multivendor MR-IMPACT II (Magnetic Resonance Imaging for Myocardial Perfusion Assessment in Coronary Artery Disease Trial)*. J Cardiovasc Magn Reson, 2012. **14**: p. 61.
129. Kramer, C.M., et al., *Standardized cardiovascular magnetic resonance (CMR) protocols 2013 update*. J Cardiovasc Magn Reson, 2013. **15**: p. 91.
130. Maredia, N., et al., *Effect of improving spatial or temporal resolution on image quality and quantitative perfusion assessment with k-t SENSE acceleration in first-pass CMR myocardial perfusion imaging*. Magn Reson Med, 2010. **64**(6): p. 1616-24.
131. Hannan, E.L., et al., *Appropriateness of Diagnostic Catheterization for Suspected Coronary Artery Disease in New York State*. Circ Cardiovasc Interv, 2014.
132. Patel, M.R., et al., *Prevalence and predictors of nonobstructive coronary artery disease identified with coronary angiography in contemporary clinical practice*. Am Heart J, 2014. **167**(6): p. 846-52 e2.
133. Shiralkar, S., et al., *Doctors' knowledge of radiation exposure: questionnaire study*. BMJ, 2003. **327**(7411): p. 371-2.
134. Razavi, R., et al., *Cardiac catheterisation guided by MRI in children and adults with congenital heart disease*. Lancet, 2003. **362**(9399): p. 1877-82.
135. Fox, K.A. and S. McLean, *Nice guidance on the investigation of chest pain*. Heart, 2010. **96**(12): p. 903-6.
136. Sharples, L., et al., *Cost-effectiveness of functional cardiac testing in the diagnosis and management of coronary artery disease: a randomised controlled trial. The CECaT trial*. Health Technol Assess, 2007. **11**(49): p. iii-iv, ix-115.
137. Hendel, R.C., et al., *ACCF/ASNC/ACR/AHA/ASE/SCCT/SCMR/SNM 2009 appropriate use criteria for cardiac radionuclide imaging: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the American Society of Nuclear Cardiology, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the Society of Cardiovascular Computed Tomography, the Society for Cardiovascular Magnetic Resonance, and the Society of Nuclear Medicine*. Circulation, 2009. **119**(22): p. e561-87.
138. Pryor, D.B., et al., *Value of the history and physical in identifying patients at increased risk for coronary artery disease*. Ann Intern Med, 1993. **118**(2): p. 81-90.

139. Ripley, D.P., et al., *Rationale and design of the Clinical Evaluation of Magnetic Resonance Imaging in Coronary heart disease 2 trial (CE-MARC 2): a prospective, multicenter, randomized trial of diagnostic strategies in suspected coronary heart disease*. Am Heart J, 2015. **169**(1): p. 17-24 e1.
140. Kramer, C.M., et al., *Standardized cardiovascular magnetic resonance imaging (CMR) protocols, society for cardiovascular magnetic resonance: board of trustees task force on standardized protocols*. J Cardiovasc Magn Reson, 2008. **10**: p. 35.
141. Anagnostopoulos, C., et al., *Procedure guidelines for radionuclide myocardial perfusion imaging*. Heart, 2004. **90 Suppl 1**: p. i1-10.
142. Hesse, B., et al., *EANM/ESC guidelines for radionuclide imaging of cardiac function*. Eur J Nucl Med Mol Imaging, 2008. **35**(4): p. 851-85.
143. Holly, T.A., et al., *Single photon-emission computed tomography*. J Nucl Cardiol, 2010. **17**(5): p. 941-73.
144. Abbara, S., et al., *SCCT guidelines for performance of coronary computed tomographic angiography: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee*. J Cardiovasc Comput Tomogr, 2009. **3**(3): p. 190-204.
145. Koo, B.K., et al., *Optimal intravascular ultrasound criteria and their accuracy for defining the functional significance of intermediate coronary stenoses of different locations*. JACC Cardiovasc Interv, 2011. **4**(7): p. 803-11.
146. Hundley, W.G., et al., *Society for Cardiovascular Magnetic Resonance guidelines for reporting cardiovascular magnetic resonance examinations*. J Cardiovasc Magn Reson, 2009. **11**: p. 5.
147. Thygesen, K., et al., *Third universal definition of myocardial infarction*. Circulation, 2012. **126**(16): p. 2020-35.
148. Hussain, S.T., et al., *Design and rationale of the MR-INFORM study: stress perfusion cardiovascular magnetic resonance imaging to guide the management of patients with stable coronary artery disease*. J Cardiovasc Magn Reson, 2012. **14**: p. 65.
149. Fleiss, J.L., A. Tytun, and H.K. Ury, *A Simple Approximation for Calculating Sample Sizes for Comparing Independent Proportions*. Biometrics, 1980. **36**: p. 343-346.
150. Greenwood, J.P., et al., *Effect of Care Guided by Cardiovascular Magnetic Resonance, Myocardial Perfusion Scintigraphy, or NICE Guidelines on Subsequent Unnecessary Angiography Rates: The CE-MARC 2 Randomized Clinical Trial*. JAMA, 2016. **316**(10): p. 1051-60.
151. Goff, D.C., Jr., et al., *2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines*. J Am Coll Cardiol, 2014. **63**(25 Pt B): p. 2935-59.
152. Schonenberger, E., et al., *Patient acceptance of noninvasive and invasive coronary angiography*. PLoS One, 2007. **2**(2): p. e246.
153. Genders, T.S., et al., *A clinical prediction rule for the diagnosis of coronary artery disease: validation, updating, and extension*. Eur Heart J, 2011. **32**(11): p. 1316-30.



154. Diamond, G.A. and J.S. Forrester, *Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease*. N Engl J Med, 1979. **300**(24): p. 1350-8.
155. Cheng, V.Y., et al., *Performance of the traditional age, sex, and angina typicality-based approach for estimating pretest probability of angiographically significant coronary artery disease in patients undergoing coronary computed tomographic angiography: results from the multinational coronary CT angiography evaluation for clinical outcomes: an international multicenter registry (CONFIRM)*. Circulation, 2011. **124**(22): p. 2423-32, 1-8.
156. Douglas, P.S., et al., *Outcomes of anatomical versus functional testing for coronary artery disease*. N Engl J Med, 2015. **372**(14): p. 1291-300.
157. Marwick, T.H., et al., *Finding the Gatekeeper to the Cardiac Catheterization Laboratory: Coronary CT Angiography or Stress Testing?* J Am Coll Cardiol, 2015. **65**(25): p. 2747-56.
158. Bradley, S.M., et al., *Patient selection for diagnostic coronary angiography and hospital-level percutaneous coronary intervention appropriateness: insights from the National Cardiovascular Data Registry*. JAMA Intern Med, 2014. **174**(10): p. 1630-9.
159. Motwani, M., et al., *Advances in cardiovascular magnetic resonance in ischaemic heart disease and non-ischaemic cardiomyopathies*. Heart, 2014. **100**(21): p. 1722-33.
160. Fair, M.J., et al., *A review of 3D first-pass, whole-heart, myocardial perfusion cardiovascular magnetic resonance*. J Cardiovasc Magn Reson, 2015. **17**(1): p. 68.
161. Manka, R., et al., *BOLD cardiovascular magnetic resonance at 3.0 tesla in myocardial ischemia*. J Cardiovasc Magn Reson, 2010. **12**: p. 54.
162. Zun, Z., et al., *Arterial spin labeled CMR detects clinically relevant increase in myocardial blood flow with vasodilation*. JACC Cardiovasc Imaging, 2011. **4**(12): p. 1253-61.
163. Jahnke, C., et al., *Navigator-gated 3D blood oxygen level-dependent CMR at 3.0-T for detection of stress-induced myocardial ischemic reactions*. JACC Cardiovasc Imaging, 2010. **3**(4): p. 375-84.

## List of Abbreviations

AAR	Area At Risk
ACCF	American College of Cardiology Foundation
AHA	American Heart Association
ASTM	American Society for Testing Materials
bSSFP	Balanced Steady-State Free Precession
CAD	Coronary Artery Disease
CHD	Coronary Heart Disease
CMR	Cardiovascular Magnetic Resonance
CTCA	Computed Tomography Coronary Angiography
DRA	Dark Rim Artefact
DSE	Dobutamine Stress Echocardiography
EGE	Early Gadolinium Enhancement
ESC	European Society of Cardiology
FFR	Fractional Flow Reserve
FOV	Field Of View
GE	Gradient Echo
HYPR	Highly Constrained Back Projection
ICD	Implantable Cardiac Defibrillator
IMH	Intramyocardial Haemorrhage

LGE	Late Gadolinium Enhancement
LMS	Left Main Stem
LR	Likelihood Ratio
LR-	Likelihood Ratio for Negative Tests
LR+	Likelihood Ratio for Positive Tests
LV	Left Ventricle
LVEF	Left Ventricular Ejection Fraction
MACE	Major Adverse Cardiovascular Events
MI	Myocardial Infarction
MO	Microvascular Obstruction
MR	Magnetic Resonance
MRA	Magnetic Resonance Angiography
NICE	National Institute for Health and Care Excellence
NPV	Negative Predictive Value
OMT	Optimal Medical Therapy
PPV	Positive Predictive Value
RF	Radiofrequency
RWMA	Regional Wall Motion Abnormality
PET	Positron Emission Tomography
QCA	Quantitative Invasive Coronary Angiography
SCD	Sudden Cardiac Death

SCMR	Society for Cardiovascular Magnetic Resonance
SDS	Summed Difference Score
SE	Spin Echo
SENSE	Sensitivity Encoding
SNR	Signal-to-Noise Ratio
SPECT	Single Photon Emission Computed Tomography
SRS	Summed Rest Score
SSS	Summed Stress Score
QALY	Quality Adjusted Life Year
QCA	Quantitative Invasive Coronary Angiography
T	Tesla
TE	Echo Time
TR	Repetition Time
US	United States
XRA	X-Ray Angiography

## Appendices

### 9.1 Appendix 1

#### 9.1.1 Ethics Committee Approval for Study 1 & 2

Leeds (West) Research Ethics Committee  
6th Floor, Wellcome Wing  
Leeds General Infirmary  
Great George Street  
Leeds  
LS 1 3EX

Telephone: 0113 392 6788  
Facsimile: 0113 392 2863

24 August 2005

Professor Stephen Ball  
Professor of Cardiology  
Leeds Teaching Hospitals NHS Trust  
Institute of Cardiovascular Research  
G Floor, Jubilee Building  
Leeds General Infirmary  
Leeds  
LS 1 3EX

Dear Professor Ball

Full title of study: Cardiac Magnetic Resonance Imaging in Coronary Heart  
Disease: From Research to Clinical Practice  
REC reference number: 05/Q1205/126

Thank you for your letter of 03 August 2005, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

The favourable opinion applies to the research sites listed on the attached form.

Conditions of approval

The favourable opinion is given provided that you comply with the conditions set out in the attached document. You are advised to study the conditions carefully.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	Version	Date
Application		13 June 2005
<u>Investigator</u> CV		<u>(None Specified)</u>
Protocol		<u>(None Specified)</u>
GP/Consultant Information Sheets		<u>(None Specified)</u>
Participant Information Sheet		<u>(None Specified)</u>
Participant Consent Form		(None Specified)

05/126

Page 2

Response to Request for Further Information  
Review document from the Radiation Advisor, LTHL

03 August 2005  
(None Specified)

Management approval

The study should not commence at any NHS site until the local Principal Investigator has obtained final management approval from the R&D Department for the relevant NHS care organisation.

Notification of other bodies

The Committee Administrator will notify the research sponsor and the R&D Department for NHS care organisation(s) that the study has a favourable ethical opinion.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

05/Q1205/126

Please quote this number on all correspondence

With the Committee's best wishes for the success of this project,

Yours sincerely



Lucy Enever  
Assistant Administrator  
On Behalf Of  
Dr John Puntis  
Chairman

[Email: Lucy.Enever@leadsth.nhs.uk](mailto:Lucy.Enever@leadsth.nhs.uk)

Enclosures:

Standard approval conditions  
Site approval form (SF1)

## 9.1.2 Ethics Committee Approval for Study 3



### **Health Research Authority** NRES Committee Yorkshire & The Humber - Leeds West

First Floor  
Millside  
Mill Pond Lane  
Leeds  
LS6 4RA

Telephone: 0113 3050122  
Facsimile: 0113 8556191

24 January 2013

Dr John P Greenwood  
Consultant Cardiologist, Senior Lecturer  
University of Leeds  
Academic Unit of Cardiovascular Medicine  
G floor, Jubilee Wing  
Leeds General Infirmary  
LS1 3EX

Dear Dr Greenwood

**Study title:** CE-MARC 2: Optimization of Image Acquisition and Analysis Methods  
**REC reference:** 12/YH/0551  
**IRAS project ID:** 116093

Thank you for your letter of 18 January 2013, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the NRES website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the Co-ordinator Mrs Elaine Hazell, [nrescommittee.yorkandhumber-leedswest@nhs.uk](mailto:nrescommittee.yorkandhumber-leedswest@nhs.uk).

#### **Confirmation of ethical opinion**

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

#### **Ethical review of research sites**

#### NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

#### Non-NHS sites

##### **Conditions of the favourable opinion**

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

*Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.*

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at <http://www.rdforum.nhs.uk>.

*Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.*

*For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.*

*Sponsors are not required to notify the Committee of approvals from host organisations*

**Please insert spaces between paragraphs in the section 'What will happen to me if I take part' to improve readability.**

**It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).**

**You should notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which can be made available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.**

#### **Approved documents**

The final list of documents reviewed and approved by the Committee is as follows:

<i>Document</i>	<i>Version</i>	<i>Date</i>
-----------------	----------------	-------------



Advertisement	1.1	
Covering Letter		23 November 2012
Evidence of insurance or indemnity		29 September 2012
Investigator CV		10 August 2012
Letter of invitation to participant		22 November 2012
Participant Consent Form: Healthy volunteers	1.1	18 January 2013
Participant Consent Form	1.1	18 January 2013
Participant Information Sheet: Volunteer	1.1	18 January 2013
Participant Information Sheet	1.1	18 January 2013
Protocol	1.0	05 November 2012
REC application	3.4	23 November 2012
Response to Request for Further Information		18 January 2013

### Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

### After ethical review

#### Reporting requirements

The attached document "*After ethical review – guidance for researchers*" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

#### Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

<b>12/YH/0551</b>	<b>Please quote this number on all correspondence</b>
-------------------	---

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at <http://www.hra.nhs.uk/hra-training/>

A Research Ethics Committee established by the Health Research Authority

With the Committee's best wishes for the success of this project.

Yours sincerely



pp  
**Dr Rhona Bratt**  
**Chair**

Email: [nrescommittee.yorkandhumber-leedswest@nhs.uk](mailto:nrescommittee.yorkandhumber-leedswest@nhs.uk)

*Enclosures:* "After ethical review – guidance for researchers"

*Copy to:* *Ms Clare E Skinner*  
*Ms Anne Gowing, Leeds Teaching Hospitals NHS Trust*

### 9.1.3 Ethics Committee Approval for Study 4



## Health Research Authority

NRES Committee Yorkshire & The Humber - South Yorkshire

Millside  
Mill Pond Lane  
Meanwood  
Leeds  
LS6 4RA

Telephone: 0113 3050116  
Facsimile: 0113 8556191

12 September 2012

Dr John P Greenwood  
Consultant Cardiologist, Senior Lecturer  
University of Leeds  
Academic Unit of Cardiovascular Medicine  
G floor, Jubilee Wing  
Leeds General Infirmary  
LS1 3EX

Dear Dr Greenwood

**Study title:** Clinical Evaluation of Magnetic Resonance imaging in  
Coronary heart disease 2  
**REC reference:** 12/YH/0404  
**IRAS Project reference:** 109822

The Research Ethics Committee reviewed the above application at the meeting held on 30 August 2012. Thank you for sending Ms Petra Bijsterveld to discuss the study.

#### **Ethical opinion**

##### Discussion with Ms Bijsterveld

- The Committee asked the Researcher whilst determining CMR guided care and CV events (MACE) in the study, if a large number of false negatives are identified going through CMR, will it be stopped? The Researcher confirmed that a Safety Monitoring Committee will be established on the study. She stated that the previous C-MARC study has already monitored this, so it is highly unlikely that these patients will be missed.
- The Committee informed the Researcher that they had agreed that the Participant Information Sheet was rather lengthy, but informative. However, they asked that some wording be changed i.e. under the section 'Purpose of the study' the wording in the 8<sup>th</sup> line down states 'Importantly, MRI is also a safer test than most other heart scans, because it does not use radiation'. The Committee stated that it should only state 'MRI does not use radiation', as at this point they have not been allocated into one of the three groups. They also stated that the word 'No' should be inserted at the beginning of the paragraph under the heading 'Do I have to take part?'

The members of the Committee present gave a favourable ethical opinion of the above

A Research Ethics Committee established by the Health Research Authority

research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

### **Ethical review of research sites**

#### **NHS Sites**

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

#### **Non NHS sites**

The Committee has not yet been notified of the outcome of any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. I will write to you again as soon as one Research Ethics Committee has notified the outcome of a SSA. In the meantime no study procedures should be initiated at non-NHS sites.

### **Conditions of the favourable opinion**

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

*Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.*

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at <http://www.rdforum.nhs.uk>.

*Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.*

*For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.*

*Sponsors are not required to notify the Committee of approvals from host organisations*

**It is responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).**

**You must notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which can be made available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.**

### Approved documents

The documents reviewed and approved at the meeting were:

<i>Document</i>	<i>Version</i>	<i>Date</i>
Covering Letter		10 August 2012
Evidence of insurance or indemnity		28 September 2011
Investigator CV		10 August 2012
Letter of invitation to participant	1.0	10 August 2012
Other: Study Flow Diagram/ Study Summary		
Other: General Practitioner Information Sheet	1.0	10 August 2012
Participant Information Sheet	1.0	10 August 2012
Protocol	1.0	10 August 2012
Questionnaire: Seattle Angina Questionnaire		
Questionnaire: Your Health & Wellbeing		
Questionnaire: Health Questionnaire		
REC application		23 July 2012

### Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

Dr Rhona Bratt (co-opted member) expressed that the Research Nurse attending on behalf of the Chief Investigator, Petra Bijsterveld, was once a Committee Member on the REC that she chairs. The Committee agreed that Rhona Bratt remain in the room and take part in all deliberations and decision making for this study, as they did not deem this to be a conflict of interest.

### Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

### After ethical review

#### Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

#### Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

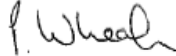
**12/YH/0404**

**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely

pp



**Mr Neil Marsden  
Vice-Chair**

Email: trish.wheat@nhs.net

*Enclosures: List of names and professions of members who were present at the meeting and those who submitted written comments "After ethical review – guidance for researchers"*

*Copy to: Rachel de Souza, University of Leeds*

*Ms Anne Gowing, R&D Department, Leeds Teaching Hospitals NHS Trust*

**NRES Committee Yorkshire & The Humber - South Yorkshire**

**Attendance at Committee meeting on 30 August 2012**

**Committee Members:**

<i>Name</i>	<i>Profession</i>	<i>Present</i>	<i>Notes</i>
Ms Jo Abbott	Consultant in Public Health (Chair)	No	
Dr A H Abdelhafiz	Consultant Physician, Elderly Medicine	No	
Reverend Joan Ashton	Co-ordinator of Chaplaincy Services	Yes	
Ms Helen Barlow	Knowledge Service Manager	No	
Professor Nigel Beail	Consultant Clinical Psychologist & Professor of Psychology	Yes	
Dr Rhona Bratt	Retired Multimedia Project Manager	Yes	Co-opted
Mr Ian Cawthorne	Chief Pharmacist	No	
Ms Susan Hampshaw	Head of Research, Evaluation and Innovation	No	
Mr Neil Marsden	Police Staff (Vice Chair)	Yes	Chairing
Dr Anton Mayer	Consultant in Paediatric Intensive Care	No	
Mrs Andrea Porritt	Community Specialist Practitioner	Yes	
Mrs Claire M Ramsden	Health visitor	Yes	Co-opted
Mr Jaydip Ray	Consultant ENT Surgeon	No	
Ms Stephanie Rhodes	Neonatal Sister	Yes	
Dr Paul Spencer	Consultant Radiologist	Yes	
Mrs Carole Taylor	Deputy Chief Pharmacist	No	
Dr Ian Woollands	Clinical Director, Occupational Health	Yes	Co-opted

**Also in attendance:**

<i>Name</i>	<i>Position (or reason for attending)</i>
Ms Trish Wheat	REC Committee Co-ordinator



## 9.2 Appendix 2

### 9.2.1 Patient Information Leaflet Study 1 & 2



# CE-MARC STUDY

## Clinical Evaluation of Magnetic Resonance imaging in Coronary heart disease

### *PATIENT INFORMATION LEAFLET* Version 2.1 December 2005

Dear patient,

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

#### ***WHY HAVE I BEEN CHOSEN?***

This study is looking at people like you, who have been referred to a cardiology clinic with chest pain. We will be asking 750 people to take part in this study.

#### ***WHAT IS THE PURPOSE OF THE STUDY?***

We currently have several tests available to help us find out if chest pain is caused by heart disease. These include treadmill exercise testing, coronary angiography and SPECT perfusion imaging. More recently we have begun to use another test, Magnetic Resonance Imaging (MRI) to obtain pictures of the heart. MRI produces pictures with much greater detail than with other types of heart scans. Importantly, MRI is also a safer test than most other heart scans, because it does not expose patients to any harmful radiation and pictures of the heart can be taken "from the outside". Because of all of these qualities, MRI might become one of the most important tests in patients who suffer with chest pain and coronary heart disease. As for any new test, before being able to use MRI on a daily basis, we need to find out how accurate it really is compared with the currently available tests. This is why we are carrying out this research study.



***DO I HAVE TO TAKE PART?***

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. This will not affect the standard of care you receive.

***WHAT WILL HAPPEN TO ME IF I TAKE PART?***

All patients in this study will have three or four heart tests. One of the tests is the MRI scan, which is done solely for research purposes. The other three tests are those that are currently used to detect coronary heart disease, namely an exercise treadmill test, a SPECT myocardial perfusion study (to obtain information on the blood flow to the heart muscle) and an x-ray angiogram (to detect any blockages in the heart arteries). Of these other three tests, your hospital consultant may want you to have some or even all anyway. However, because for this study all patients must have all four tests (to allow us to compare them with each other), if any of the other three tests are not requested by your hospital consultant, we will carry them out for this research study.

All tests will be performed at the Leeds General Infirmary and we will try to carry out as many as possible on the same day to minimise the time you have to spend travelling to the hospital. Information leaflets that give you more details about all of the tests will be provided.

1. The MRI scan will take approximately 60 minutes to complete. You lie in a short 'tunnel', which holds a large magnet. Short bursts of magnetic fields and radio waves from the MRI scanner allow images to be created. You will hear periodical loud "banging" noises while we are acquiring the images of your heart. We will remain in communication with you throughout the scan. Twice during the scan, we will inject an MRI contrast medication into a vein in your arm. The needle used for this will feel like a sharp scratch. Usually people are not aware of the contrast dye injection. At one point we will also inject a medication (Adenosine) into a vein in your arm, which is a drug to increase the blood flow to your heart. This can cause a brief feeling of warmth, breathlessness or chest discomfort. However all of these feelings, if they occur, usually settle within one or two minutes.
2. The exercise treadmill test requires you to walk on a treadmill while your heart trace (ECG) and blood pressure are measured. This test will of course only be carried out if you are physically able to walk on the treadmill. Almost all patients referred to hospital with chest pain have a treadmill test anyway.
3. The SPECT perfusion study is carried out on two separate days and takes approximately 2 hours on each day. On one day pictures of the heart will be taken at rest and on the second day after injection of the same medication (Adenosine) that we use for the MRI scan to increase the blood flow to your heart. On both days you will also have an injection of a radioactive dye into the blood, which is taken up by the heart muscle. Usually people are not aware of the contrast dye injection. One hour after the injection, pictures of the heart are taken with a special camera that slowly moves around you while you lie on a bed with one arm raised above your head. Taking these pictures takes approximately 20 minutes.
4. With the x-ray angiogram, we take x-ray pictures of the heart arteries. This test requires you to come into hospital for one day. You will be taken to an x-ray room and lie down on your back. After cleaning the groin area, local anaesthetic is given into the

groin or the forearm and a needle put into the artery in the groin or arm. Because of the local anaesthetic putting the needle in should not be painful. A fine, hollow tube called a 'catheter' is then introduced into the artery and is gently advanced through the blood vessels to the heart. The catheter is roughly the diameter of the lead in a lead pencil. You will not feel the catheter being moved around inside your chest. A dye is then injected into the heart blood vessels and X-rays taken from several angles. Some injections cause a hot, flushing sensation which lasts a few seconds. When the test is over, the catheter is removed and simple pressure is applied to the leg or arm for about 10 minutes. Most patients referred to hospital with chest pain will have an x-ray angiogram at some point.

In addition to the heart scans you will have one blood sample taken and stored to measure a number of biochemical markers of cardiovascular risk. The sample would be taken by a qualified nurse or doctor and if at all possible will be taken at a time when you are having blood taken for another reason.

After you have had the heart tests, we will monitor your progress for three years. This will involve a short telephone call once a year to find out how your health has been.

Sometimes we collaborate with commercial companies to pursue our research. This may be necessary for example if we find a new blood marker and need to develop a kit to measure it. Although this may involve the use of samples or research results from patients, these would be anonymised and there would be no direct financial gain to patients taking part in the study.

#### ***WHAT ARE THE RISKS AND DISCOMFORTS?***

Magnetic Resonance Imaging (MRI) is safe and no x-rays or radiation are used for this scan. There are no known risks from this technique. Some patients may experience claustrophobia. The staff will provide every possible means to reduce this sensation. The contrast medication which we use is very safe but, as with any injection, reactions may occur. These include a warm sensation at the injection site, nausea or vomiting and transient skin rash. These effects usually only last for a few minutes. People with a history of allergy are more likely to suffer a more severe reaction, but this is rare (less than 1 in 3000). The department is equipped to cope with allergic reactions if they happen. Adenosine, the medication we use to increase the blood flow to the heart, can cause flushing, breathlessness and chest discomfort. However, all of these feelings usually subside within one or two minutes or even more quickly if the medication is stopped.

The Exercise treadmill test can cause angina or heart rhythm changes in some people. Should you develop such side effects, the test would be stopped immediately.

SPECT imaging is very safe but exposes patients to a small amount of radiation. As for MRI, Adenosine, the medication we use to increase the blood flow to the heart, can cause flushing, breathlessness and chest discomfort. However, all of these feelings usually subside within one or two minutes or even more quickly if the medication is stopped.

The most common complication of the X-ray angiogram is for a bruise to form in the groin. This is not serious, but may be inconvenient for a few days. Serious complications are very rare, but there is a small risk of the test causing a heart attack, stroke or kidney damage (about 1 in 1000). The test also exposes patients to a small amount of radiation.

All radiation doses carry a small risk. The radiation dose that you would receive from all the tests in this study together would be equivalent to between two and ten years of exposure to natural background radiation.

***BENEFITS TO YOU***

If you take part in this study, your chest pain will be studied very thoroughly and a lot of information about the health of your heart will be obtained. Most, but not all of this information would be gathered if you did not take part in the study and some of the information could help to plan what is the best treatment for you.

***EXPENSES***

We will provide reasonable travel expenses should this be necessary for you to attend the follow-up scan. We are also happy to arrange transport to the hospital and return you home if needs be.

***WILL MY TAKING PART BE KEPT CONFIDENTIAL?***

All information, which is collected about you during the course of the research will be kept strictly confidential. This information will be securely stored at the Clinical Trials Research Unit (CTRU) at the University of Leeds and at the Cardiac MRI Unit at Leeds General Infirmary on paper and electronically, under the provisions of the 1998 Data Protection Act. You will not be identified in any publication that may result from this research.

We will inform your General Practitioner (GP) of your participation in this study as well as in the event of an unexpected abnormality on the scan. We will also contact the Office of National Statistics at a later stage for information that they already hold on patients treated in the UK.

With your permission, your data may also provide a resource for future studies. If any information from this study is used to develop new research, data protection regulations will be observed and strict confidentiality maintained. Ethical approval will be obtained for any future studies involving your data. You will not be identified in the results of any future studies.

If you withdraw consent from further study follow-up, your data will remain on file and will be included in the final study analysis.

***WHAT WILL HAPPEN TO THE RESULTS OF THE RESEARCH STUDY?***

When the study is complete the results will be published in a medical journal, but no individual patients will be identified. If you would like a copy of the published results, please ask your doctor.

***INDEMNITY/COMPENSATION***

If you are harmed as a direct result of taking part in this study, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds to a legal action. Regardless of this, if you have any cause to complain about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms are available to you.

If you have a private medical insurance please ensure that participation in the study does not affect your cover.

***WHO IS ORGANISING AND FUNDING THE STUDY?***

This is a research project of the Cardiac MRI department at Leeds General Infirmary, which is funded by the British Heart Foundation.

***WHO HAS REVIEWED THE STUDY?***

The study has been reviewed and approved by an independent local NHS Research Ethics Committee

***For further information please contact:***

Dr. Neil Maredia, Research Fellow, or  
Petra Bijsterveld, Research Nurse  
British Heart Foundation Cardiac MRI Department,  
B Floor, Clarendon Wing,  
Leeds General Infirmary.  
Tel: 0113 39 2 5481 Mobile: 07922 512 887.  
<http://www.cmr.leeds.ac.uk/>



When you attend for your Cardiology out-patient appointment, a Doctor or Nurse connected with the research programme will talk to you about the study and give you further information.

If, after reading this information leaflet you definitely do not want to consider this study, please tear off this slip and give it to the receptionist with your name written below.

Name:

.....  
.....

Thank you for your time.

## 9.2.1 Patient Information Leaflet Study 3

### PATIENT INFORMATION SHEET Version 1.3 16 February 2017

#### **CE-MARC 2: Optimization of acquisition and analysis methods (patients).**

**Chief Investigator: Dr John Greenwood**

Dear Patient,

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

#### **Purpose of the study**

Magnetic Resonance Imaging (MRI) is a test which produces detailed pictures of your internal organs by putting you within a strong magnetic field. With Cardiac MRI we are able to detect a number of important abnormalities that are caused by heart disease. Importantly, MRI is a safe test and does not use any radiation. MRI may become one of the most important tests in patients who suffer with different types of heart disease.

We have been doing MRI scans of the heart in Leeds since 1995. However, research into improving the images is a continuous process. We always work at developing and improving the scanning protocols, i.e. the computer programmes that produce the images of patients' hearts.

#### **Why have I been chosen?**

This study is looking at up to 300 people like you, who either have heart disease, are currently being investigated for heart disease, or have risk factors for heart disease. We are also recruiting 400 healthy volunteers.

#### **Do I have to take part?**

No. It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. This will not affect the standard of care that you receive from the NHS. If there is a possibility that you might be pregnant, you should not take part in the study. Our research team will be happy to discuss any other questions that you may have concerning your suitability for the study, before you decide whether to take part.

#### **What will happen to me if I take part?**

Most patients will have a single MRI scan. A small group of participants in this study will be asked to undergo up to four MRI scans to allow comparisons between different ways of obtaining MRI pictures. It is entirely up to you how many scans you wish to volunteer for, and you will remain free to withdraw from the study at any

time. All scans will be performed at the Leeds General Infirmary, and will be performed on separate days.

The MRI scan will take approximately 60 minutes to complete. You lie in a short 'tunnel', which holds a large magnet. Short bursts of radio waves from the MRI scanner allow images to be created. You will hear periodical loud "banging" noises while we are acquiring the images of your heart, so we protect your ears with headphones through which you can listen to the radio or one of your own CDs. We will remain in communication with you throughout the scan. For most scans we will insert one or two cannulae (small plastic tubes) into veins in your arm. It is likely that we will inject a contrast dye during the scan. Usually people are not aware of the contrast dye injection. At one point we may also inject a medication (Adenosine) into a vein in your arm, which is a drug to increase the blood flow to your heart. This can cause a brief feeling of warmth, breathlessness or chest discomfort. However all of these feelings, if they occur, usually settle within one or two minutes. A doctor will stay in the room with you whilst you are having the medication. In some cases instead of using adenosine we may immerse your hands or feet in cold water for up to 2 minutes to achieve the same increased blood flow to the heart muscle, or we may ask you to use a cycle ergometer, a bicycle which can be used whilst lying down in the scanner.

If we wish to obtain specific images of your heart arteries we will wrap a belt around your abdomen to help improve the quality of the pictures. This is not painful and is a recognized method of doing this type of scan. You may be given a nitrate (GTN) spray under the tongue which helps us to obtaining good images. If your heart beat is quite fast we would give you a beta blocker to reduce your heart rate. Again, these methods are widely used in other centres worldwide and are used in normal clinical work too.

Some of the MRI methods used in the heart are also applicable to other body organs. In some patients we will, for example, take images of the blood vessels and/or muscles in the abdomen, or a leg or arm during the same scan. The only difference to the heart scans is that we will use a different receiver coil (the aerial used for reception of MRI signals) to obtain these images.

As this study is about improving our scan protocols on an ongoing basis for a period of five years the information we give you has to describe all the different techniques we wish to use in the study overall, but not all the techniques described above will be used during your scan(s). Before you sign the consent form we will discuss with you the specific scanning protocol that we are going to use.

We may ask you for a blood sample, which would be taken whilst we insert the cannula in your arm for the contrast, so there are no extra needles involved. Knowing your haematocrit (the volume percentage of red blood cells in the blood) helps us to create specific images which are applicable to clinical practice. We may also test your blood glucose and lipid levels. In the unlikely event of an abnormality we will, with your permission, inform your GP.

We may ask you to have an ECG, this is a heart tracing to measure the electrical impulses within the heart. It involves having 10 stickers applied to your chest for 5 minutes.

### **Risks and discomforts**

Magnetic Resonance Imaging (MRI) is safe and no x-rays or radiation are used for this scan. There are no known risks from this technique. Some people may experience claustrophobia. Our MRI staff will do all that they can to make you feel comfortable during the scan, and will be monitoring you via a video camera and an audio link. If we are unable to make you feel comfortable in the scanner, we will not go ahead with scanning. The contrast medication which we use is very safe but, as with any injection, reactions may occur. These include a warm sensation at the injection site, nausea or vomiting and transient skin rash. These effects usually only last for a few minutes. People with a history of allergy are more likely to suffer a more severe reaction, but this is rare (less than 1 in 3000). The department is equipped to cope with allergic reactions if they happen. Adenosine, the medication we use to

increase the blood flow to the heart, can cause flushing, breathlessness and chest discomfort. However, all of these feelings usually subside within one or two minutes or even more quickly if the medication is stopped. Immersing your hands or feet in cold water is unpleasant, but the effects wear off very quickly. Nitrates and a beta blocker can cause temporary light headedness. For this reason if these drugs are used you will be kept under observation until the effects have worn off.

### **Benefits to you**

This study does not form part of your normal clinical care and is done solely for research purposes. Your participation may however benefit future patients.

### **Expenses**

We will provide reasonable travel expenses should this be necessary for you to attend the MRI scan. We are also happy to arrange transport to the hospital and return you home if needs be.

### **Will my taking part be kept confidential?**

All information, which is collected about you during the course of the research will be kept strictly confidential. This information will be securely stored at the Cardiac MRI Unit at Leeds General Infirmary on paper and electronically, under the provisions of the 1998 Data Protection Act. You will not be identified in any publication that may result from this research.

We will inform your General Practitioner (GP) in the event of an unexpected abnormality on the scan.

With your permission, your data may also provide a resource for future studies. If any information from this study is used to develop new research, data protection regulations will be observed and strict confidentiality maintained. Ethical approval will be obtained for any future studies involving your data. You will not be identified in the results of any future studies.

### **What will happen to the results of the research study?**

When the study is complete the results will be published in a medical journal, but no individual patients will be identified. If you would like a copy of the published results, please ask your doctor.

### **Indemnity/Compensation**

If you are harmed as a direct result of taking part in this study, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds to a legal action. Regardless of this, if you have any cause to complain about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms are available to you.

### **The research organisation**

This is a research project of the Cardiac MRI department at Leeds General Infirmary.

### **For further information please contact:**

Petra Bijsterveld  
Research Nurse  
CMR Clinical Research Group  
X47, Sunshine Corridor

Leeds General Infirmary  
Leeds  
LS1 3EX  
T 0113 392 5481  
F 0113 392 5225  
M 07922 512 887  
Email [p.bijsterveld@leeds.ac.uk](mailto:p.bijsterveld@leeds.ac.uk)

I am interested in hearing more about this study

(study code: CE-MARC 2 physics - patients)

I give permission for a researcher to contact me by telephone to discuss the study further.

My phone number is.....

Name.....

Address.....

.....

Please return this slip to Petra Bijsterveld in the stamped addressed envelope provided.

Thank you.



## 9.2.2 Patient Information Leaflet Study 4

### CE-MARC 2

Clinical Evaluation of Magnetic Resonance imaging in Coronary heart disease.

### QUICK GUIDE

(v 4.0 June 12 2013)

- You are invited to take part in a research study, comparing different ways of investigating patients who have chest pain.
- The study is funded by the British Heart Foundation.
- If you consent to take part in the study you will be randomly assigned to be in one of three groups:

<b>Group 1</b>	<b>This group will be investigated with an MRI scan of the heart</b>
<b>Group 2</b>	<b>This group will be investigated with a SPECT scan of the heart</b>
<b>Group 3</b>	<b>This group will be investigated following national (NICE) guidelines and you will either have a CT scan, a SPECT scan or an X-Ray angiogram (depending on the likelihood of you having narrowings in your heart arteries).</b>

- The test you have will be reported and if it is abnormal you will have an X-Ray coronary angiogram (unless that was your 1<sup>st</sup> test anyway) with measurement of the blood flow in the heart arteries.
- All patients will be followed up and therefore members of the research team will have access to your records during and after study participation
- You will not benefit directly from taking part in the study
- You do not have to take part if you do not want to, in which case you would receive standard care instead.

**If you would like to read more the study is explained in detail in the information sheet which follows. The research team will also be happy to explain the study to you in person.**

## **CE-MARC 2**

### **Clinical Evaluation of Magnetic Resonance imaging in Coronary heart disease.**

#### **PATIENT INFORMATION SHEET**

**Version 4.0 June 12 2013**

Chief Investigator: Prof J Greenwood

#### **Dear Patient,**

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

#### **Purpose of the study**

We have several tests available to help us find out if chest pain is caused by narrowings of the heart arteries (coronary heart disease). Currently many patients in whom coronary artery disease is suspected, have an angiogram (=X-ray test taking pictures of the heart arteries). We know from other studies that some of these angiograms will show normal heart arteries. Before having an angiogram many patients have had another heart test, for instance a CT scan or a SPECT scan. Doctors are always looking to develop and improve tests that can reliably tell us if a patient needs an angiogram as their next test or not. Nowadays we can use Magnetic Resonance Imaging (MRI) to obtain pictures of the heart and see how well the heart is supplied with blood and oxygen. MRI is becoming an important test in patients who suffer with chest pain and coronary heart disease, and may eventually reduce the need for invasive tests such as coronary angiograms. Doctors have been doing research for many years to see how accurate MRI is compared to other heart tests. This study is part of that on-going research. In this study we will be using a magnet with a stronger magnetic field (called 3Tesla) than used in our previous CEMARC I study. This gives sharper pictures with even more detail.

#### **Why have I been chosen?**

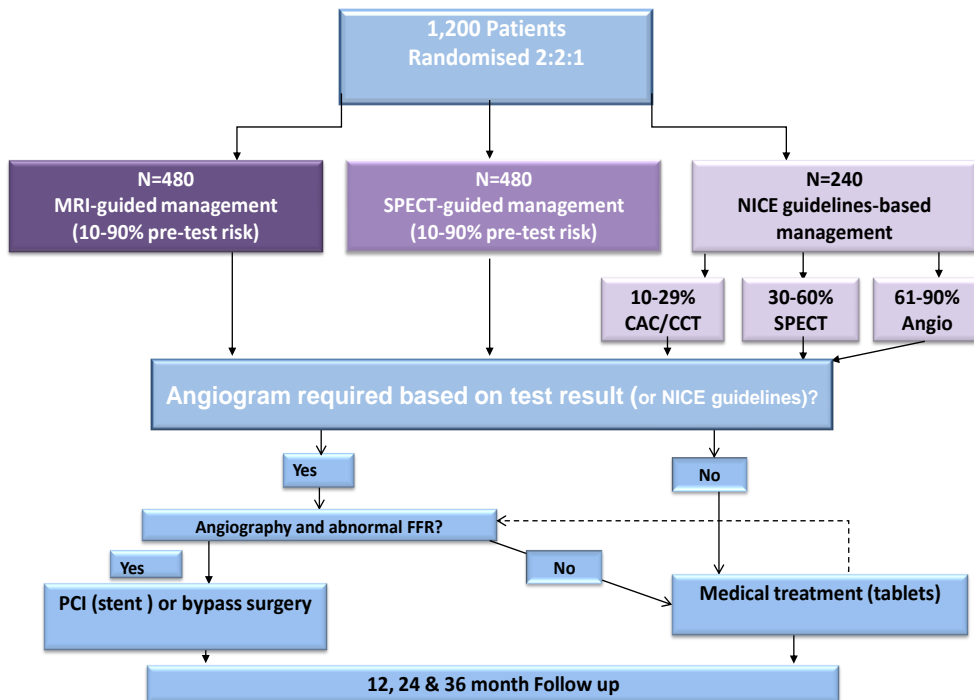
This study is looking at people like you, who have been referred to a cardiology clinic with chest pain. We will be asking 1200 people, in several UK hospitals, to take part in this study.

### Do I have to take part?

No. It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. This will not affect the standard of care that you receive from the NHS. If there is a possibility that you might be pregnant, you should not take part in the study. Our research team will be happy to discuss any other questions that you may have concerning your suitability for the study, before you decide whether to take part.

### What will happen to me if I take part?

If you take part in this study you will be assigned to one of three groups. We call one group 'MRI guided', the second group SPECT-guided, and the third group 'NICE guidelines based'. The choice will be made randomly, like tossing a coin. Neither you nor your doctor can influence what group you will be in. The groups will not be the same size: you have more chance of being in either the MRI or the SPECT group than of being in the NICE guidelines group. As the names suggest, your treatment in this study will be guided by the results of either the MRI scan, the SPECT scan, or one of the tests recommended by NICE (which also includes SPECT).



**1. MRI guided group:** (480 out of the 1200 patients will be in this group). If you are allocated to the MRI group you will have an **MRI scan** next. The scan will take approximately 60 minutes to complete. You lie in a short 'tunnel', which holds a large magnet. Short bursts of magnetic fields and radio waves from the MRI scanner allow images to be created. You will hear periodical loud "banging" noises while we are acquiring the images of your heart, though we do protect your ears with headphones. You can listen to the radio, or to one of your own CDs. We will remain in communication with you throughout the

scan. During the scan, we will inject an MRI contrast medication into a vein in your arm. At one point we will also inject a medication (Adenosine) into a vein in your other arm, which is a drug to increase the blood flow to your heart. This medication is used routinely in many heart tests. **What happens next:** The MRI scan will be reported by a consultant who is an expert in this area. If the test is normal your further treatment will be decided by your own cardiologist. If the test shows that there may be one or more narrowings in your heart arteries you will be offered a further test called an X-Ray coronary angiogram (see page 4).

**2. SPECT guided group:** (480 out of the 1200 patients will be in this group). If you are allocated to the SPECT group you will have a **SPECT scan** next. The SPECT perfusion study is carried out on two separate days and each visit takes approximately 2 hours. On one day pictures of the heart will be taken at rest, and on a second day after injection of a medication (Adenosine) to increase the blood flow to your heart. On both days you will also have an injection of a radioactive dye into the blood, which is taken up by the heart muscle. One hour after the injection, pictures of the heart are taken with a special camera that slowly moves around you while you lie on a bed with one arm raised above your head. Taking these pictures takes approximately 20 minutes. **What happens next:** The SPECT scan will be reported by a consultant who is an expert in this area. If the test is normal your further treatment will be decided by your own cardiologist. If the test shows that there may be one or more narrowings in your heart arteries you will be offered a further test called an X-Ray coronary angiogram (see page 4).

**3. NICE guidelines group:** (240 out of the 1200 patients will be in this group). If you are allocated to the NICE guidelines group you will have the heart test recommended by these guidelines, published by NICE, the National Institute for Health and Clinical Excellence, in 2010. This will be one of the following: a CT calcium score (followed by a CT coronary angiogram if required), a SPECT scan, or an X-Ray coronary angiogram. Which test you are offered depends on how likely it is that you have narrowings of the heart arteries. We can calculate this from your medical history and you will fall into either a low, intermediate, or high likelihood group.

**a. For patients with a low likelihood:**

**CT calcium score:** CT stands for 'computerised tomography' and is a sophisticated type of X-ray. You will lie on a bed under a scanner and will be asked to hold your breath briefly for the scan to be performed. This scan will let us see how much calcium there is in your heart arteries. If there is very little then the scan will be stopped at that point and you will have no further tests. If there is a lot of calcium the scan will also be stopped and you will be offered an X-Ray coronary angiogram (see below). If there is a moderate amount of calcium we will continue to see whether there are any narrowings, this is called a **CT coronary angiogram**. For this you will receive an injection of a contrast dye into a vein in your arm. You may also receive an injection of a medicine (a beta-blocker) to slow your heart rate down a little bit. This can help reduce the time you will need to hold your breath for.

**b. For patients with an intermediate likelihood:**

**SPECT scan:** this is the same scan as the patients in the SPECT guided group have, and is described on page 3. If the test shows that there may be one or more narrowings in your heart arteries you will be offered a further test called an X-Ray coronary angiogram (see below).

**c. For patients with a high likelihood:**

**X-Ray Coronary angiography:** This test requires you to come into hospital for one day. With a coronary angiogram we take X-ray pictures of the heart arteries. You will be taken to an X-ray room and asked to lie down on a bed. After cleaning the skin, local anaesthetic is given and a needle put into the artery in the wrist or occasionally the groin. A fine, hollow tube called a “catheter” is then introduced into the artery and is gently advanced through the blood vessels to the heart. You will not feel the catheter being moved around inside your chest. A dye is then injected into the heart blood vessels and X-rays taken from several angles. A narrowing or a blockage may be seen which would confirm the diagnosis of coronary artery disease. To assess the importance of a narrowing in a heart artery a **pressure wire** will be used. This technique is increasingly used during a coronary angiogram to guide further treatment. This is a very small wire inserted through the catheter into the vessel of the heart to measure the blood flow. It also involves the injection of Adenosine to improve blood flow to the heart. When the test is over, the catheter is removed and simple pressure is applied to the wrist (or groin).

After the angiogram the doctor carrying out the test will discuss the findings with you, and the options for treatment if any narrowings were found. Any treatment you receive is not part of the study and will be carried out following current best practice. If you do need an angiogram for any reason within a year of joining the study we will do the pressure wire test on narrowings seen in your heart arteries.

**Health Questionnaires**

If you agree to participate in this study, you will be asked to complete three simple health questionnaires when you join the study, after six months, and then once a year for three years.

**Follow-up:** As part of the study we would like to see how you are getting on once a year for three years. We may telephone you to ask you some simple questions about your health. With your permission we may also look at your hospital records, request access to your GP records, central NHS records and/or use information from The Health and Social Care Information Centre.

It is very helpful if we can continue to track your health condition over a long term period. The Health and Social Care Information Centre (HSCIC) allows us to access health information about you with your permission. In order to this we are seeking your permission to provide HSCIC with some of your personal details (including your name, date of birth, address and NHS number) and with this information HSCIC will be able to provide us with simple health information about you beyond the 3 year follow up period of this study, for a period of up to 20 years. It is very important to understand the long term health condition of patients to find out if the treatments we are giving are effective. Information will be provided to HSCIC in strict confidence and will be kept securely by them and will not be released to a third party.

**What are the possible disadvantages and risks of taking part?** It is important to remember that if you were not in the study you would be having one of these tests anyway.

**MRI scan:** Magnetic Resonance Imaging (MRI) at 3Tesla is safe and no radiation is used for this scan. There are no known risks from the technique. Some people may experience

claustrophobia. Our MRI staff will do all that they can to make you feel comfortable during the scan, and will be monitoring you via a video camera and an audio link. If we are unable to make you feel comfortable in the scanner, we will not go ahead with scanning. We will need to insert two small tubes (cannulae) into your arms for the contrast dye and the adenosine medication. The contrast medication we use during the scan is very safe but, as with any injection, reactions may occur. These include a warm sensation at the injection site, nausea or vomiting and transient skin rash. These effects usually only last for a few minutes. People with a history of allergy are more likely to suffer a more severe reaction, but this is rare (less than 1 in 3000). The department is equipped to cope with allergic reactions if they happen. Adenosine, the medication we use to increase the blood flow to the heart, can cause flushing, breathlessness and chest discomfort. However, all of these feelings usually subside within one or two minutes or even more quickly when the medication is stopped.

**SPECT scan:** SPECT imaging is very safe but exposes patients to a small amount of radiation. The dose is equivalent to receiving approximately 3 years of natural background radiation in the UK. We will need to insert one small tube (cannula) into your arm for the contrast dye and the adenosine medication. Adenosine, the medication we use to increase the blood flow to the heart, can cause flushing, breathlessness and chest discomfort. However, all of these feelings usually subside within one or two minutes after the medication is stopped.

**CT coronary angiogram:** CT imaging is very safe but exposes patients to a small amount of radiation. The dose of a CT calcium score only scan is equivalent to receiving approximately 6 months to 1 year of natural background radiation in the UK. The dose of a CT angiogram is equivalent to receiving approximately 3 years of natural background radiation in the UK. We will need to insert one small tube (cannula) into your arm for the contrast dye. The contrast medication we use during the scan is very safe but, as with any injection, reactions may occur. The department is equipped to cope with allergic reactions if they happen. You may also be given a medication (by mouth or into a vein) to slow your heart rate down a little, this is called a beta-blocker. If this is the case you will usually be kept under observation until the after effects of any possible light headedness have worn off, which is usually for about half an hour.

**X-Ray Coronary angiography and pressure wire:**

At present most patients with chest pain or other symptoms consistent with coronary artery disease will have an angiogram at some point. The advantage of an angiogram is that it can look inside the arteries. However this also means that it is invasive and bears some risks. The most common complication of the X-ray angiogram is for a bruise to form on the wrist or in the groin. This is not serious, but may be inconvenient for a few days. Allergic reactions to the iodine based dye are rare and the department is equipped to cope with reactions. Other serious complications are very rare, but the test can cause a heart attack, stroke or kidney damage. This is estimated at about 1 or 2 in every 1000 people. However the level of risk depends on your overall health and your individual heart condition. A pressure wire test is safe, but as a wire is passed down the coronary artery a small risk of damage to the blood vessel wall or heart muscle is added.

The amount of radiation you are exposed to during a coronary angiogram is approximately equivalent to the radiation you are exposed over the course of 3 years from the natural environment.

**What are the alternatives?**

If you do not wish to take part in the study you will have the heart test your cardiologist chooses for you.

### **Benefits to you**

We cannot promise the study will directly benefit you, but the information we get from this study might help the treatment of future patients. If you take part in a study you will have more contact with us, and have more opportunities to ask questions and be informed about your health, which some patients find helpful.

### **Expenses**

You will not be asked to undergo any extra tests as a result of taking part in this study, so you will incur no extra expenses.

### **Will my taking part be kept confidential?**

All information collected about you during the course of the study will be kept strictly confidential. This information will be securely stored, electronically on Leeds Teaching Hospitals NHS Trust and University of Leeds secure servers, and on paper, under the provisions of the 1998 Data Protection Act. Images (scans) and data, after your personal details have been removed, may be sent to participating study centres, or to an independent laboratory, for analysis. Your data, including personal data such as your name, address and NHS number will be sent to the Clinical Trials Research Unit at the University of Leeds. The data collected will be coded and your personal details will be kept entirely separately from details about your health and treatment. You will not be identified in any publication that may result from this research.

We may contact the Health and Social Care Information Centre or other central NHS UK bodies at a later stage for information which they hold on your health status. This means some of your personal data will be shared with the Health and Social Care Information Centre. Any information exchanged between us Health and Social Care Information Centre will be subject to strict data protection regulations.

With your permission, your data may also provide a resource for future studies. If any information from this study is used to develop new research, data protection regulations will be observed and strict confidentiality maintained. Any information about you which leaves the hospital will have your name and address removed so that you cannot be identified. Your data and or images may be sent to institutions in the UK, the European Economic Area or outside the EEA. Ethical approval will be obtained for any future studies involving your data. With your consent we may also wish to contact you in future about new studies you may wish to participate in. We will never give your personal details to any researchers outside of our department.

If you withdraw consent from further study follow-up, or if you were to become incapacitated, any data collected about you up to that point will remain on file and will be included in the final study analysis.

### **What will happen to the results of the research study?**

When the study is complete the results will be published in a medical journal, but no

individual patients will be identified. If you would like a copy of the published results, please ask your doctor.

### **Indemnity/Compensation**

If you are harmed as a direct result of taking part in this study, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds to a legal action. Regardless of this, if you have any cause to complain about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms are available to you.

### **The research organisation**

This is a research project of the Cardiac MRI department at the University of Leeds and the Leeds Teaching Hospitals NHS Trust, in collaboration with the Clinical Trials Research Unit at the University of Leeds. It is being funded by the British Heart Foundation.

### **Who has reviewed the study?**

The study has been reviewed and approved both by the South Yorkshire Research Ethics Committee and by your hospital trust's Research and Development Office. More details can be provided, on request, by your study doctor.

### **For further information please contact:**

Dr David Ripley, CMR Research Fellow                      or

Cardiac MRI Department

B Floor Clarendon Wing

Leeds General Infirmary

LS1 3EX

[d.ripley@leeds.ac.uk](mailto:d.ripley@leeds.ac.uk)

Petra Bijsterveld

Research Nurse

Cardiovascular Research

Sunshine Corridor

Leeds General Infirmary

LS1 3EX

Tel: 0113 392 5481 / 0113  
392 6286

Mob: 07922 512 887

[p.bijsterveld@leeds.ac.uk](mailto:p.bijsterveld@leeds.ac.uk)



### 9.3 Appendix 3

#### 9.3.1 Consent Form for Study 1& 2

#### CONSENT FORM – Version 2.1 December 2005

### **CE-MARC Study** **Clinical Evaluation of Magnetic Resonance imaging in Coronary heart disease**

Patient Study Number: .....

Date of Birth: .....

Hospital Number: .....

Initials: .....

*Please initial boxes*

1. I have read the Patient Information Sheet dated December 2005 (Version 2.1) for the above study and I have had the opportunity to ask questions and discuss the research study and I am satisfied with the answers to my questions.
2. I have received enough information about this study.
3. I understand that my participation is voluntary and that I am free to withdraw from the study at any time without giving a reason and without affecting my future care.
4. I understand that my medical records may be looked at by authorised individuals from the Clinical Trials Research Unit in order to check that the study is being carried out correctly.
5. I understand that information held by the NHS and records maintained by the Office of National Statistics (ONS) may be used to follow up my health status, should I lose contact with my hospital doctor. I give permission for this information to be obtained from the ONS and/or NHS if necessary.
6. I agree that my medical data maybe used to help develop future research studies and I understand that my identity will remain anonymous.
7. I understand that my samples may be used in future research projects which may involve collaborations with commercial companies and I understand that I will not benefit financially if the research leads to the development of a new test or treatment.
8. I agree to take part in this research study.

Signature.....

Name (block capitals)..... Date.....

Signature of witness.....

Name (block capitals).....Date.....

### 9.3.2 Consent Form for Study 3

CONSENT FORM v 1.3 16 February 2017

#### **CE-MARC 2: Optimization of acquisition and analysis methods (healthy volunteers).**

**Chief Investigator: Professor John Greenwood**

Patient Number: .....

Date of Birth: .....

Name .....

*Please initial boxes*

1. I have read the Volunteer Information Sheet dated 16 February 2017 (Version 1.3) for the above study and I have had the opportunity to ask questions and discuss the research study and I am satisfied with the answers to my questions  
.
2. I have received enough information about this study.
3. I understand that my participation is voluntary and that I am free to withdraw from the study at any time without giving a reason.
4. I give my consent for my General Practitioner to be informed in the event of any abnormality being discovered.
5. I understand that images collected will be stored on a computer system, and, after my personal details have been removed, may be available to researchers at other institutions.
6. I understand that some of the blood samples taken from me may be stored and may be analyzed in the future for markers related to heart disease
7. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from the University of Leeds, from regulatory authorities, or from the Leeds Teaching Hospitals NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.
8. If I were to lose capacity, I understand that data already collected will be kept and used for the purposes of the study.

9. I agree to take part in this research study and that the general results of the study will be made available to the medical community most likely through publication in a reputable medical journal.

Signature.....

Name (block capitals)..... Date.....

Signature of researcher.....

Name (block capitals).....Date.....

### 9.3.1 Consent Form for Study 4

CONSENT FORM v 4.0 June 12 2013

#### CE-MARC 2

Clinical Evaluation of MAgnetic Resonance imaging in Coronary heart disease.

CI: Prof John Greenwood

Patient Study Number: .....

Patient Initials.....

NHS number: .....

Date of Birth: .....

Please initial boxes

1. I have read the Patient Information Sheet dated June 12 2013 (version 4.0) for the above study and I have had the opportunity to ask questions and discuss the research study and I am satisfied with the answers to my questions.

2. I understand that my participation is voluntary and that I am free to withdraw from the study at any time without giving a reason.

3. I give my consent for my General Practitioner to be informed, and I understand that my cardiologist will be informed only if we find any abnormality over and above what is already known.

4. I understand that data and images collected will be stored on a computer system, and, after my personal details have been removed, may be sent to participating study centres or to an independent laboratory, and may be available to researchers at other institutions in the UK, the EEA, and countries outside the EEA.

5. I understand that relevant sections of my medical notes and data collected during the study (including personal data) may be looked at by individuals from the University of Leeds, the Clinical Trials Research Unit, from regulatory authorities, or from the Leeds Teaching Hospitals NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.

- 6. I understand that information held by the NHS, by my General Practitioner, and information held and managed by the Health and Social Care Information Centre and other central UK NHS bodies, may be used to contact me and provide information about my health status. I give permission for this information to be obtained from The Health and Social Care Information Centre, the NHS Central Register and/or my GP if necessary. To do this, I understand that my details (including my name, address, NHS number and date of birth) will be shared with The Health and Social Care Information Centre.
  
- 7. If I were to lose capacity or withdraw consent for further follow-up I understand that data already collected will be kept and used for the purposes of the study.
  
- 8. I agree to take part in this research study and that the general results of the study will be made available to the medical community most likely through publication in a reputable medical journal.
  
- 9. I am willing to be contacted again in the future with regard to potentially taking part (without any obligation) in further related research studies.
  
- 10. I agree to a copy of this consent form being sent to the Clinical Trials Research Unit.

Signature.....

Name (block capitals)..... Date.....

Signature of researcher.....

Name (block capitals).....Date.....