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A national registry to assess the value of cardiovascular magnetic resonance imaging after primary percutaneous coronary intervention pathway activation: a feasibility cohort study

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Abstract

A national registry to assess the value of cardiovascular magnetic resonance imaging after primary percutaneous coronary intervention pathway activation: a feasibility cohort study

Jessica M Harris,[1] Rachel C Brierley,[1] Maria Pufulete,[1] Chiara Bucciarelli-Ducci,[2] Elizabeth A Stokes,[3] John P Greenwood,[4] Stephen H Dorman,[2] Richard A Anderson,[5] Chris A Rogers,[1] Sarah Wordsworth,[3] Sunita Berry[6] and Barnaby C Reeves[1]*

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Background: Cardiovascular magnetic resonance (CMR) is increasingly used in patients who activate the primary percutaneous coronary intervention (PPCI) pathway to assess heart function. It is uncertain whether having CMR influences patient management or the risk of major adverse cardiovascular events in these patients.

Objective: To determine whether or not it is feasible to set up a national registry, linking routinely collected data from hospital information systems (HISs), to investigate the role of CMR in patients who activate the PPCI pathway.

Design: A feasibility prospective cohort study.

Setting: Four 24/7 PPCI hospitals in England and Wales (two with and two without a dedicated CMR facility).

Participants: Patients who activated the PPCI pathway and underwent an emergency coronary angiogram.

Interventions: CMR either performed or not performed within 10 weeks of the index event.

Main outcome measures: A. Feasibility parameters – (1) patient consent implemented at all hospitals, (2) data extracted from more than one HIS and successfully linked for > 90% of consented patients at all four hospitals, (3) HIS data successfully linked with Hospital Episode Statistics (HES) and Patient Episode Database Wales (PEDW) for > 90% of consented patients at all four hospitals and (4) CMR requested and carried out for ≥ 10% of patients activating the PPCI pathway in CMR hospitals. B. Key drivers of cost-effectiveness for CMR (identified from simple cost-effectiveness models) in patients with (1) multivessel disease and (2) unobstructed coronary arteries. C. A change in clinical management arising from having

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CMR (defined using formal consensus and identified using HES follow-up data in the 12 months after the index event).

Results: A. (1) Consent was implemented (for all hospitals, consent rates were 59–74%) and 1670 participants were recruited. (2) Data submission was variable – clinical data available for ≥ 82% of patients across all hospitals, biochemistry and echocardiography (ECHO) data available for ≥ 98%, 34% and 87% of patients in three hospitals and medications data available for 97% of patients in one hospital. (3) HIS data were linked with hospital episode data for 99% of all consented patients. (4) At the two CMR hospitals, 14% and 20% of patients received CMR. B. In both (1) multivessel disease and (2) unobstructed coronary arteries, the difference in quality-adjusted life-years (QALYs) between CMR and no CMR ['current' comparator, stress ECHO and standard ECHO, respectively] was very small [0.0012, 95% confidence interval (CI) –0.0076 to 0.0093 and 0.0005, 95% CI –0.0050 to 0.0077, respectively]. The diagnostic accuracy of the ischaemia tests was the key driver of cost-effectiveness in sensitivity analyses for both patient subgroups. C. There was consensus that CMR leads to clinically important changes in management in five patient subgroups. Some changes in management were successfully identified in hospital episode data (e.g. new diagnoses/procedures, frequency of outpatient episodes related to cardiac events), others were not (e.g. changes in medications, new diagnostic tests).

Conclusions: A national registry is not currently feasible. Patients were consented successfully but conventional consent could not be implemented nationally. Linking HIS and hospital episode data was feasible but HIS data were not uniformly available. It is feasible to identify some, but not all, changes in management in the five patient subgroups using hospital episode data. The delay in obtaining hospital episode data influenced the relevance of some of our study objectives.

Future work: To test the feasibility of conducting the study using national data sets (e.g. HES, British Cardiovascular Intervention Society audit database, Diagnostic Imaging Dataset, Clinical Practice Research Datalink).

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List of abbreviations

ACS	acute coronary syndrome
A&E	accident and emergency
ARVC	arrhythmogenic right ventricular cardiomyopathy
BCIS	British Cardiovascular Intervention Society
CABG	coronary artery bypass graft
CCAD	Central Cardiac Audit Database
CI	confidence interval
CMR	cardiovascular magnetic resonance
CPRD	Clinical Practice Research Datalink
CRIS	clinical radiology information system
CRT	cardiac resynchronisation therapy
CT	computed tomography
DID	Diagnostic Imaging Dataset
ECHO	echocardiography
EF	ejection fraction
EQ-5D	EuroQol-5 Dimensions
FFR	fractional flow reserve
GP	general practitioner
HCM	hypertrophic cardiomyopathy
HES	Hospital Episode Statistics
HIS	hospital information system
ICD	implantable cardioverter defibrillator
ICD-10	*International Classification of Diseases*, Tenth Edition
ICE	Integrated Clinical Environment
ICER	incremental cost-effectiveness ratio
IMD	Index of Multiple Deprivation
IQR	interquartile range
IS	infarct size
IT	information technology
IVUS	intravascular ultrasound
LGE	late gadolinium enhancement
LV	left ventricular
MACE	major adverse cardiovascular event
MeSH	medical subject headings
MI	myocardial infarction
MINAP	Myocardial Ischaemia National Audit Project
MVO	microvascular obstruction
NAPCI	National Audit of Percutaneous Coronary Intervention
NICOR	National Institute for Cardiovascular Outcomes Research
NSTEMI	non-ST elevation myocardial infarction
NWIS	NHS Wales Information Service
OHCA	out-of-hospital cardiac arrest
ONS	Office for National Statistics
OPCS	Office of Population Censuses and Surveys
OR	odds ratio
PAS	Patient Administration System
PCI	percutaneous coronary intervention
PEDW	Patient Episode Database Wales
PET	positron emission tomography
PIPA	Primary percutaneous coronary Intervention Pathway Activation
PPCI	primary percutaneous coronary intervention
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year
RCT	randomised controlled trial

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SD	standard deviation	SSC	Study Steering Committee
SE	standard error	STEMI	ST-elevation myocardial infarction
SMD	standardised mean difference	VSD	ventricular septal defect
SPECT	single-photon emission computed tomography	WIMD	Welsh Index of Multiple Deprivation

Plain English summary

Cardiovascular magnetic resonance (CMR) is a non-invasive test that can be used to assess damage to the heart and help guide treatment in people who have had a suspected heart attack. CMR is expensive (≈£300), so it is important to know whether or not it benefits patients or the NHS.

This study had two aims. The first was to find out whether or not it is feasible to create a database of patients who had a suspected heart attack by bringing together information collected routinely during patients' hospital care. The second was to determine the ways in which CMR changes treatment. A registry database could be used to test whether or not patients who undergo CMR do better than those who do not undergo CMR.

Attempts were made to identify all eligible individuals at four hospitals, obtain their consent to participate, collect information from the hospital where they were treated, including whether or not they had CMR, and combine this with other information collected routinely during patients' hospital care over the following year.

A group of experts discussed and agreed in whom, and in what ways, CMR can influence treatment. Some of these treatments could be identified in the data about participants' care in the year after their heart attack. However, most hospitals were unable to provide all the information requested about the suspected heart attack. Using conventional ways of recruiting participants, it was not possible to invite many patients who would have been eligible. Therefore, it is not currently feasible to establish the database.

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Scientific summary

Background

Cardiovascular magnetic resonance (CMR) is a non-invasive imaging technique that assesses heart structure and function with high spatial and temporal resolution. The use of CMR has increased in all subgroups of acute coronary syndrome (ACS) patients, including those who activate the primary percutaneous coronary intervention (PPCI) pathway. It is unknown if undergoing CMR influences patient management or reduces the length of hospital stay or the risk of major adverse cardiovascular events (MACEs) in these patients.

Objectives

- To determine whether or not it is feasible to set up a national registry linking routinely collected data from hospital information systems (HISs) for the index event (emergency angiography with or without PPCI) with hospital episode data [from Hospital Episode Statistics (HES) and Patient Episode Database Wales (PEDW), which collects equivalent information for the NHS Wales hospitals] and death registration data [from the Office for National Statistics (ONS)] for follow-up in the 12 months after the index event, in order to investigate the role of CMR in patients who activate the PPCI pathway.
- To describe resource use and associated costs of having CMR and to identify key drivers of cost-effectiveness for CMR.
- To identify an outcome measure representing a definitive change in clinical management, conditional on having undergone CMR, that would be credible to cardiologists and other stakeholders as an interim measure of the 'value added' by doing CMR.

Design

The study included three components to address the objectives listed in the preceding section:

1. Feasibility prospective cohort study – we established if we could implement patient consent, extract data about the index event from multiple HISs and link these data with hospital episode data for follow-up. We also quantified the proportion of patients who undergo CMR. We explored whether or not the cohort study could be set up using only hospital episode data.
2. Simple cost-effectiveness models – we developed economic decision models in two subgroups of patients who activate the PPCI pathway: (1) patients with multivessel disease and (2) patients with unobstructed coronary arteries. These subgroups were identified in the protocol (before commencing work on the study) as having the potential to benefit from CMR.
3. Formal consensus study – we defined important changes in management resulting from CMR and subgroups of patients to whom these changes relate. Potential changes in management were described from literature review and cardiologist expert opinion and were reviewed by a consensus panel and additional cardiologists (from across the UK). We determined whether or not changes in management defined as being important by formal consensus could be identified in hospital episode data in the 12 months following the index event, with the intention to formulate an 'interim' outcome measure representing a definitive change in clinical management that could be used for a future registry.

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Setting

- Feasibility prospective cohort study: four 24/7 PPCI hospitals in England and Wales (two with and two without a dedicated CMR facility, both representing usual care in the NHS).
- Cost-effectiveness models: usual care (with or without CMR) in the NHS.
- Formal consensus study: secondary care (cardiology departments) across the UK.

Study population

Feasibility prospective cohort study

This comprised patients who activated the PPCI pathway and underwent an emergency coronary angiogram whether or not they received PPCI. We included patients if they were aged ≥ 18 years and underwent an emergency angiogram, defined as taking place within 2 hours of arrival at the hospital, unless specified otherwise by local protocols. We excluded patients if they were prisoners or lacked mental capacity to consent.

Cost-effectiveness models

- Model 1 (multivessel disease): patients who activate the PPCI pathway, have their index angiography and PPCI and are identified as having multivessel disease (commonly defined as stenosis of > 50% from the angiogram) in two or more coronary arteries.
- Model 2 (unobstructed coronary arteries): patients who activated the PPCI pathway, had their index angiography and were found to have unobstructed coronary arteries.

Formal consensus study

This comprised consultant cardiologists with CMR, interventional, echocardiography (ECHO), electrophysiology and heart failure expertise from across the UK.

Intervention(s)

Feasibility prospective cohort study

Cardiovascular magnetic resonance performed/not performed within 10 weeks of the index event (whether during the index admission or subsequently as an outpatient). All patients were assumed to receive standard ECHO as part of usual care.

Cost-effectiveness models

- Model 1 (multivessel disease): three different ischaemia testing methods; CMR versus stress ECHO versus pressure wire.
- Model 2 (unobstructed coronary arteries): CMR and standard ECHO versus standard ECHO alone.

Formal consensus study

For each statement, CMR was considered alongside standard or stress ECHO as appropriate.

Main outcome measures

Feasibility prospective cohort study

- Patient consent implemented at all four hospitals.
- Data linkage and extraction from multiple local HISs achieved for > 90% of consented patients at all four hospitals.
- Local data successfully linked with hospital episode data for > 90% of consented patients at all four hospitals.

- CMR requested and carried out for ≥ 10% of patients activating the PPCI pathway in CMR hospitals.
- Whether or not the registry could be compiled from hospital episode data rather than from multiple HISs.

Cost-effectiveness model

The main outcomes were key drivers of cost-effectiveness for CMR in patients with (1) multivessel disease (model 1) and (2) unobstructed coronary arteries (model 2).

Formal consensus study

- Identification, through formal consensus, of the important changes in management resulting from CMR and the subgroups of patients to whom these changes relate.
- Identification of relevant subgroups of patients in the data sets obtained (local HISs and follow-up hospital episode data).
- Ascertainment of the consequences of important changes in management from hospital episode data.

Data sources

Feasibility prospective cohort study

- Index procedure: local HIS at each participating hospital –
    - basic demography [local Patient Administration System (PAS)/British Cardiovascular Intervention Society – Central Cardiac Audit Database (BCIS-CCAD)]
    - clinical characteristics on presentation at the index admission, peri- and post-procedural (PPCI) characteristics (local catheter laboratory database/BCIS-CCAD)
    - ECHO and CMR reports (local imaging databases)
    - biochemistry (local biochemistry databases)
    - medications on discharge (one hospital only).
- Follow-up: hospital episode data. We requested inpatient, outpatient, accident and emergency and critical care data sets.

Cost-effectiveness models

Data were sourced from a literature review for model parameter estimates and *NHS Reference Costs* (Department of Health and Social Care. *NHS Reference Costs 2015 to 2016*. London: Department of Health and Social Care; 2016) for unit costs.

Formal consensus study

For the formal consensus study, data were sourced from a literature review and cardiologist expert opinion. In-hospital data were sourced from local HIS data and follow-up data were sourced from HES data.

Results

Feasibility prospective cohort study

- Consent using conventional methods was successfully implemented (across all hospitals, consent rates were 59–74%); 2462 patients were screened (May 2013–September 2014) but only 1670 participants (68%) were recruited.
- Hospitals submitted varying numbers of requested data: clinical data (for ≥ 82% of patients across all hospitals), biochemistry data (three hospitals, for ≥ 98% of patients), ECHO data (three hospitals, for 34–87% of patients) and medications data (for 97% of patients in one hospital). Imaging data (ECHO and CMR data from one hospital) were submitted as free-text reports extracted from radiology databases.

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- HIS data were linked with hospital episode data for 99% of all consented patients. We identified an admission that matched the index admission within ± 1 day for 93% and 97% of consented patients.
- At the two CMR hospitals, 14% and 20% of patients received CMR.
- We identified 98% of patients who underwent PPCI and 85% of patients who had an emergency angiogram but no PCI in hospital episode data. We could identify CMR exposure in hospital episode data for only 29% (55/189) of patients who had a CMR in our cohort.

Cost-effectiveness models

- In both model 1 (multivessel disease) and model 2 (unobstructed coronary arteries), the difference in quality-adjusted life-years (QALYs) between CMR and no CMR was very small (0.0012, 95% CI –0.0076 to 0.0093 and 0.0005, 95% CI –0.0050 and 0.0077, respectively) (the 'current' comparator for model 1 is stress ECHO; the 'current' comparator for model 2 is standard ECHO). The diagnostic accuracy of the ischaemia tests was the key driver of cost-effectiveness in sensitivity analyses for both model 1 and model 2.

Formal consensus study

- There was consensus that CMR leads to clinically important changes in management in five patient subgroups, namely those with: (1) out-of-hospital cardiac arrest, (2) unobstructed coronary arteries, (3) left ventricular (LV) thrombus, (4) multivessel disease and (5) PPCI with CMR markers indicating poor prognosis.
- Patients with unobstructed arteries and PPCI patients could be identified from both the local HIS data set and hospital episode data. Patients with an out-of-hospital cardiac arrest and PPCI patients who developed a LV thrombus could not be identified from the local HIS data set, but could be identified in hospital episode data. Patients with multivessel disease could be identified only from the local HIS data set, not from hospital episode data.
- We identified the following changes in management in hospital episode data: new diagnoses and procedures (those that resulted in hospital admission and were recorded in outpatient visits) and the frequency of outpatient appointments related to cardiac events. We could not identify changes in medications because there were no medication data in the hospital episode data.

Limitations

Feasibility prospective cohort study

We could not identify all eligible patients from local HISs. The conventional consent model failed to capture a sizeable proportion of the eligible population, but we could not identify and test a more efficient model of obtaining consent. The study population did not include patients presenting with a broader diagnosis of ACS but not requiring emergency coronary angiography (e.g. those with non-ST elevation myocardial infarction), who may also benefit from CMR.

The study took longer than anticipated to complete after the end of recruitment because our application for hospital episode data coincided with the moratorium on all data requests imposed by NHS Digital (formerly known as the Health and Social Care Information Centre). During this time, data availability/quality is likely to have changed/improved given the rapidly evolving NHS information technology (IT) systems/platforms. New diagnostic tests for detecting ischaemia (e.g. pressure wire), directly competing with CMR, were also introduced during the time frame of the study and were rapidly adopted by many cardiologists. These changes to usual care weakened the importance of the research question that we described at the outset – the comparison of CMR versus standard ECHO/stress ECHO (usual care at the start of the study) – but highlighted the importance of different research questions.

Cost-effectiveness models

There is uncertainty around the majority of parameter estimates in both models. Many estimates were based on single studies with small sample sizes. Some of these studies were conducted outside the UK, where patient pathways differ. In the base-case analyses, CMR and pressure wire were treated as reference standards and both were assumed to have 100% sensitivity and specificity. This assumption may not be true and, if not, this will influence findings because the diagnostic accuracy of the ischaemia tests was found to be the key driver of cost-effectiveness.

Individual patient data on resource use from hospital episode data were not available in time to be used in the cost-effectiveness analyses. Therefore, we estimated resource use associated with each of the patient pathways, so, although the standard care pathways have been costed, it is likely that we have underestimated the variability between individual patients and their actual patient pathways. Finally, there was also uncertainty about the utility estimates used in the cost-effectiveness models because we did not find good-quality primary data.

Formal consensus study

The number of panel members in our expert panel was lower than the recommended 8–12 members for a consensus panel. We extended the survey to other UK cardiologists to compensate for this and prevent the possibility of introducing bias (given the self-selected nature of the panel). We did not include different stakeholder groups in the consensus panel because the technical wording of the statements would not have been easily understood by non-cardiologists. Therefore, we cannot be certain that the changes in management that were identified are relevant to other stakeholders (e.g. commissioners and patients).

Conclusions

Feasibility prospective cohort study

We did not identify all patients who were eligible for the study; for example, patients with unobstructed arteries (i.e. those who had an emergency angiogram but did not receive PPCI) were difficult to identify from catheter laboratory databases. We successfully consented patients but obtaining individual, opt-in consent would not be feasible for a national registry. We explored several consent models (i.e. opt out on procedural consent form, standard consent at discharge) but none was implemented because of logistic difficulties. Linkage of data from HIS with hospital episode data was feasible, but data from HIS are not uniformly available/exportable. Information about whether or not participants had had CMR in CMR hospitals was successfully obtained from HIS, although some referrals for CMR were for research rather than clinical purposes. It is feasible to identify important changes in management in the five patient subgroups in hospital episode data.

Cost-effectiveness models

For each of the base-case models, the differences in QALYs between strategies were very small; therefore, the results were largely driven by the differences in costs, although these were also modest. Sensitivity analyses around the two models identified the diagnostic accuracy of the ischaemia tests as the key driver of cost-effectiveness.

Formal consensus study

We defined five subgroups of patients who activate the PPCI pathway for whom there was consensus that CMR changes patient management in a clinically important way. All subgroups could be identified in either the local HIS data set, hospital episode data or both. Some, but not all, important changes in management could be identified in follow-up HES/PEDW data. The main constraints on identifying important changes in management were (1) outpatient hospital episode data were poorly coded with respect to the diagnosis, (2) medication data were not available at baseline or follow-up (preventing inspection of/prescription of changes in medication after the index event) and (3) data about diagnostic investigations were poorly coded in both acute care and outpatient data sets.

Future work

- Identify/test a more efficient method of obtaining consent.
- Some limitations of our study are now historic and others are being addressed. Therefore, it is recommended to test the feasibility of conducting the study using national data sets [HES/BCIS/Diagnostic Imaging Dataset (DID), Clinical Practice Research Datalink (CPRD) for medications], which are likely to be able to capture all of the eligible population, without the need for individual patient consent; MACEs could be used as the outcome.
- Cost-effectiveness models suggest that it is important for the NHS to have a definitive answer about the relative diagnostic accuracy of CMR versus pressure wire, despite the fact that the pressure wire is rapidly superseding CMR across catheter laboratories.
- A feasible registry is a goal worth pursuing, offering a test bed for the rapid evaluation of changes in practice in this expensive and fast-moving area of clinical care (often driven by commercial interest).

Funding

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Chapter 1 Introduction

Background and rationale

Cardiovascular magnetic resonance (CMR) is a non-invasive imaging technique that assesses heart structure and function with high spatial and temporal resolution. The use of CMR has increased in recent years in all subgroups of acute coronary syndrome (ACS) patients, including those who activate the primary percutaneous coronary intervention (PPCI) pathway.[1] It is not clear whether or not having CMR influences patient management or reduces the length of hospital stay or the risk of major adverse cardiovascular events (MACEs) in these patients. Systematic reviews from 2014 highlighted the lack of high-quality, adequately powered studies to establish the prognostic value of CMR findings in patients who activate the PPCI pathway.[2,3] Similarly, few studies have assessed how CMR changes patient management, despite the fact that cardiologists believe that CMR brings about important changes in management.[4]

Primary percutaneous coronary intervention

Primary percutaneous coronary intervention is the primary therapeutic approach for restoring blood flow to the heart in ACS patients who have had a ST-elevation myocardial infarction (STEMI). Currently, across the UK ≈97% of patients with a STEMI who received any reperfusion treatment were treated with PPCI.[5] Management of the in-hospital stay and follow-up after PPCI is determined by the final infarct size, the presence or absence of comorbidities and patient characteristics. About 10% of patients with ACS who activate the PPCI pathway (i.e. those that present with chest pain and ST-elevation or chest pain and new-onset left bundle branch block on electrocardiogram) are found to have unobstructed coronary arteries on angiography and, therefore, do not receive PPCI. There are no long-term outcome data from well-designed, multicentre trials on CMR use in different subgroups of patients who activate the PPCI pathway. There are also no studies reporting on the cost-effectiveness of CMR in these patients (or indeed patients from other clinical areas), which makes decision-making regarding the provision of CMR services within the NHS difficult.

Subgroups of patients who activate the primary percutaneous coronary intervention pathway and may benefit from cardiovascular magnetic resonance

Two subgroups of patients were identified in the protocol as having the potential to benefit from CMR: (1) patients with multivessel disease and (2) patients with unobstructed coronary arteries on angiography.

It is estimated that 40–65% of the patients presenting with a STEMI have multivessel disease (depending on the baseline characteristics, e.g. age, of the population studied).[6–11] There is ongoing debate about the optimal treatment strategy for these patients. Three main treatment management strategies have been proposed/are currently used: (1) conservative, PPCI of the infarcted artery followed by medical therapy (unless ischaemia occurs), (2) staged, in which only the infarct-related artery is treated acutely and other lesions are treated at a later date and (3) aggressive, percutaneous coronary intervention (PCI) of all significant lesions at the time of PPCI.

The role of CMR in patients with multivessel disease is undefined. CMR allows the volume of ischaemic or poorly perfused myocardium to be quantified but it is not known whether or not access to CMR to plan further revascularisation influences management. Since the Primary percutaneous coronary Intervention Pathway Activation (PIPA) study was commissioned, there has also been a rapid increase in the use of fractional flow reserve (FFR) testing (a guide wire-based procedure done through a standard diagnostic catheter at the time of a coronary angiography) to assess ischaemia; this technology is available to interventional cardiologists in the catheter laboratory. CMR is comparable to FFR for detecting ischaemia; studies have shown excellent diagnostic accuracy of perfusion CMR to detect areas of ischaemia identified by FFR.[12,13] However, while FFR may be appropriate in symptomatic, high-risk patients for whom the benefit of an invasive approach to ischaemia testing may outweigh the risks (i.e. the likelihood of revascularisation is high; therefore, lesions can

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be revascularised at the same time as the FFR), the benefit is less clear in asymptomatic multivessel disease patients. CMR may, therefore, have a role in selecting patients who will receive the greatest benefit from these invasive procedures. The non-inferiority of CMR in managing patients with multivessel disease is the subject of the magnetic resonance perfusion imaging to guide management of patients with stable coronary artery disease (MR-INFORM) trial.[14]

The reported variation in the incidence of normal coronary angiograms in patients activating the PPCI pathway is between 3% and 16%.[15,16] It is in this group that cardiologists believe that CMR has the greatest potential to change patient management. In these patients, the lack of an accurate diagnosis may result in inappropriate treatment and/or follow-up,[17,18] associated with a poorer prognosis.[19] A definitive diagnosis of myocardial infarction (MI) or not is also important so that these patients can be managed and followed up appropriately. Studies have shown that CMR can facilitate differential diagnosis in the context of a normal coronary angiogram,[20–22] providing a definitive diagnosis (e.g. MI, myocarditis, Takotsubo cardiomyopathy) in 65–90% of these patients.[20,23,24] Although the prognostic implications of non-MI CMR abnormalities are not known, two studies showed that the pattern of CMR abnormalities in myocarditis was predictive of long-term outcome.[25,26]

The benefit of CMR to other subgroups of patients who activate the PPCI pathway is less clear. However, given that not all of these patients will have access to centres with dedicated CMR facilities, there is potential for health inequality across the UK, which needs to be identified. Therefore, the population of interest for this study (target population) includes all ACS patients who activate the PPCI pathway, regardless of whether or not they receive PPCI.

Rationale for the study

We wanted to set up a multicentre, prospective cohort study (registry) in ACS patients who activate the PPCI pathway by linking routinely collected data from hospital information systems (HISs) with follow-up data from Hospital Episode Statistics (HES) and the Office for National Statistics (ONS). The aims of the registry were to document CMR activity in patients who activate the PPCI pathway and to provide information on CMR use, uptake over time, patients' characteristics associated with being referred for CMR, the impact of CMR on patient management (e.g. early discharge of a patient with a normal coronary angiogram or the placement of an additional stent for a patient with multivessel disease) and the prognostic value of CMR after PPCI.

We were uncertain whether or not it would be feasible to set up a registry in this patient population using routinely collected data. In particular, we were uncertain if we could (1) easily identify the eligible population, (2) implement a 'light-touch' consent system across multiple hospitals and (3) extract and link data sets from multiple HISs in different hospitals. We also wanted (4) to provide a reliable estimate of the CMR rate in patients who activate the PPCI pathway and (5) to define a 'proxy' primary composite outcome, acceptable to cardiologists and other stakeholders (e.g. clinical commissioners) as representing a clinically important change in management as a result of an eligible patient having undergone CMR (e.g. expected to prevent future MACEs). Item number 5 was included so that the registry would be able to assess effectiveness in the medium term. A long-term objective of the registry would be to compare the incidence of MACEs in patients who do or do not have CMR after the index event, but the low frequency of MACEs means that the study would have to accrue over 37,000 subjects to detect a clinically important reduction in the incidence of MACEs with adequate power.

Chapter 2 Aims and objectives

The aim of the study was to evaluate the feasibility of setting up a UK multicentre registry study to document CMR use in patients who activate the PPCI pathway. There were three elements to the study, listed below with the associated objectives.

A. To determine whether or not it is feasible to set up a CMR registry in this patient population by linking sources of routinely collected data.

- Objective A1: to implement consent and establish patient consent rate.
- Objective A2: to provide evidence of whether or not data linkage and extraction can be carried out across PPCI centres.
- Objective A3: to determine whether the registry can be compiled from hospital episode data [HES and Patient Episode Database Wales (PEDW)] rather than multiple HISs.

B. To estimate the proportion of the target population who have CMR at two centres with dedicated CMR facilities and to describe resource use and associated costs of having CMR after PPCI.

- Objective B1: to estimate the proportion of the target population who get a CMR scan following PPCI pathway activation.
- Objective B2: to develop simple cost-effectiveness models in relevant subgroups of patients who activate the PPCI pathway in order to identify key drivers of cost-effectiveness for CMR imaging in patients who activate the PPCI pathway.

C. To identify an outcome measure representing a definitive change in clinical management, conditional on having undergone CMR, that would be credible to cardiologists and other stakeholders as an interim measure of the value added by doing CMR.

- Objective C1: to define, using formal consensus methods, a treatment/process outcome that will constitute a definitive change in clinical management arising from having undergone CMR.
- Objective C2: to identify patient subgroups in whom CMR use is indicated using formal consensus methods and illustrative data from the registry.
- Objective C3: to determine whether or not hospital episode data adequately capture the main changes in clinical management that are identified using formal consensus.
- Objective C4: to pilot the implementation of a primary outcome that is based on the changes in management, for which consensus was achieved using hospital episode data.

Conditional on the success of achieving objectives A, B and C, there was a final objective, D, for which we envisaged that we would define the research objectives and calculate the sample size needed for a cohort study to achieve the aim of evaluating the clinical effectiveness and cost-effectiveness of CMR after PPCI pathway activation, with respect to the outcome identified by objective C.

Changes to objectives during the study

The objectives described above comprise all objectives that were studied rather than the objectives at the outset. The following objectives were added or modified during the course of the study.

With respect to objective A3, we faced several challenges when identifying the eligible population and implementing patient consent in the PPCI centres. These are described in detail in *Chapter 3*. We therefore wanted to determine whether or not we could identify ACS patients who activate the PPCI pathway in hospital episode data in order to determine whether or not a future registry in this patient population

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could be set up solely from hospital episode data (*Chapter 4*, *Identifying the eligible study cohort and cardiovascular magnetic resonance exposure in hospital episode data*).

With respect to objective B2, we originally planned to identify key cost drivers empirically, by describing resource use and associated costs of having CMR after PPCI pathway activation from HES and PEDW data for participants during follow-up of the cohort. We experienced considerable delays in obtaining HES data, which prevented us from doing this. Therefore, the economists used an alternative approach, seeking secondary sources of data as inputs into economic decision models to identify the key drivers of cost-effectiveness, that is the model parameters that most influence estimates.

With respect to objective C4, we had initially intended to collect follow-up data from each participating hospital to identify the changes in clinical management that could result from CMR (defined through the formal consensus). However, we realised early on that this would not be possible for a proportion of our cohort because many patients whom we recruited had their treatment at the PPCI centres but were quickly repatriated to their local hospital. We therefore decided that following the cohort through hospital episode data would provide more complete data because follow-up data would be available for all patients regardless of which hospital (within England or Wales) they attended after their index admission/procedure.

With respect to objective C3, some of the cardiologists in the research team were sceptical about our ability to pick up potential changes in clinical management resulting from CMR using HES and PEDW data. They highlighted that changes in clinical management may be too subtle to be captured in a data set that records only information about inpatient, outpatient and accident and emergency (A&E) attendances. In contrast, electronic data sources in many hospitals capture a range of additional information, for example prescribing data and patient-level nursing observation data. We therefore designed a questionnaire requesting specific information from the referring cardiologists about how CMR changed management in all patients in our study who were referred for a CMR. We determined whether or not changes in management described in the questionnaire were adequately reflected in hospital episode data [see *Chapter 6*, *Implementation of a primary outcome based on the changes in management for which consensus was achieved (objectives C3 and C4)*].

Major delays with the study

The major delay to the study was receiving the HES/ONS linked data set from NHS Digital. Below is a timeline of our data request and the processing of our application:

- 24 June 2013 – application was submitted to NHS Digital. We were told that our application would be processed closer to the time at which we required the data (September 2014), because our request was straightforward and the data set would not take long to assemble.
- March 2014 – NHS Digital commissioned an independent review into data release and stopped processing all applications.
- March 2015 – NHS Digital began processing our application.
- August 2016 – linked HES/ONS data received.

This process added a 23-month delay to the study.

Chapter 3 Methods

Feasibility prospective cohort study (objectives A1, A2, A3 and B1)

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Study population

We aimed to approach all ACS patients who activated the PPCI pathway. This population included all patients who underwent an emergency angiogram, whether or not they received PPCI. We included patients if they were aged ≥ 18 years and underwent an emergency angiogram, defined as taking place within 2 hours of arrival at the hospital, unless specified otherwise by local protocols. We excluded patients if they were prisoners or lacked mental capacity to consent. There were no changes to the eligibility criteria during the study recruitment period. The study was reviewed and approved by the National Research Ethics Committee South West-Central Bristol (reference number 12/SW/0326).

Setting

Four NHS hospitals in England and Wales hosting 24/7 PPCI centres took part:[27] the Bristol Heart Institute (University Hospitals Bristol NHS Foundation Trust), Leeds General Infirmary (Leeds Teaching Hospitals NHS Trust), Morriston Hospital (Abertawe Bro Morgannwg University Health Board, Swansea) and University Hospital of Wales (Cardiff & Vale University Health Board). Two of these hospitals (Bristol and Leeds) were defined as 'coronary magnetic resonance (CMR) centres', that is hospitals that had a dedicated CMR service. The other two hospitals (Swansea and Cardiff) were defined as 'non-CMR centres', that is hospitals that did not have access to a dedicated CMR service.

Patient identification and consent

Each hospital implemented its own methods for identifying and consenting patients. Most eligible patients were identified manually (e.g. by checking catheter laboratory records, by checking the local cardiology database or both). One of the participating hospitals set up a database query (including the search terms 'PPCI', 'QueryNot' and 'QuerProc') in the local cardiology database to flag up eligible patients. However, the query was broad and relied on data input by staff in the catheter laboratory, which changed in 'real-time'. This made identification of some eligible patients difficult. For example, if a patient was originally marked as 'PPCI' but was subsequently found to have an unobstructed coronary artery on the angiogram, the 'PPCI' label was removed, but no further information was added, necessitating manual searches by local research staff to identify whether or not the patient was eligible.

We gave eligible patients information about the study once they had recovered sufficiently from their angiography and consented them before they were discharged from hospital (see *Appendix 1* for a copy of the consent form). In some hospitals, this was often not possible because of quick repatriation to the originating hospital or research staff not being available over the weekend. Patients who could not be approached in person were sent study information and consent forms by post. Postal consents were managed locally at each hospital. We requested consent to use all the information collected by the hospital in relation to the patients' suspected MI (index admission) and all the information related to subsequent NHS care and vital status in the first 12 months following the index admission.[27]

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Exposure

Patients were classified as exposed if they received CMR within 10 weeks of the index admission (whether during the index admission or subsequently as an outpatient). CMR had to be documented (i.e. CMR report, including the date of the CMR) in the clinical radiology information system (CRIS) or similar imaging database when the date/time of the CMR was < 10 weeks (70 days) after the date of the index admission.

Data collection: index procedure

We asked each hospital to provide the following data from local HISs for all recruited patients:

- basic demography [local Patient Administration System (PAS)/British Cardiovascular Intervention Society (BCIS) Central Cardiac Audit Database (CCAD)]
- clinical characteristics on presentation at the index admission, peri- and post-procedural (PPCI) characteristics {local catheter laboratory database [e.g. Siemens (Munich, Germany) CARDDAS in Bristol]/BCIS-CCAD}
- echocardiography (ECHO) and CMR reports (local imaging databases, e.g. Picture Archiving and Communication System, CRIS, CRIS in Bristol)
- biochemistry [local biochemistry databases, e.g. Virtual Pathology Laboratory System/Integrated Clinical Environment (ICE) in Bristol]
- medications on discharge (local biochemistry database, e.g. ICE in Bristol).

Each hospital had the option to submit a linked data set (i.e. the participating hospital linked data from different HISs within the hospital) or unlinked data extracts from each of the above categories with a unique patient identifier in each extract. We established a data linkage model at Bristol (by liaising with the appropriate HIS managers at University Hospitals Bristol NHS Foundation Trust) and informed the other hospitals that we would undertake linkage at Bristol based on this model, although the decision about how to submit the data was left to each participating hospital.[27]

We collected a limited anonymised data set to characterise the eligible patients who were not recruited, that is those who declined to consent or did not respond to an invitation to consent before study recruitment ended. Hospitals were provided with a look-up table containing the Index of Multiple Deprivation (IMD)[28] or Welsh Index of Multiple Deprivation (WIMD)[29] for English or Welsh postcodes, so that the anonymised data sets could contain information on deprivation, both as scores and ranks, without including postcodes, which might have compromised anonymity. IMD and WIMD are calculated from combined information from several domains (e.g. income, employment, education, health) to produce an overall relative measure of deprivation.

Data collection: follow-up

For subsequent inpatient and outpatient activity in the 12 months following the index admission, we applied to NHS Digital to link our data set with HES (i.e. inpatient, outpatient, A&E and critical care data) for the hospitals in England and to NHS Wales Information Service (NWIS) for PEDW (which collects equivalent information for NHS Wales hospitals) for the hospitals in Wales. Inpatient episode data (HES and PEDW) contain details of hospital admissions (including dates of admission and discharge) and main diagnoses/procedures. Outpatient data contain appointment dates and consultant specialty. A&E data contain dates, methods and sources of arrival at hospital.

NHS Digital routinely links HES with ONS mortality data. Mortality data were unavailable through NWIS, so the two Welsh hospitals provided these data for their patients. Identifiers and evidence of signed consent were submitted via a secure portal to NHS Digital and NWIS; HES, ONS and PEDW data were received with our unique patient identifier embedded within each file for linkage.

Admissions data were provided as data relating to an episode (i.e. admission under one consultant), but we restructured the data to relate to a 'continuous inpatient spell' regardless of any transfers to another consultant that may have taken place within the same admission.[30] We created a data set containing the admissions data that included the index admission and the admissions, outpatient, critical care and A&E data in the 12 months after the index admission. This was used to characterise the frequency and duration of outpatient follow-up, unscheduled cardiac-related hospital readmissions and cardiac-related investigations/procedures, such as diagnostic angiography, repeat PCI or cardiac surgery up to 1 year after the index admission.

We assumed that, if patients had any HES/PEDW data (e.g. admissions, outpatient and A&E), data not recorded in any of the data sets were absent (i.e. patient did not have an episode) rather than missing (i.e. data not entered). In addition, for those patients with a CMR within 10 weeks of their index admission, outpatient visits that occurred within this window were excluded from any counts.

Main outcome measures

The main prespecified outcome measures were feasibility parameters (criteria that would have to be met before making the decision to progress to setting up a full registry):

- patient consent implemented at all four hospitals
- data linkage and extraction from multiple local HISs achieved for > 90% of consented patients at all four hospitals
- local data successfully linked with HES and PEDW for > 90% of consented patients at all four hospitals
- CMR scan requested and carried out for ≥ 10% of patients activating the PPCI pathway in CMR hospitals.[27]

Feasibility of compiling the registry from hospital episode data

We tested the feasibility of compiling the registry entirely through hospital episode data. We determined whether or not we could identify the following from hospital episode data:

- the index event (PPCI or emergency angiography, cohort entry)
- CMR within 10 weeks of the index event (exposure)
- relevant subgroups of the population in which CMR may influence clinical management [identified through formal consensus, see *Formal consensus study (objectives C1 and C2)*]
- clinical outcomes [MACEs, comprising death, MI, stroke, repeat PCI and a coronary artery bypass graft (CABG)].

We identified events corresponding to the index admission, exposure or outcome in HES and PEDW data sets (inpatient and outpatient) using the *International Classification of Diseases*, Tenth Edition (ICD-10)[31] and the Office of Population Censuses and Surveys (OPCS) classification procedure codes.[32] The index admission was identified from the inpatient data set using the OPCS codes for PCI (K49, K50, K75) and ICD-10 codes for ST-elevation myocardial infarction (STEMI) (I21.0, I21.1, I21.2, I21.3) to identify PPCI patients, and OPCS codes for angiography (K63.3, K63.5 or K63.6) with a method of admission coded as emergency to identify patients who underwent an emergency angiogram. We identified exposure (OPCS code U10.3) in the inpatient and outpatient data sets. We regarded all procedure codes within 1 day of the index admission (PCI and emergency angiography) or subsequent CMR to relate to the same event recorded in our HIS data set. Clinical outcomes were identified using the following codes: ICD-10 I21 for MI and I64 for stroke, and OPCS K49, K50 or K75 for PCI and OPCS K40, K41, K42, K43, K44, K45 or K46 for CABG. A full list of codes is shown in *Appendix 2*.

Sample size considerations

This was a feasibility study. We aimed to recruit sufficient patients to address the study objectives, not to provide a definitive answer to questions about the clinical effectiveness and cost-effectiveness of CMR in patients who activate the PPCI pathway. None of the objectives was analytic and, therefore, a power-based sample size justification was not appropriate.

Objective A2 and objective B1 required quantitative estimates to be reported. The target sample size of 1600 patients was assessed as sufficient to allow these proportions to be estimated with satisfactory

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precision. For example, we expected that ≥ 90% of patients who were invited to take part in the study would give consent; the 95% confidence interval (CI) for this proportion would be 88.4% to 91.4%. Similarly, we estimated that 12.5% of the target population would have CMR, although this proportion was less certain. The 95% CIs for proportions 5%, 10% and 15% would be, respectively, 4.0% to 6.2%, 8.6% to 11.6% and 13.3% to 16.8%.

Data analysis

Data were analysed using Stata/IC® version 13 (StataCorp LP, College Station, TX, USA). The analysis of feasibility outcomes was descriptive, with quantitative results expressed as counts, percentages and 95% CIs. Feasibility was assessed by comparing descriptive statistics with the corresponding criteria. We compared patients who did not consent (and for whom we received anonymised data) with those who did consent using standardised mean differences (SMDs).[27,33] We used means and standard deviations (SDs), or medians and interquartile ranges (IQRs), for continuous variables and number (per cent) for categorical variables to report the demographic variables and baseline characteristics of patients recruited from the four hospitals.

Clinical events were expressed as rates per 1000 person-years at risk, along with 95% CIs calculated using the Poisson distribution. Time at risk of death was calculated as the time from index admission to death for those known to have died within 12 months, or the time from index admission to the calendar date on which death data were provided for that site. Any time at risk of death of > 12 months was capped at 12 months.

Time at risk for MI, stroke, repeat PCI and CABG was calculated as the time from index admission to the event, or the time from index admission to the calendar date that follow-up data were provided for that site. If the patient died before experiencing the event, the time at risk of death was time from index admission until death. Any time at risk of death of > 12 months was capped at 12 months.

Formal consensus study (objectives C1 and C2)

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Literature review

We searched for studies reporting the impact of CMR on prognosis, patient management and risk stratification in the population of patients who activate the PPCI pathway. We intended to identify studies providing background knowledge to inform the formulation of statements about how CMR could change patient management in specific subgroups and as supporting evidence for the final consensus statements. We did not intend to carry out a formal quantitative systematic review of the effectiveness of CMR in the target population.

We searched without restriction by study design or search terms related to outcomes, so that we could determine the full extent of the literature in this area and identify all studies that used CMR in our population. Thus, the search identified studies that had diverse objectives and measured a range of outcomes (e.g. clinical outcomes, changes in patient management, classifications of patients into prognostic groups, new diagnoses). The search was conducted on MEDLINE, EMBASE, The Cochrane Library, Web of Science (Citations Index and Proceedings) and Bioscience Information Service (BIOSIS) (date range for all searches: 1950 to 16 January 2014). The following search terms were used, both as free text and medical subject headings (MeSH) when possible: ‘acute coronary syndrome’, ‘myocardial infarction’, ‘angioplasty’, 'percutaneous coronary intervention' and 'cardiovascular magnetic resonance imaging'. We applied no restriction on publication date or language. The literature search is shown in *Appendix 3*.

We included all studies reporting the use of CMR in patients undergoing PPCI or patients who activated the PPCI pathway but did not proceed to PPCI (e.g. had an emergency angiogram). We excluded studies investigating the use of CMR in populations with stable coronary artery disease or patients with non-ST elevation myocardial infarction (NSTEMI), because these patients do not routinely undergo emergency angiography. One researcher triaged the titles and abstracts identified by the search to remove duplicate reports of the same study and studies that did not meet the inclusion criteria. Reference lists of full-text papers were scanned to ensure that no additional studies had been missed during the search.

The broad search identified many different types of study (e.g. diagnostic, prognostic, controlled or uncontrolled, prospective or retrospective, cohort studies) and case reports. They were grouped as follows: (1) studies assessing the prognostic value of a comprehensive CMR scan or specific CMR markers, (2) studies in which CMR was used to 'diagnose' a specific feature (e.g. type of MI) or complication arising from the index MI [e.g. left ventricular (LV) thrombus, ventricular septal defect (VSD)], or procedure-related complications, (3) studies in which CMR was used to 'diagnose' incidental findings or conditions unrelated to MI, (4) studies in which indices of heart function (e.g. myocardial viability, necrosis, perfusion, myocardium at risk, ischaemia) assessed by CMR and other imaging modalities [e.g. ECHO and single-photon emission computed tomography (SPECT)] were compared and (5) other studies not fitting into any of the categories above.

Formulation of consensus statements

An expert group was convened, consisting of two cardiologists with CMR expertise (CBD and JPG), two interventional cardiologists from sites participating in the feasibility study (SHD and RAA), one cardiac network director (SB), two methodologists (BCR and MP), two statisticians (CAR and JMH), one health economist (SW or EAS) and the study manager (RCB). Draft statements were generated independently by three cardiologists (CBD, JPG and SHD) based on their cardiological expertise and by one methodologist (MP) based on evidence from the literature review. The cardiologists and methodologist had no prior communication with each other. The cardiologists were advised to be as inclusive as possible at this stage and to not be concerned about the strength or quality of the evidence available to support their draft statements.

Three members of the expert group (study manager, RCB; systematic reviewer, MP; and cardiologist with CMR expertise, CBD) collated the statements, organised them according to patient subgroup and standardised the wording of each statement. A 1-day meeting was organised for all members of the group. The structure of the meeting was as follows: an introduction to the aims of the study and the formal consensus process; a review of each statement in turn, considering the relevance, format and wording of each statement; and a discussion about the structure of the survey. Key papers from the literature review were circulated to all members of the group prior to the meeting and these were also considered in the discussions. At the meeting, it was decided that each statement would benefit from a 'supporting paragraph', citing key references from the literature review, to provide background information and put the statement in context.

The structure of the process used to generate the statements is summarised in *Table 1*. We documented all of the discussions that led to the final statements.

Survey design

Statements and supporting paragraphs were worded in a consistent manner and collated in the form of a web-based survey (SurveyMonkey®, Palo Alto, CA, USA) (see *Appendix 4*). The survey included an introductory page explaining the purpose and layout of the survey and instructions about how to complete it. Each statement was followed by its supporting paragraph that contained links to Portable Document Format (PDF) references. Each statement was accompanied by a nine-point Likert scale asking the respondent to indicate whether or not he/she agreed with the statement (with 1 indicating 'completely disagree' and

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TABLE 1 Structure of the process used to generate the survey statements for use in a formal consensus process

Step	Description
Literature review	Published literature was identified on the use of CMR in patients who activate the PPCI pathway and the patient subgroups that may benefit from CMR
Generate draft statements	Statements were generated independently in writing by clinical and non-clinical members of the internal group using systematic review and clinical expertise
Collate statements	Statements were categorised into patient subgroups and reworded into a standard style
Expert group meeting	All members of the expert group convened for a 1-day meeting during which the consensus process was introduced and each statement was discussed in turn. Discussions focused on the relevance, format and wording of each statement, and on how to structure the online survey
Generate final list of statements	A final list of statements was produced based on internal group meeting discussions. Each statement was accompanied by a supporting paragraph presenting 'key' supporting references from the literature

9 'completely agree'). There was also a free-text box for each statement for respondents to comment in and justify their score.

Expert panel

Establishing the expert panel

Clinicians in the working group identified consultant cardiologists with CMR, interventional, ECHO, electrophysiology and heart failure expertise from across the UK (see *Acknowledgements*). The cardiologists were invited by e-mail to form an expert consensus panel.

Completion of first survey

The expert panel completed the survey independently. Responses were collated and analysed by members of the working group.

Face-to-face meeting

The expert panel attended a face-to-face meeting, chaired by a non-cardiology clinician experienced in facilitating formal consensus panels. The meeting was also attended by non-clinical members of the working group, whose role was to introduce the study, describe the structure of the formal consensus process, provide study-related information and take minutes of the meeting. The expert panel discussed each statement and anonymised responses to the first survey in turn and agreed on modifications to the survey.

Completion of the modified survey

The survey was modified by members of the working group as agreed in the face-to-face meeting (see *Appendix 4*).[4] The expert panel completed the modified survey independently and rated the statements a second time.

Extension of survey to other UK cardiologists

The survey was extended to other UK cardiologists through the British Cardiovascular Society, which advertised the survey in their monthly newsletter to members (over 2 consecutive months). We offered an incentive to encourage participation: the option of entering a prize draw for an iPad (Apple Inc., Cupertino, CA, USA).

Main outcome measure

A definition of a primary outcome measure (acceptable to cardiologists and other stakeholders) that represents a definitive change in clinical management arising from a patient having CMR.

Criteria for consensus

Data for each statement are shown as medians and IQRs. A median score ≥ 7 and an IQRs 6–9 was considered to be in agreement, or consensus, that the change in management described by the statement was clinically important. These statements were used to identify the patient subgroups perceived to benefit from CMR and define the treatment/process outcome that constitutes a definitive management change as a result of having CMR. A median score ≤ 3 and an IQR 1–3 was considered to be in consensus that the statement did not constitute a clinically important change in management. Data were analysed using Stata/IC version 14.

Implementation of a primary outcome based on the changes in management for which consensus was achieved (objectives C3 and C4)

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Patient subgroups

Patient subgroups were identified from HIS data extracts provided by hospitals. When this was not possible, hospital episode data (the admissions data sets) were used to identify the ICD-10 diagnostic codes associated with the index admission.

Manual review of patient notes

We undertook a review of patient notes because of the uncertainty regarding the identification of the subgroup of patients with unobstructed coronary arteries. Forty-seven patients were selected, all identified as having unobstructed arteries in hospital A at the time of the index event. We undertook a thorough review of their patient notes to identify the reason why they activated the PPCI pathway.

Identifying changes in management

We used HES/PEDW inpatient and outpatient data to identify changes in management defined through the formal consensus in the 12 months after the index admission (cohort entry). For those patients who underwent CMR, any outpatient appointments that occurred between the index admission and the date of CMR were excluded. We decided not to use the A&E data set because most of the changes in management identified in the formal consensus were unlikely to occur in the A&E setting.

Cardiologist members of the clinical team identified key clinical 'events' that they expected to reflect the important changes in management characterised through the consensus process. For example, new non-ischaemic diagnoses (an important change in management resulting from CMR) were identified as Takotsubo cardiomyopathy, myocarditis, pericarditis, endocarditis and coronary spasm.

We then compiled a list of ICD-10 and OPCS codes representing the key clinical events with the help of a clinical coder. Most changes in management encompassed a number of ICD-10/OPCS codes, for example the use of additional diagnostic tests during follow-up required OPCS codes for positron emission tomography (PET), ECHO, intravascular ultrasound (IVUS) or pressure wire. We identified the changes in management in HES/PEDW for each statement (patient subgroup) separately. The full code list used to identify changes in management is shown in *Appendix 2*.

Implementation of the consensus statements

We calculated the frequency of all events representing changes in management (e.g. number of new diagnoses, additional diagnostic tests, number of outpatient appointments) in patients who did/did not

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receive CMR for each patient subgroup in the 12 months following the index admission. We also calculated the time to first event for each change in management (e.g. time to first new diagnosis, time to the first diagnostic test, time to next revascularisation in patients with multivessel disease) and summarised these with medians and IQRs. We did not compare differences between patients who did/did not receive CMR in any of the subgroups because we were interested primarily in the feasibility of identifying relevant events; the number of patients in most subgroups was also small.

Cardiovascular magnetic resonance questionnaire

We determined whether or not the changes in management identified in HES/PEDW accurately reflected the changes in management implemented by the cardiologists who referred patients in the study for CMR. We designed a questionnaire based on the patient subgroups identified in the formal consensus (see *Appendix 5*) and asked all referring cardiologists to complete it for each patient whom they referred for CMR. The questionnaire asked about whether or not and how CMR changed management (using tick boxes and free text). We used the questionnaire to identify whether or not the changes in management reported by cardiologists were accurately reflected in HES/PEDW, and whether or not there were additional changes in management that could not be picked up from HES/PEDW.

Health economic study (objective B2)

We built two separate cost-effectiveness models to explore the impact of CMR for two patient subgroups: (1) multivessel disease and (2) unobstructed (normal) coronary arteries.

- Model 1: simulated the costs and effects of introducing CMR for patients with multivessel disease, compared with current practice.
- Model 2: simulated the costs and effects of introducing CMR for patients with normal coronary arteries, compared with current practice.

From these two models, inferences can be made about the likely drivers of the cost-effectiveness of introducing CMR for all patients who activate the PPCI pathway, because, in practice, this is how CMR might be introduced, and is, therefore, the key issue for policy-makers.

The decision trees model the patient pathway after PPCI pathway activation to 1 year. Each possible patient pathway within the model is associated with a probability, and each pathway incurs costs and outcomes. The analysis was conducted from a NHS and personal social services perspective.[34] Outcomes were measured in quality-adjusted life-years (QALYs), a composite measure of quality and quantity of life.

The structure of the model for patients with multivessel disease is described next, along with the sources of parameter estimates, before the model for patients with normal coronary arteries is considered.

Model 1: patients with multivessel disease

This model was designed to address the question ‘Which is the most cost-effective type of ischaemia testing for patients with multivessel disease who activate the PPCI pathway?’

When the study started, stress ECHO was the ischaemia-testing option commonly used and the study was comparing this with CMR. During the study, the use of FFR increased[35] and, therefore, this test was included as an additional arm in the model. Thus, the model compares the cost-effectiveness of three ischaemia testing options: (1) CMR, (2) pressure wire and (3) stress ECHO.

The cohort of patients of interest are those who activate the PPCI pathway, have their index angiography and PPCI, and are identified as having multivessel disease (commonly defined as stenosis of > 50% from the angiogram). This model considers the patient pathway thereafter: whether or not to treat non-culprit lesions with a second revascularisation, the need (or not) for ischaemia testing to help determine the need for the revascularisation of a second vessel and any MACEs that occur. *Figure 1* summarises the scenarios in the patient pathways included in the model structure for one arm of the model (CMR).

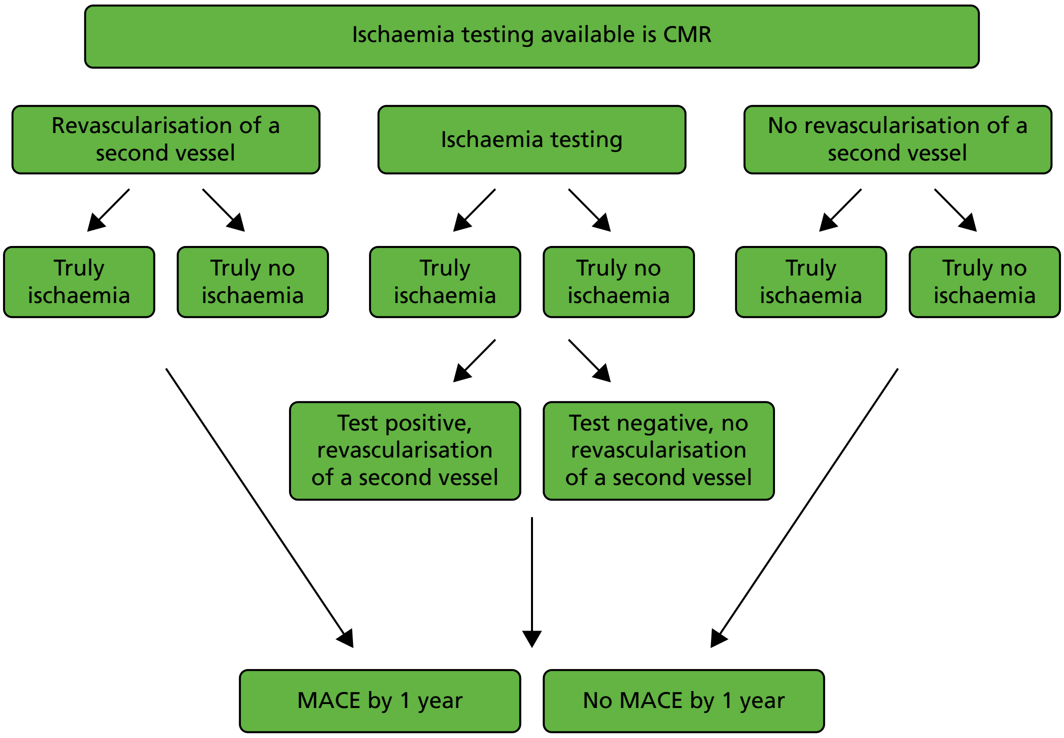
Ischaemia testing available is CMR
Revascularisation of a second vessel
Ischaemia testing
No revascularisation of a second vessel
Truly ischaemia
Truly no ischaemia
Truly ischaemia
Truly no ischaemia
Truly ischaemia
Truly no ischaemia
Test positive, revascularisation of a second vessel
Test negative, no revascularisation of a second vessel
MACE by 1 year
No MACE by 1 year

FIGURE 1 Scenarios in the patient pathway included in the model structure for patients with multivessel disease.

The model structure (shown in detail in *Figure 2* splitting into three arms, representing the three different types of ischaemia testing) considered the following: the top branch models the scenario in which the ischaemia-testing option available is CMR, the middle branch models the scenario for pressure wire and the bottom branch models the scenario for stress ECHO. The structure of each of these three main arms is the same for each scenario, but the associated probabilities, costs and outcomes for each arm vary.

Considering the CMR arm, the decision tree first divides the starting cohort of patients after PPCI in accordance with the results of their index angiography. A clinician may determine that a patient requires or does not require the revascularisation of a second vessel directly from their angiogram, without the need for ischaemia testing; alternatively, there may be uncertainty from the index angiogram of the need for further revascularisation, and, therefore, ischaemia testing is used, in this case CMR. For each of these three categories, patients are then divided by whether or not they truly have ischaemia.

Patients whose index angiography leads to a firm decision on revascularisation are then divided by whether or not they had any MACEs in the 12 months after PPCI. MACE is a composite end point of all-cause mortality, MI, stroke and revascularisation.

Patients for whom ischaemia testing is needed are divided in accordance with whether that test result was positive, and therefore assumed to result in the revascularisation of a second vessel, or negative. Thereafter, patients are divided by whether or not they had a MACE in the 12 months after PPCI.

Although the model structure is the same for each of the ischaemia testing options, there are differences in the timing of events between these arms for patients who have ischaemia testing that leads to a second revascularisation. For CMR and stress ECHO, this is a two-step process, that is a patient has the ischaemia test and then separately has revascularisation of a second vessel. For pressure wire, this all happens in the catheterisation laboratory at the same time, that is a patient has their diagnostic angiography and pressure wire, and, if required, has their PCI at the same time (note that this is entirely separate and subsequent to their index angiography and PPCI). This affects costs, but not the model structure.

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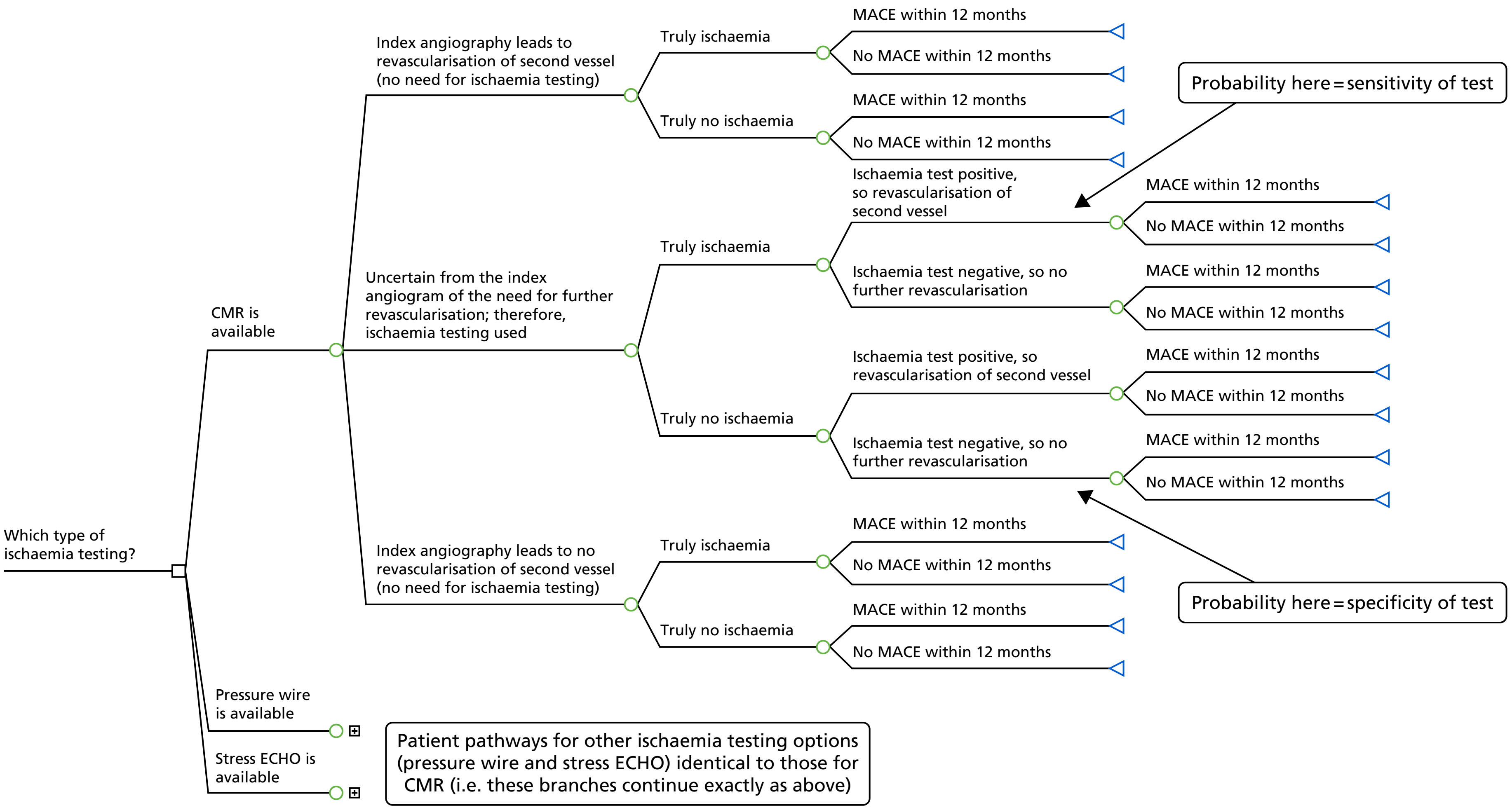
Which type of ischaemia testing?
CMR is available
Index angiography leads to revascularisation of second vessel (no need for ischaemia testing)
Truly ischaemia
MACE within 12 months
No MACE within 12 months
Truly no ischaemia
MACE within 12 months
No MACE within 12 months
Uncertain from the index angiogram of the need for further revascularisation; therefore, ischaemia testing used
Truly ischaemia
Ischaemia test positive, so revascularisation of second vessel
MACE within 12 months
No MACE within 12 months
Ischaemia test negative, so no further revascularisation
MACE within 12 months
No MACE within 12 months
Truly no ischaemia
Ischaemia test positive, so revascularisation of second vessel
MACE within 12 months
No MACE within 12 months
Ischaemia test negative, so no further revascularisation
MACE within 12 months
No MACE within 12 months
Probability here = sensitivity of test
Probability here = specificity of test
Index angiography leads to no revascularisation of second vessel (no need for ischaemia testing)
Truly ischaemia
MACE within 12 months
No MACE within 12 months
Truly no ischaemia
MACE within 12 months
No MACE within 12 months
Pressure wire is available
Stress ECHO is available
Patient pathways for other ischaemia testing options (pressure wire and stress ECHO) identical to those for CMR (i.e. these branches continue exactly as above)

FIGURE 2 Model 1 structure: patients with multivessel disease.

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Data for the multivessel disease model

Most model parameters were populated with estimates derived from the literature. The following sections describe how transition probabilities, costs and outcomes were estimated to 1 year.

Probabilities for the multivessel disease model

Table 2 shows the probabilities used in the model and their sources. These are the probabilities associated with each branch in the model; probabilities along pathways are multiplied together in the analyses. MEDLINE searching was used to identify relevant papers, and was conducted using MeSH and keywords for each imaging type (e.g. exp/pressure-wire or pressure-wire.mp or fractional flow reserve.mp and exp/myocardial infarction). Any relevant reviews were read in order to identify relevant references, and references and citations of any relevant references were checked for prior or more recent published work.

In the base-case analyses, CMR and pressure wire were treated as reference standards and both were assumed to have 100% sensitivity and specificity. Therefore, the probabilities and outcomes are the same in these arms and they differ only in terms of costs.

The probabilities of MACEs were estimated from Smits *et al.*,[38] in which MACE was defined as a composite end point of all-cause mortality, non-fatal MI, revascularisation and cerebrovascular events at 12 months. Outcomes for subgroups of patients in the trial were used to estimate MACE for three groups of patients: (1) truly ischaemic patients who had a second revascularisation ($p = 0.09$), (2) truly ischaemic patients who did not have a second revascularisation ($p = 0.31$) and (3) truly not ischaemic patients, whether or not they had a second revascularisation ($p = 0.13$). Based on subgroups of the trial patients, the probability of a MACE at 12 months for truly ischaemic patients who had a second revascularisation was actually lower than for patients without ischaemia. This might seem anomalous, but is a genuine finding. Although the probability estimates for these three subgroups were all based on ≥ 200 patients, only 18 truly ischaemic patients who had a second revascularisation had a MACE; these findings might be an artefact of modest numbers, and larger studies might show different results.

Costs for the multivessel disease model

For each ischaemia testing strategy considered, the costs included were the cost of ischaemia testing (CMR, pressure wire or stress ECHO) if required, the cost of revascularisation of a second vessel, costs associated with adverse events included in MACEs (both the initial inpatient costs and subsequent costs post discharge), costs of cardiac medications and cardiac rehabilitation offered to all patients and additional health-care costs beyond hospital discharge to 1 year, including follow-up outpatient appointments for all patients.

Unit costs were largely obtained from *NHS Reference Costs 2015 to 2016*[40] and are shown in *Table 3*; details of assumptions made in estimating unit costs are also provided in *Table 3*. *NHS Reference Costs* provide upper and lower quartiles around mean estimates; the difference between the mean and the upper quartile was captured and used as a crude estimate of standard error (SE) in the probabilistic sensitivity analyses (PSAs) (described in *Model analyses*). When this was not possible, the SE was assumed to be 20% of the mean cost. All costs were parameterised using a gamma distribution in the PSAs.

Outcomes for the multivessel disease model

Outcomes were measured in QALYs. Estimates of survival and quality of life utility weights were obtained from the literature and combined to estimate the QALYs gained to 1 year. As death is one of the components of MACEs, patients without a MACE are all alive at 1 year in the model. The probability of dying in the first year was taken from the same source as the MACE estimates above, and was 8% for patients with a MACE.[38]

The Tufts Cost-effectiveness Analysis Registry[46] was searched for appropriate utility weights. This registry is a database of 5655 cost–utility analyses on a wide variety of diseases and treatments and has 21,900 utility weights. Search terms such as ‘primary percutaneous coronary intervention’ and ‘major adverse

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TABLE 2 Probabilities for the multivessel disease model

Branch of model	Base-case value (positive/total)	Distribution for PSA	Source
For each ischaemia testing option			
Probability that index angiography leads to revascularisation of second vessel	0.30 (30/100)[a]	Dirichlet	Expert opinion within the PIPA study team
Probability of uncertainty following index angiography and need for ischaemia testing	0.60 (60/100)[a]		
Probability that index angiography leads to no revascularisation of second vessel	0.10 (10/100)[a]		
Index angiography leads to revascularisation of second vessel			
Probability of true ischaemia	0.84 (598/709)	Beta	FAME[37]
Probability of MACE by 12 months, true ischaemia	0.09 (18/202)[b]	Beta	Smits *et al.*[38]
Probability of MACE by 12 months, truly no ischaemia	0.13 (54/432)[b]	Beta	Smits *et al.*[38]
Uncertainty following index angiography and need for ischaemia testing			
Probability of true ischaemia	0.35 (218/620)	Beta	FAME[37]
Index angiography leads to no revascularisation of second vessel			
Probability of true ischaemia	0.35 (218/620)	Beta	FAME[37]
Probability of MACE by 12 months, true ischaemia	0.31 (71/231)[b]	Beta	Smits *et al.*[38]
Probability of MACE by 12 months, truly no ischaemia	0.13 (54/432)[b]	Beta	Smits *et al.*[38]
CMR or pressure wire *Uncertainty following index angiogram and need for ischaemia testing, true ischaemia*			
Probability of ischaemia test positive and revascularisation	1[c]	Beta	
Probability of MACE by 12 months, revascularisation	0.09 (18/202)[b]	Beta	Smits *et al.*[38]
Probability of MACE by 12 months, no revascularisation	0.31 (71/231)[b,d]	Beta	Smits *et al.*[38]
Uncertainty following index angiogram and need for ischaemia testing, truly no ischaemia			
Probability of ischaemia test positive and revascularisation	0[c]	Beta	
Probability of MACE by 12 months, revascularisation	0.13 (54/432)[b,d]	Beta	Smits *et al.*[38]
Probability of MACE by 12 months, no revascularisation	0.13 (54/432)[b]	Beta	Smits *et al.*[38]
Stress ECHO *Uncertainty following index angiogram and need for ischaemia testing, true ischaemia*			
Probability of ischaemia test positive and revascularisation	0.70 (32/46)	Beta	Gurunathan *et al.*[39]
Probability of MACE by 12 months, revascularisation	0.09 (18/202)[b]	Beta	Smits *et al.*[38]
Probability of MACE by 12 months, no revascularisation	0.31 (71/231)[b]	Beta	Smits *et al.*[38]
Uncertainty following index angiogram and need for ischaemia testing, truly no ischaemia			
Probability of ischaemia test positive and revascularisation	0.23 (39/171)	Beta	Gurunathan *et al.*[39]
Probability of MACE by 12 months, revascularisation	0.13 (54/432)[b]	Beta	Smits *et al.*[38]
Probability of MACE by 12 months, no revascularisation	0.13 (54/432)[b]	Beta	Smits *et al.*[38]

FAME, Fractional Flow Reserve versus Angiography in Multivessel Evaluation; PSA, probabilistic sensitivity analysis.

[a] To incorporate uncertainty around the percentage of patients in each of these three groups estimated by experts on the study team, it was assumed that experts were estimating the number of patients out of 100 in each group.

[b] For further information on the estimates of MACEs, please see the final paragraph in *Probabilities for the multivessel disease model*.

[c] In the base-case analyses, CMR and pressure wire are assumed to have perfect sensitivity and specificity, but these parameters are incorporated into the model so that alternative assumptions can be tested in sensitivity analyses.

[d] These probabilities are not required in the base-case analysis (since the probability in the preceding branch is zero), but are included here as they are required in sensitivity analyses.

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TABLE 3 Costs for the multivessel disease model

Resource	Unit cost, £ (SE)	Source
Revascularisation of second vessel (assumed to be PCI)	2682 (533)	*NHS Reference Costs 2015 to 2016*.[40] Elective Inpatient. Weighted average of codes EY40 and EY41, Standard/Complex Percutaneous Transluminal Coronary Angioplasty
CMR	264 (154)	*NHS Reference Costs 2015 to 2016*.[40] Diagnostic Imaging. Weighted average of all Cardiovascular Magnetic Resonance Imaging Scan codes
Angiography and pressure wire	1340 (374)	*NHS Reference Costs 2015 to 2016*.[40] Day case. Weighted average of code EY42, Complex Cardiac Catheterisation
Angiography, pressure wire and revascularisation (as a single catheter laboratory admission)	2971 (594)	Cost of revascularisation above, and angiography and pressure wire above, minus the cost of an angiography, £1051 (*NHS Reference Costs 2015 to 2016*.[40] Day case. Weighted average of code EY43, Standard Cardiac Catheterisation)
Stress ECHO	182 (3)	*NHS Reference Costs 2015 to 2016*.[40] Outpatient procedures. Cardiology. EY50Z, Complex Echocardiogram
MACE	3251 (650)	The proportion of each component of MACE was taken from Smits *et al.*[38] and a weighted average of the costs of each component was calculated, based on the unit costs below
Revascularisation (PCI)	2682	As above
Revascularisation (CABG)	10,944	*NHS Reference Costs 2015 to 2016*.[40] Elective Inpatient. Weighted average of codes ED26, ED27, ED28 Complex/Major/Standard Coronary Artery Bypass Graft
MI	2177	*NHS Reference Costs 2015 to 2016*.[40] Non-elective long stay. Weighted average of code EB10 A, Actual or Suspected Myocardial Infarction
Stroke	3723	*NHS Reference Costs 2015 to 2016*.[40] Non-elective long stay. Weighted average of code AA22, Cerebrovascular Accident, Nervous System Infections or Encephalopathy
Death	0 (0)	
Cardiac rehabilitation	364 (73)	Assume offered eight sessions, but only 50% uptake, so cost four sessions (one first and three follow-up appointments, individual costs below)
First appointment	97	*NHS Reference Costs 2015 to 2016*.[40] Consultant Led. 327, Cardiac Rehabilitation. Non-Admitted Face-to-Face Attendance, First
Follow-up appointment	89	*NHS Reference Costs 2015 to 2016*.[40] Consultant Led. 327, Cardiac Rehabilitation. Non-Admitted Face-to-Face Attendance, Follow-Up
Cardiac medications for treatment of MI (all once daily by mouth). Assumed given for 12 months (or 6 months for patients who died)		
Aspirin (75 mg)	0.04	BNF[41]
Prasugrel (Efient®; Eli Lilly and Company, Indianapolis, IN, USA) (5 mg)	1.70	BNF[41]
Atorvastatin (80 mg)	0.07	BNF[41]
Bisoprolol (2.5 mg)	0.02	BNF[41]
Ramipril (2.5 mg)	0.04	BNF[41]
Total daily cost	1.87	
Total annual cost	683 (137)	

continued

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TABLE 3 Costs for the multivessel disease model (*continued*)

Resource	Unit cost, £ (SE)	Source
Outpatient follow-up appointment (assumed to occur at 4–6 weeks and 6 months post discharge)	122 (22)	*NHS Reference Costs 2015 to 2016*.[40] Consultant-led appointments. Non-Admitted Face-to-Face Attendance, Follow-Up. Cardiology
Additional health-care costs to 1 year	2221 (444)	The Office of Health Economics' estimate of the annual cost per person of NHS care, inflated to 2015/16 prices using the hospital and community health services inflation index.[42,43] For patients who die, costs are assumed to be half of this (£1111)
Additional health-care costs to 1 year for those with a MACE	263 (53)	MI and stroke were assumed to be associated with continuing care costs post discharge. Costs from Greenhalgh *et al.*[44] were inflated to 2015/16 prices.[42] Separate costs were provided for disabling and non-disabling stroke. According to Davies *et al.*,[45] 58% of strokes are disabling; this percentage was used to weigh the two continuing care costs for stroke. Additional costs to 1 year associated with a MACE were calculated by weighting estimates of the annual costs of MI and stroke by the number of patients with these complications across the number of patients with a MACE, from Smits *et al.*[38]

BNF, *British National Formulary*.

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cardiac events' were used. Estimates from the Swedish Early Decision reperfusion Study (SWEDES) by Aasa *et al.*[47] were deemed to be the most appropriate; this study measured health status using the EuroQol-5 Dimensions (EQ-5D) in a group of PPCI patients, and quality weights were obtained using the UK EQ-5D tariff.[47] Patients completed the EQ-5D at three time points: baseline (within 3 days of randomisation, at the end time of index hospitalisation), and at 1 and 12 months. Mean utilities for patients were 0.72, 0.77 and 0.77 at each time point, respectively. Although the patient group included some patients with a MACE, here the estimates are applied to patients without a MACE.

Quality-adjusted life-years were calculated assuming a patient's utility changed linearly between each time point, so between baseline and 1 month, and between 1 and 12 months. Patients who died were assumed to die midway through the time period (i.e. at 6 months); their utility was assumed to change linearly between time points up to death, and a value of zero was given from death onwards. A QALY estimate for patients without a MACE – who, therefore, were all alive at 1 year – was calculated based on the utilities provided by Aasa *et al.*[47] For the QALY estimate for patients with a MACE 8% of patients were assumed to die,[38] this was used to produce a weighted average for patients alive and dead at 1 year, based on the utility weights and assumptions above. A utility decrement of 0.05 was then applied to this weighted average to reflect the reduced quality of life of patients with a MACE compared with those without a MACE.[48] QALY estimates for patients who had revascularisation of a second vessel were modified to assume their utility for month 1 was repeated for month 2. QALY estimates used in the model are summarised in *Table 4*. QALYs were parameterised using a beta distribution in the PSAs and a SD of 0.09 was assumed, as used elsewhere.[49]

Model 2: patients with normal coronary arteries

For a starting cohort of patients with normal coronary arteries, this model compares standard ECHO and CMR with standard ECHO only, and is designed to address the question: 'Is it cost-effective to introduce CMR in patients with normal coronaries who activate the PPCI pathway?'. For the standard ECHO and CMR arm of the model, *Figure 3* summarises the scenarios in the patient pathways included in the model structure.

TABLE 4 QALYs for the multivessel disease model

Patient group	Mean QALYs to 1 year
No revascularisation of a second vessel and MACE	0.686
No revascularisation of a second vessel and no MACE	0.768
Revascularisation of a second vessel and MACE	0.684
Revascularisation of a second vessel and no MACE	0.766

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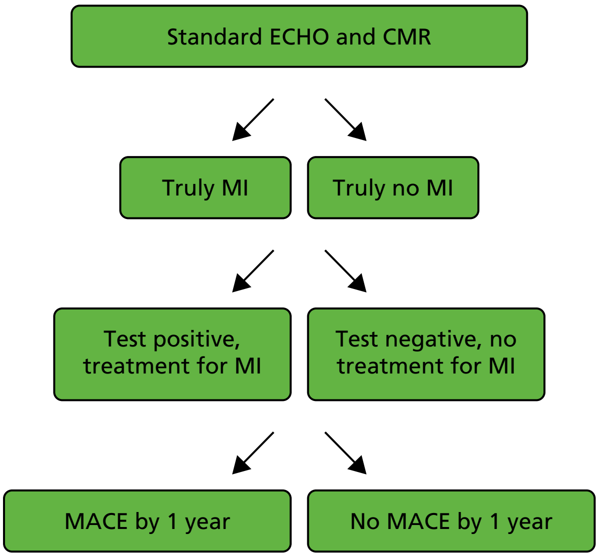

FIGURE 3 Scenarios in the patient pathway included in the model structure for patients with normal coronaries.

The model structure, shown in detail in *Figure 4*, is split into two main arms (branches): the top branch represents standard ECHO and CMR and the bottom branch represents standard ECHO only. The structure is the same in each arm, and starts by dividing patients into those who truly did have a MI and those who truly did not. Patients are then divided according to their ischaemia test result. For those with a positive test result, and therefore assumed to have had a MI, treatment for MI in the form of cardiac medications and cardiac rehabilitation will be given. Those with a negative test result will be treated for other causes of their chest pain, and given fewer cardiac medications or none at all. Thereafter, patients are divided into whether or not they had a MACE within 12 months. A MACE is defined in the same way as above: a composite end point of all-cause mortality, MI, stroke and revascularisation.

Data for the normal coronaries model

The decision tree for patients with normal coronaries was set up in a similar way to the model for patients with multivessel disease. The following sections describe how transition probabilities, costs and outcomes were estimated to 1 year, the majority of which were derived from the literature.

Probabilities for the normal coronaries model

Table 5 shows the probabilities used in the model and their respective sources. From initial MEDLINE searching, a 2016 review paper by Dastidar *et al.*[55] identified the first paper to use CMR for diagnosis in patients with normal coronaries,[20] and this was confirmed by later reviews. All citations of the Assomull *et al.*[20] paper were reviewed, and relevant (English) results read. Two meta-analyses were identified,[50,56]

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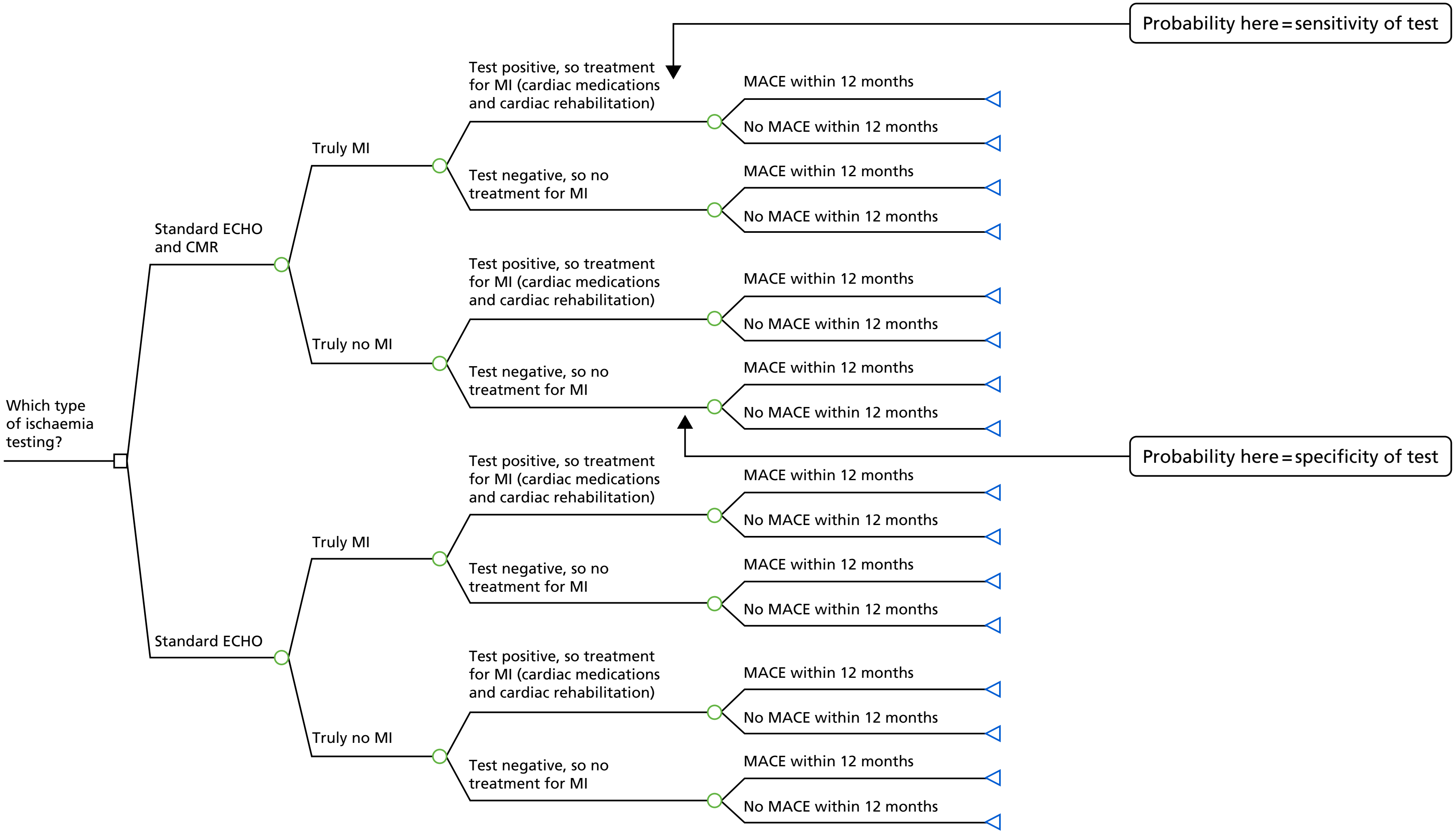
Probability here = sensitivity of test
Test positive, so treatment for MI (cardiac medications and cardiac rehabilitation)
MACE within 12 months
No MACE within 12 months
Truly MI
Test negative, so no treatment for MI
MACE within 12 months
No MACE within 12 months
Standard ECHO and CMR
Test positive, so treatment for MI (cardiac medications and cardiac rehabilitation)
MACE within 12 months
No MACE within 12 months
Truly no MI
Test negative, so no treatment for MI
MACE within 12 months
No MACE within 12 months
Which type of ischaemia testing?
Probability here = specificity of test
Test positive, so treatment for MI (cardiac medications and cardiac rehabilitation)
MACE within 12 months
No MACE within 12 months
Truly MI
Test negative, so no treatment for MI
MACE within 12 months
No MACE within 12 months
Standard ECHO
Test positive, so treatment for MI (cardiac medications and cardiac rehabilitation)
MACE within 12 months
No MACE within 12 months
Truly no MI
Test negative, so no treatment for MI
MACE within 12 months
No MACE within 12 months

FIGURE 4 Model structure for patients with normal coronaries (no blocked arteries).

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TABLE 5 Probabilities for the normal coronaries model

Branch of model	Base-case value (positive/total)	Distribution for PSA	Source
For both arms			
Probability of truly having had a MI	0.24 (429/1801)	Beta	Pasupathy *et al.*[50]
Standard ECHO and CMR			
Probability of ischaemia test positive and treatment for MI | MI	1[a]	Beta	
Probability of MACE within 12 months | treatment for MI	0.21	Beta	Kang *et al.*,[51] Pathik *et al.*[52]
Probability of MACE within 12 months | no treatment for MI	0.26[b]	Beta	Kang *et al.*,[51] Pathik *et al.*[52] and Lindahl *et al.*[53]
Probability of ischaemia test positive and treatment for MI | no MI	0[a]	Beta	
Probability of MACE within 12 months | treatment for MI	0.03[b]	Beta	Kang *et al.*,[51] Pathik *et al.*[52]
Probability of MACE within 12 months | no treatment for MI	0.03	Beta	Kang *et al.*,[51] Pathik *et al.*[52]
Standard ECHO			
Probability of ischaemia test positive and treatment for MI | MI	0.47 (25/53)[c]	Beta	Dastidar *et al.*[54]
Probability of MACE within 12 months | treatment for MI	0.21	Beta	Kang *et al.*,[51] Pathik *et al.*[52]
Probability of MACE within 12 months | no treatment for MI	0.26	Beta	Kang *et al.*,[51] Pathik *et al.*[52] and Lindahl *et al.*[53]
Probability of ischaemia test positive and treatment for MI | no MI	0.62 (93/151)[c]	Beta	Dastidar *et al.*[54]
Probability of MACE within 12 months | treatment for MI	0.03	Beta	Kang *et al.*,[51] Pathik *et al.*[52]
Probability of MACE within 12 months | no treatment for MI	0.03	Beta	Kang *et al.*,[51] Pathik *et al.*[52]

[a] In the base-case analyses, standard ECHO combined with CMR is assumed to have perfect sensitivity and specificity, but these parameters are incorporated into the model so that alternative assumptions can be tested in sensitivity analyses.

[b] These probabilities are not required in the base-case analyses (since the probability in the preceding branch is zero), but are included here as they are required in sensitivity analyses.

[c] For further information on how estimates of sensitivity and specificity for standard ECHO were obtained, please see the final paragraph in *Probabilities for the normal coronaries model*.

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and the citations of these papers were also reviewed, as were the references of more recent papers. In a final check to ensure that key papers had been identified, MEDLINE searching of keywords, such as 'myocardial infarction with non-obstructive coronary arteries', and synonyms was conducted (there are no relevant MeSH terms).

In the base-case analyses, standard ECHO and CMR was treated as a reference standard and assumed to have 100% sensitivity and specificity. Alternative scenarios were considered in sensitivity analyses.

Although there is evidence in the literature of the probability of a MACE, the definition frequently varies and studies follow patients for varying lengths of time. Although mortality at 1 year in patients with normal coronaries is lower than in patients with obstructed vessels,[50,57] it is still significant; a recent systematic review estimated this to be 4.7%.[50]

For the group as a whole, Kang *et al.*[51] reported MACEs at 12 months in 7.8% of patients with no or < 50% coronary artery stenosis. Their definition of a MACE included death, MI and ischaemic target vessel revascularisation, but did not include stroke. It should also be noted that, although the study began with 372 patients with no or < 50% coronary artery stenosis, only 126 had follow-up data at 12 months.

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Three studies[52,58,59] were identified that reported MACE for patients with normal coronaries, broken down by different CMR diagnoses. Pathik *et al.*[52] reported MACE for 0.27 (7/26) patients diagnosed with MI, and for 0.05 (5/99) patients not diagnosed with MI (diagnosed with myocarditis, cardiomyopathy or normal CMR) over a median of 24 months ($n = 125$). In the other two studies[58,59] of 124 and 87 patients, no MACE outcomes were observed in the non-MI patients. The MACE estimates reported in Pathik *et al.*[52] were converted to continuous rates (events were assumed to occur evenly over the median 24 months of follow-up). The ratio of events in the MI patients compared with the non-MI patients was six, and was used with the overall estimate of a MACE at 1 year from Kang *et al.*[51] (0.078), and the estimate of the underlying probability of patients truly having a MI from Pasupathy *et al.*[50] (0.24), to calculate estimates of the probability of a MACE in patients who truly had a MI and in those who did not have a MI. This generated probability estimates of a MACE of 0.21 for patients with MI, and 0.03 for patients without a MI. However, we needed estimates of MACE based not only on whether or not patients had a MI, but also on whether or not they had treatment for a MI. The estimate generated for patients with MI (0.21) was assumed to apply to patients who had treatment. The hazard ratio reported by Lindahl *et al.*[53] for a MACE for patients who were taking statins compared with those who were not (0.77) was used to adjust this estimate of a MACE for patients who had a MI and treatment, to give a probability of a MACE for those with MI but without treatment of 0.26. For patients without MI, the probability of a MACE of 0.03 was assumed to apply regardless of whether or not treatment was given. A SE of 0.10 was assumed for the PSA for these probabilities. Although Pathik *et al.*[52] was the only source found to estimate the ratio of events in MI patients compared with non-MI patients (in patients with normal coronaries), it is important to highlight that the estimated ratio of six raised concerns among the study team as being very high, and that lower values are explored in sensitivity analyses.

The sensitivity and specificity of standard ECHO were estimated from Dastidar *et al.*[54] The pre-CMR diagnosis reported was treated as the standard ECHO diagnosis, and the post-CMR diagnosis was assumed to be the true underlying diagnosis. It was assumed that those with a pre-CMR diagnosis of MI or uncertain would have been given treatment for MI, and, therefore, patients in these categories were combined for the purposes of the sensitivity and specificity calculations.

Costs for the normal coronaries model

For each ischaemia testing strategy considered, the costs included were the cost of ischaemia testing (standard ECHO, CMR), the cost of treatment for MI in the form of cardiac rehabilitation and medications, the cost of medications for non-MI causes, costs associated with adverse events included in MACEs (both the initial inpatient costs and subsequent costs post discharge), and additional health-care costs beyond hospital discharge to 1 year, including a follow-up appointment for all patients. Unit costs were obtained from national sources[40,41] and are shown in *Table 6*; details of assumptions made in estimating unit costs are also provided in *Table 6*. As for the unit costs used in the previous model, when mean and upper quartile unit costs were available, the difference was used as a crude estimate of SE in the PSAs, otherwise the SE was assumed to be 20% of the mean cost. Costs were parameterised using a gamma distribution in the PSAs.

Outcomes for the normal coronaries model

The QALY estimates used in the model are shown in *Table 7*. Searches of the Tufts Cost-effectiveness Analysis Registry[46] did not yield any utility weights that were specific to patients with normal coronaries; therefore, the estimates in Aasa *et al.*[47] were also used here. The QALY estimate for patients without a MACE who were all alive at 1 year was calculated directly from the utilities in Aasa *et al.*[47] For the QALY estimate for patients with a MACE, 8% of patients were assumed to die based on the same source as the MACE estimates above;[52] this was used to produce a weighted average for patients alive and dead at 1 year, based on the utility weights and assumptions described previously, and a utility decrement of 0.05 was again applied to reflect the reduced quality of life of patients with a MACE.[48] The study team felt that the estimate of the proportion of patients with a MACE who die was low; therefore, a higher proportion (50%) is explored in the sensitivity analyses.

TABLE 6 Costs for the normal coronaries model

Resource	Unit cost, £ (SE)	Source
Standard ECHO	72 (22)	*NHS Reference Costs 2015 to 2016*.[40] Diagnostic Imaging. Outpatient. RD51 A, Simple Echocardiogram, ≥ 19 years
CMR	264 (154)	*NHS Reference Costs 2015 to 2016*.[40] Diagnostic Imaging. Weighted average of all Cardiovascular Magnetic Resonance Imaging Scan codes
Cardiac rehabilitation	364 (73)	Assume offered eight sessions, but only 50% uptake, so cost four sessions (one first and three follow-up appointments, individual costs below)
First appointment	97	*NHS Reference Costs 2015 to 2016*.[40] Consultant Led. Cardiac Rehabilitation. Non-Admitted Face to Face Attendance, First
Follow-up appointment	89	*NHS Reference Costs 2015 to 2016*.[40] Consultant Led. Cardiac Rehabilitation. Non-Admitted Face to Face Attendance, Follow-Up
Cardiac medications for treatment of MI (all once daily by mouth)		
Aspirin (75 mg)	0.04	BNF[41]
Clopidogrel (75 mg)	0.05	BNF[41]
Atorvastatin (80 mg)	0.07	BNF[41]
Bisoprolol (2.5 mg)	0.02	BNF[41]
Ramipril (2.5 mg)	0.04	BNF[41]
Total daily cost	0.22	
Total annual cost	80 (16)	
Treatment for non-MI cause (cardiac medications): total daily cost	0.11	Assume that half of these patients are taken off cardiac medications above (these medications are given for cardiomyopathy but not for myocarditis)
Outpatient follow-up appointment (assumed to occur at 4–6 weeks post discharge)	122 (22)	*NHS Reference Costs 2015 to 2016*.[40] Consultant-led appointments. Non-Admitted Face to Face Attendance, Follow-Up. Cardiology
MACE	2808 (562)	The proportion of each component of MACE was taken from Pathik *et al.*,[52] and a weighted average of the costs of each component was calculated, based on the unit costs provided in *Table 2*. Given the small number of MACE events, calculations were based on MI and non-MI patients combined
Additional health-care costs to 1 year	2221 (444)	The Office of Health Economics' estimate of the annual cost per person of NHS care inflated to 2015/16 prices using the hospital and community health services inflation index.[42,43] For patients who die, costs are assumed to be half of this (£1111)
Additional health-care costs to 1 year for those with a MACE	1602 (320)	MI and stroke were assumed to be associated with continuing care costs post discharge. Costs from Greenhalgh *et al.*[44] were inflated to 2015/16 prices.[42] Separate costs were provided for disabling and non-disabling stroke. According to Davies *et al.*[45] 58% of strokes are disabling; this percentage was used to weigh the two continuing care costs for stroke. Additional costs to 1 year associated with MACE were calculated by weighting estimates of the annual costs of MI and stroke by the number of patients with these complications across the number of patients with MACE, from Pathik *et al.*[52]

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TABLE 7 QALYs for the normal coronaries model

Patient group	QALYs to 1 year
MACE within 12 months	0.686
No MACE within 12 months	0.768

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Model analyses

All analyses were conducted in TreeAge Pro 2013 (TreeAge Software Inc., Williamstown, MA, USA). Costs and QALYs were not discounted, as the time horizon was 1 year. Cost-effectiveness analyses were run, and the expected costs and QALYs associated with each arm (each ischaemia testing strategy) to 1 year were calculated. The incremental cost-effectiveness ratio (ICER) was derived from the difference in costs and QALYs between each ischaemia testing option and current practice. The ICER is the cost per QALY gained of introducing a different form of ischaemia testing compared with current practice.

As this is a feasibility study, it is not the actual ICER and cost-effectiveness results that are the main interest, but rather how the results change in response to sensitivity analyses; this will identify the key drivers of cost-effectiveness that would require detailed measurement and consideration in any subsequent work.

Sensitivity analyses

Both one-way sensitivity analyses and PSAs were conducted. One-way sensitivity analyses were used to assess the sensitivity of the base-case results to key uncertainties in the model to identify the key drivers of cost-effectiveness. *Tables 8* and *9* describe the key sensitivity analyses that were conducted for each model. Threshold analyses were also conducted around the costs of CMR, and angiography and pressure wire to establish the cost of the test at which the costs associated with alternative strategies were the same.

To quantify the uncertainty around the one-way sensitivity analyses, parameters were assigned distributions (rather than fixed values) so that SEs and CIs could be estimated; this was done in the same way as the PSAs that were conducted. PSAs were used to investigate the joint impact of results of all uncertain parameters in the model simultaneously.

TABLE 8 Sensitivity analyses for the multivessel disease model

SA	Parameter varied	Base case	Alternative strategies for SA
1	Probabilities associated with decision on revascularisation from index angiography	Based on expert opinion	Based on PIPA data
	Probability that index angiography leads to revascularisation of a second vessel (number of patients with events/total number of patients)	0.30 (30/100)	0.11 (78/717)
	Probability of uncertainty following index angiography and need for ischaemia testing (number of patients with events/total number of patients)	0.60 (60/100)	0.15 (111/717)
	Probability that index angiography leads to no revascularisation of second vessel (number of patients with events/total number of patients)	0.10 (10/100)	0.74 (528/717)
2	Sensitivity and specificity of CMR	1 and 1	0.8 (SE 0.1) for each

TABLE 8 Sensitivity analyses for the multivessel disease model (*continued*)

SA	Parameter varied	Base case	Alternative strategies for SA
3	Sensitivity and specificity of pressure wire	1 and 1	0.8 (SE 0.1) for each
4	Sensitivity and specificity of stress ECHO	0.70 and 0.77 (reported 1 – specificity = 0.23)	Sensitivity: 0.791 (SE 0.008) and 1 – specificity 0.129 (SE 0.007)[60]
5	Probability of MACE for truly ischaemic patients who had a second revascularisation, truly ischaemic patients who did not have a second revascularisation, and truly not ischaemic patients whether or not they had a second revascularisation	0.09, 0.31, 0.13	All ± 0.05
6	Cost of CMR	£264.00	± 20%
7	Cost of angiography and pressure wire	£1340.00	± 20%
8	QALYs for patients with MACE with and without revascularisation of second vessel	0.684, 0.686	Base case –0.2 (0.484, 0.486)
9	QALYs for patients with no MACE with and without revascularisation of second vessel	0.766, 0.768	Base case +0.2 (0.966, 0.968)

SA, sensitivity analysis.
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TABLE 9 Sensitivity analyses for the normal coronaries model

SA	Parameter varied	Base case	Alternative strategies for SA
1	Sensitivity and specificity of standard ECHO plus CMR	1 and 1	0.8 (SE 0.1) for each
2	Sensitivity and specificity of standard ECHO	0.47 and 0.38	0.7 (SE 0.1) for each
3	Probability of MACE for patients who had a MI and treatment, for patients who had a MI and no treatment, and for patients without MI regardless of whether they had treatment (ratio of events in MI-to-non-MI group = 4)[a]	0.21, 0.26, 0.03	0.18, 0.23, 0.05
4	Probability of MACE (ratio = 2)	0.21, 0.26, 0.03	0.13, 0.17, 0.06
5	Probability of MACE (ratio = 1)	0.21, 0.26, 0.03	0.08, 0.10, 0.08
6	Cost of CMR	£264.00	± 20%
7	Cost of additional health-care costs to 1 year for patients with a MACE: increase the proportion who die from 8% to 50%	£1602.00	£874.00
8	QALYs for patients with MACE	0.686	Base case –0.2 (0.486)
9	QALYs for patients with no MACE	0.768	Base case 0.2 (0.968)
10	QALYs for patients with MACE: increase the proportion who die from 8% to 50%	0.686	0.525

SA, sensitivity analysis.
[a] For further information on this ratio, please see the fifth paragraph in *Probabilities for the normal coronaries model*.
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Model parameters were assigned probability distributions to describe the range of plausible values that they could take based on the precision of the estimates available. The type of distribution assigned was matched to the nature of the parameter; for example, a beta distribution lies between zero and one and is, therefore, appropriate for parameterising the probability of two mutually exclusive events. The type of distribution assigned to each parameter was described with the model inputs above.

Randomly selected values from each distribution for each model parameter were simultaneously generated using Monte Carlo simulation; this was repeated 1000 times and the results were calculated for each run of the model, generating a distribution of costs and effects that were used to calculate 95% CIs around the cost and QALY differences between testing strategies, enabling the effect of the parameter uncertainty on results to be investigated.

Changes to study design after commencement of the study

Feasibility prospective cohort study

There were two main changes to the study design, summarised below:

1. We included the option of postal consent to the recruitment protocol, mainly to be able to catch patients who were repatriated quickly to local hospitals after the index procedure.
2. We followed up patients through routinely collected hospital episode data (HES for English hospitals and PEDW for Welsh hospitals). We originally intended to obtain follow-up data for 12 months after the index procedure from each hospital. However, this was not feasible for many patients, given that they were repatriated to/followed up at a different hospital from where they had their index procedure.

Formal consensus study

There were four main changes related to the formal consensus study, summarised below:

1. We had intended to include different stakeholders [e.g. cardiologists, general practitioners (GPs) and patient representatives] in the consensus process. However, as the consensus statements developed it became evident that these were highly specialised and it would have been unreasonable to expect those without cardiology expertise to rate and discuss them. Therefore, the consensus process included only cardiologists.
2. We did not originally intend to give the final survey to cardiologists who did not participate in the consensus process. However, we had fewer than anticipated cardiologists in the consensus panel; therefore, to avoid any criticism of the number of panel members in our study and to prevent the possibility of introducing bias (given the self-selected nature of the panel), we decided to extend the survey to UK cardiologists who did not participate in the formal consensus process.
3. We had originally intended to implement our primary outcome using follow-up data from local HISs. However, given the difficulties of obtaining local follow-up data (highlighted in *Feasibility prospective cohort study*, point 2), we used HES follow-up data instead.
4. We designed and gave a questionnaire to all cardiologists who referred patients for CMR (in our two centres with dedicated CMR facilities), which requested information about how CMR changed the management of those patients. We determined whether or not changes in management described in the questionnaire were adequately reflected in hospital episode data (see *Chapter 6*, *Implementation of a primary outcome based on the changes in management for which consensus was achieved*).

Health economic study

We intended to use data collected as part of the PIPA study, particularly patient episode data from HES and the PEDW. However, because the HES data were not available in time to do this, an alternative approach was required. Secondary sources of data were sought and used as inputs into economic decision models used to identify the key drivers of cost-effectiveness for CMR imaging in patients who activate the PPCI pathway, that is, the model parameters that have the most influence.

Chapter 4 Results for aim A: feasibility of setting up a cardiovascular magnetic resonance registry by linking sources of routinely collected data

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Aim A: to determine whether or not it is feasible to set up a cardiovascular magnetic resonance registry in this patient population by linking sources of routinely collected data

- Objective A1: to implement consent and establish patient consent rate.
- Objective A2: to provide evidence of whether or not data linkage and extraction can be carried out across PPCI centres.
- Objective A3: to determine whether or not the registry can be compiled from HES and the PEDW rather than multiple HISs.

The number of data about 'usual care' provided by UK NHS hospitals that are being collected and stored electronically in HISs is rapidly increasing. Previous studies have shown that it is possible to use multiple HISs to retrieve and compile these patient-level data into a research database.[61–63] This study tested the feasibility of setting up a large multicentre registry for patients who activate the PPCI pathway by linking data from multiple HISs within several hospitals. If the registry was feasible, we had the longer-term aim of using registry data to evaluate the clinical effectiveness and cost-effectiveness of CMR in this population.

Screening and consent

Standard consent was successfully implemented at all participating hospitals. Across the four participating hospitals, a total of 2462 patients were screened between 13 May 2013 and 4 September 2014. Of these, 1670 (68%) consented to participate in the study. Consent rates ranged from 59% to 74% (an average of 68% across the four hospitals). We investigated various options for obtaining consent during the study: obtaining consent at discharge (rather than straight after the procedure), and an opt-out model on the procedural consent form (adding a paragraph to the procedural consent form explaining that the clinical data collected would be used for research unless patients 'opted out' by ticking a box on the form). These were not implemented as they were deemed not feasible.

Detailed screening data were available for only one hospital (hospital A, *Figure 5*). A total of 1210 patients were screened in hospital A; 856 were identified through the cardiology database 'query' that was set up to identify eligible participants for the study and 354 were identified independently by the research nurse team. The other hospitals did not provide detailed screening data. We anticipated that local record linkage between databases held by a hospital would allow patients who gave consent to be distinguished from those who did not. Thus, it was intended that standard aspects of data collection for prospective studies, for example a screening log with reasons for ineligibility and a record of consent, would be implemented in our study as routine reports from the database. In hospital A, we set out to identify eligible patients through a database 'query' set up in the local cardiology database. It was hoped that this screening model would be

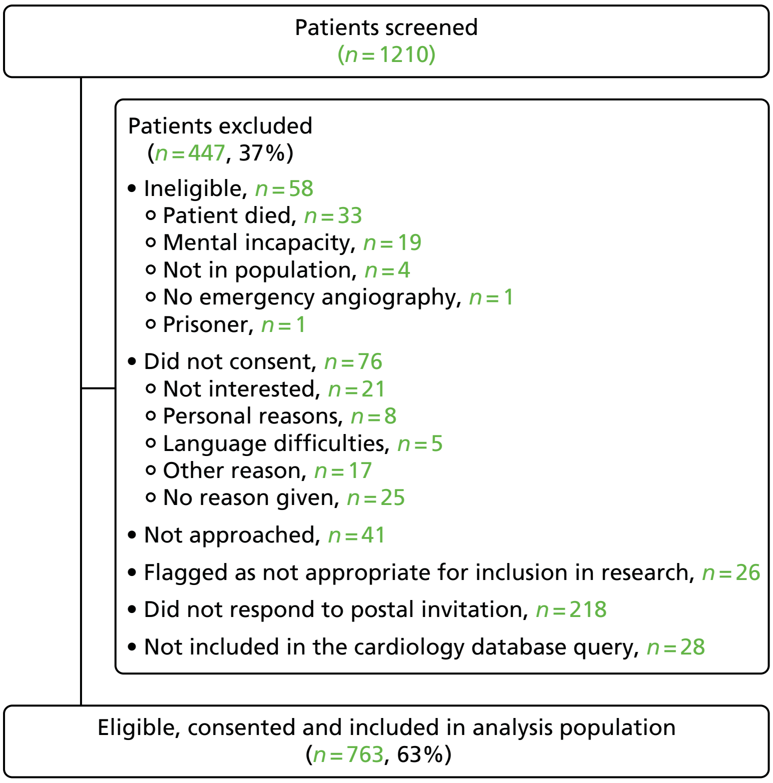
Patients screened
(n = 1210)
Patients excluded
(n = 447, 37%)
• Ineligible, n = 58
○ Patient died, n = 33
○ Mental incapacity, n = 19
○ Not in population, n = 4
○ No emergency angiography, n = 1
○ Prisoner, n = 1
• Did not consent, n = 76
○ Not interested, n = 21
○ Personal reasons, n = 8
○ Language difficulties, n = 5
○ Other reason, n = 17
○ No reason given, n = 25
• Not approached, n = 41
• Flagged as not appropriate for inclusion in research, n = 26
• Did not respond to postal invitation, n = 218
• Not included in the cardiology database query, n = 28
Eligible, consented and included in analysis population
(n = 763, 63%)

FIGURE 5 Flow chart of patient recruitment in hospital A.

exported to the other participating hospitals. However, when we started recruiting, it became clear that this screening model did not work, as many patients were identified independently of the database query. The other hospitals were, therefore, allowed to implement their own methods of screening, involving a combination of electronic processes (e.g. e-mail alerts or database searches for new potentially eligible patients) and manual processes (e.g. checking admission books) by the research nurses and/or the local principal investigator.

Recruitment

A total of 1670 participants were recruited to the study between May 2013 and September 2014. Cumulative recruitment by hospital is shown in *Figure 6*. Recruitment over time increased steadily across all hospitals. Hospital A recruited the largest number of patients.

Because we did not have screening data for three of the hospitals, we estimated the approximate number of eligible patients over the recruiting period from the data between January and December 2014 provided directly by the BCIS. This registry provides comparative data on the provision of PCI in the UK and describes the quality and patterns of care, the process of care and outcomes for patients from all PCI centres. We extrapolated the number of PPCI procedures carried out during the recruitment period at each of the hospitals from the annual data provided for each hospital. The estimated rate of recruitment at each hospital is shown in *Table 10*. The average recruitment rate across the four hospitals was 52%, but there was large variation between hospitals (22–86%). These recruitment figures do not take into account (1) patients who did not meet the study eligibility criteria or (2) patients who activated the PPCI pathway but had emergency angiography only (i.e. patients with unobstructed arteries).

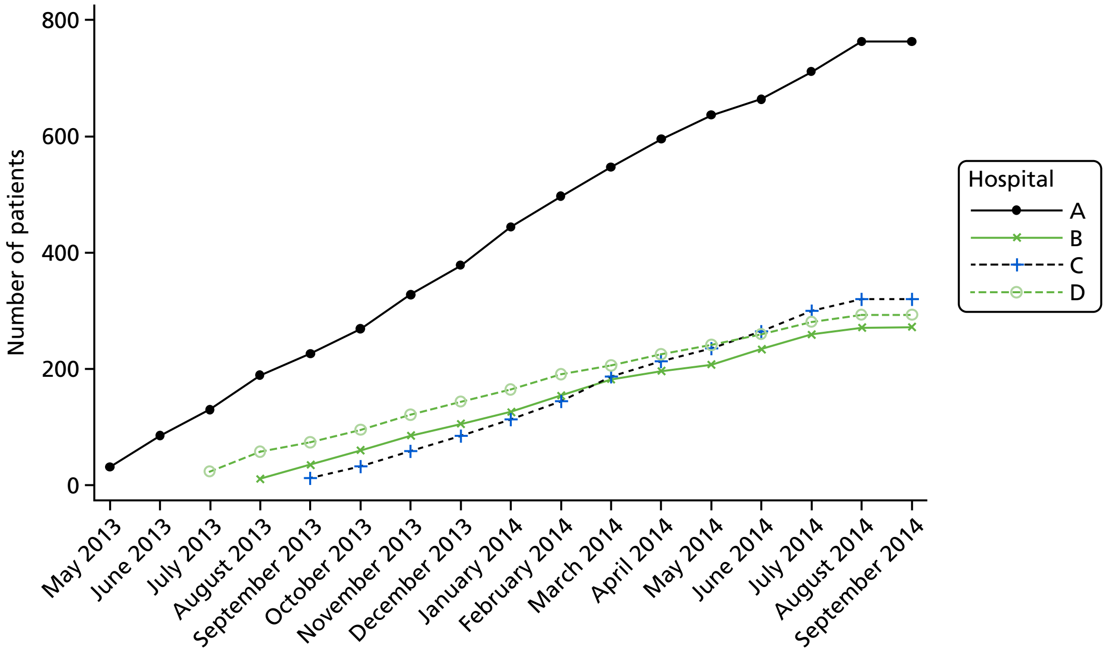

FIGURE 6 Recruitment over time, by hospital.

TABLE 10 Estimated recruitment rate, by hospital

Site	Number of months of recruitment	Estimated number of PPCIs[a] during recruitment period	Participants recruited to study[b] (*n*)	Estimated % recruited
Hospital A	15.7	765	655	86
Hospital B	12.5	1138	246	22
Hospital C	11.2	392	295	75
Hospital D	13.8	532	280	53
Total		2827	1476	52

[a] Estimated recruitment over time based on the following annual figures for January–December 2014: hospital A, *n* = 585; hospital B, *n* = 1092; hospital C, *n* = 420; and hospital D, *n* = 463.

[b] Number recruited with BCIS data.

Data linkage and extraction across hospitals

Figure 7 shows the flow chart of data availability. Anonymised data were available for 705 out of the 792 (89%) patients who were identified as eligible but who did not consent or were not approached. Clinical and biochemistry data were most readily available (for > 80% of participants), whereas data on medications were least readily available (for only 44% of participants).

Figure 8 shows the flow chart of data submitted from each hospital. One of the hospitals (hospital B) provided the data in a linked format; linkage was undertaken centrally for the other three hospitals with data linked on a local hospital identifier. Anonymised data were available for > 80% of patients from three hospitals, but for only 50% of patients from one hospital. Clinical data were available for 93% of patients at all hospitals (range 82–98%). The availability of ECHO data was variable; one hospital was unable to submit any ECHO data, one hospital submitted ECHO data for only 34% of patients and two submitted data for > 75% of patients. ECHO data were submitted as free-text reports, rather than coded data. Biochemistry data were available for ≥ 98% of patients from three hospitals; one hospital was unable to submit biochemistry data for any of its patients. Data about medications on discharge were available for

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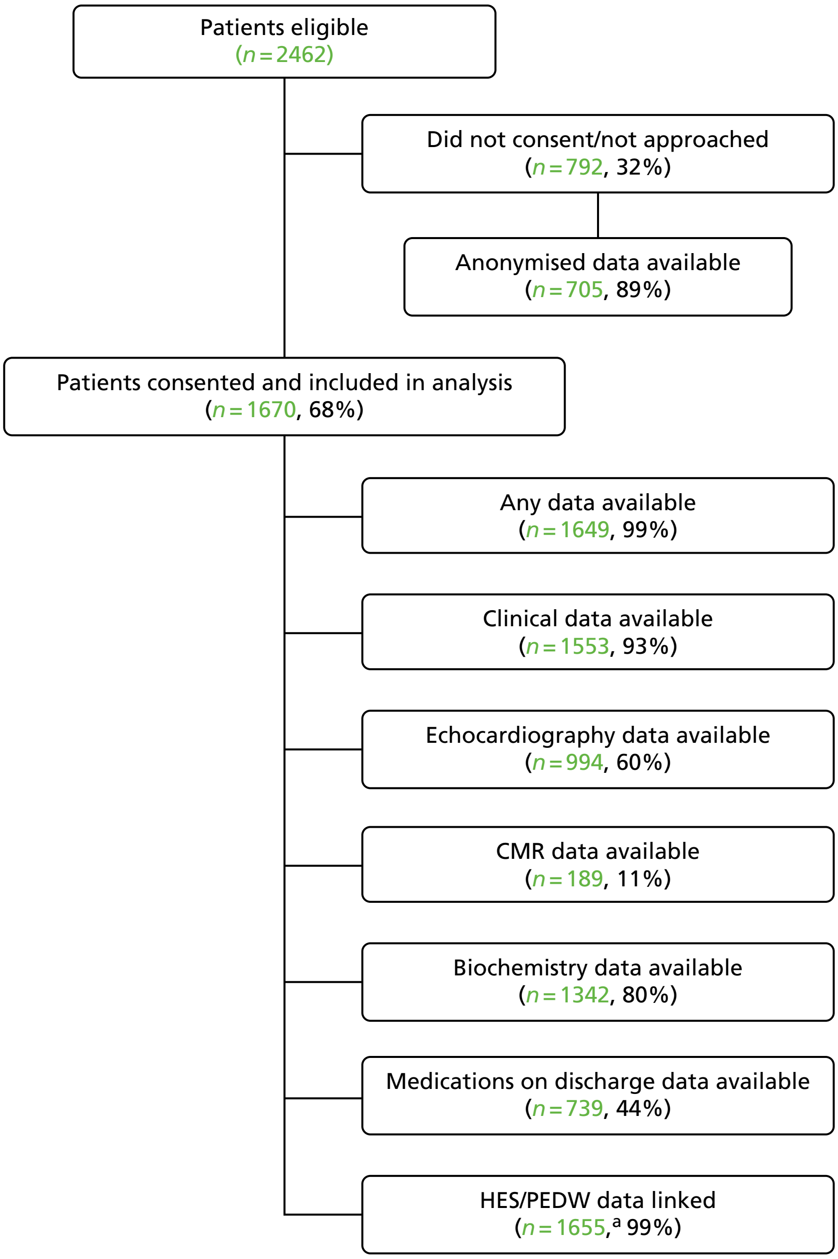
Patients eligible
(n = 2462)
Did not consent/not approached
(n = 792, 32%)
Anonymised data available
(n = 705, 89%)
Patients consented and included in analysis
(n = 1670, 68%)
Any data available
(n = 1649, 99%)
Clinical data available
(n = 1553, 93%)
Echocardiography data available
(n = 994, 60%)
CMR data available
(n = 189, 11%)
Biochemistry data available
(n = 1342, 80%)
Medications on discharge data available
(n = 739, 44%)
HES/PEDW data linked
(n = 1655,a 99%)

FIGURE 7 Flow chart of data availability.

a, The number of patients with their index procedure identified in hospital episode data (exact match on day or 1 day out) or inpatient or outpatient or A&E data available in the year following the index procedure. Note that 1612 out of 1670 (97%) patients had their index procedure identified in hospital episode data (exact match on day or 1 day out).

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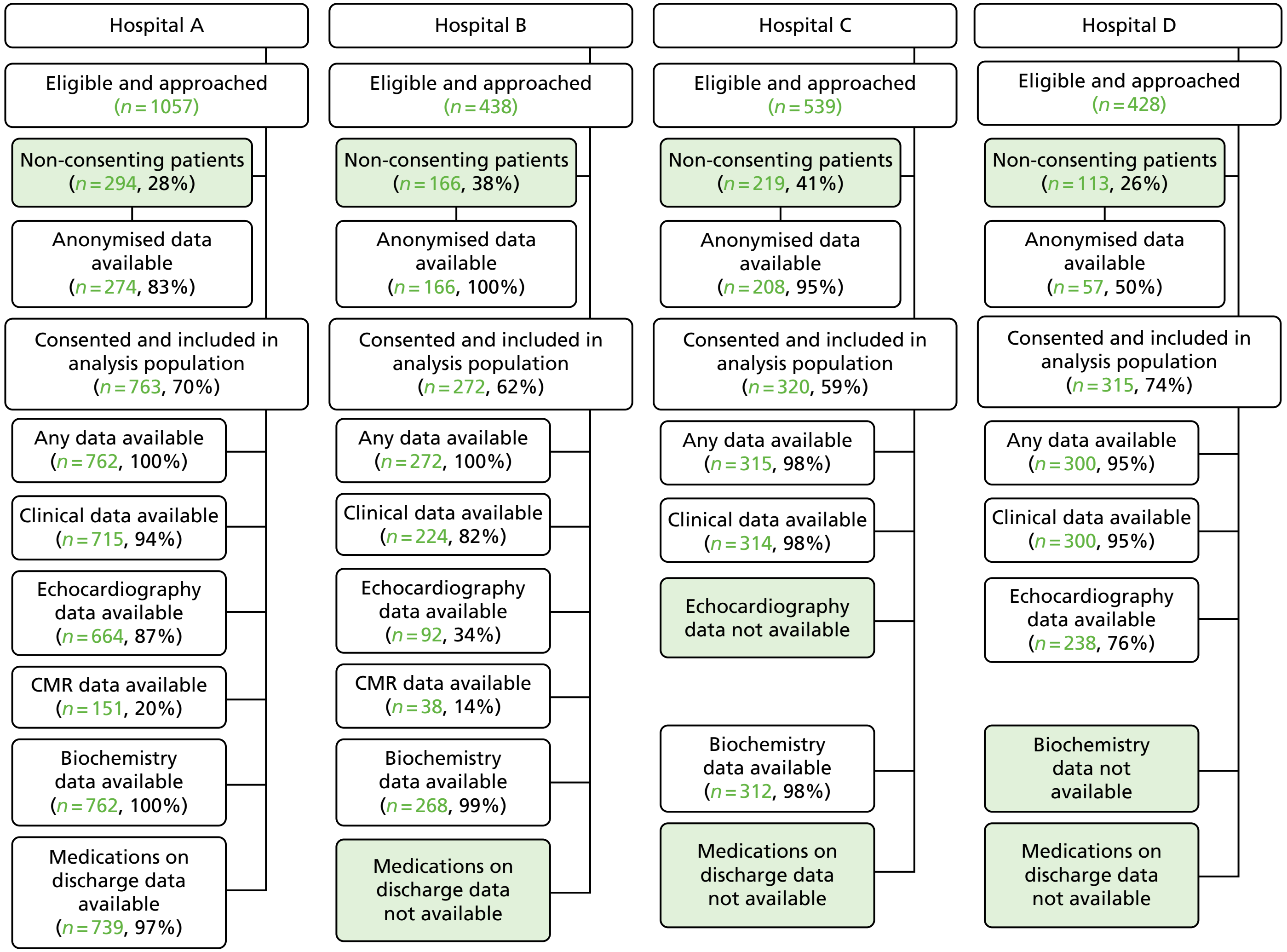
Hospital A
Eligible and approached (n = 1057)
Non-consenting patients (n = 294, 28%)
Anonymised data available (n = 274, 83%)
Consented and included in analysis population (n = 763, 70%)
Any data available (n = 762, 100%)
Clinical data available (n = 715, 94%)
Echocardiography data available (n = 664, 87%)
CMR data available (n = 151, 20%)
Biochemistry data available (n = 762, 100%)
Medications on discharge data available (n = 739, 97%)
Hospital B
Eligible and approached (n = 438)
Non-consenting patients (n = 166, 38%)
Anonymised data available (n = 166, 100%)
Consented and included in analysis population (n = 272, 62%)
Any data available (n = 272, 100%)
Clinical data available (n = 224, 82%)
Echocardiography data available (n = 92, 34%)
CMR data available (n = 38, 14%)
Biochemistry data available (n = 268, 99%)
Medications on discharge data not available
Hospital C
Eligible and approached (n = 539)
Non-consenting patients (n = 219, 41%)
Anonymised data available (n = 208, 95%)
Consented and included in analysis population (n = 320, 59%)
Any data available (n = 315, 98%)
Clinical data available (n = 314, 98%)
Echocardiography data not available
Biochemistry data available (n = 312, 98%)
Medications on discharge data not available
Hospital D
Eligible and approached (n = 428)
Non-consenting patients (n = 113, 26%)
Anonymised data available (n = 57, 50%)
Consented and included in analysis population (n = 315, 74%)
Any data available (n = 300, 95%)
Clinical data available (n = 300, 95%)
Echocardiography data available (n = 238, 76%)
Biochemistry data not available
Medications on discharge data not available

FIGURE 8 Flow chart of data availability, by hospital. Shading indicates that no data were available.

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97% of patients from one hospital; the other three hospitals were unable to submit these data.[27] Although we requested biochemistry test results relevant to the cardiovascular disease population [creatinine, full blood count (serial), electrolytes (serial), troponin (admission; 8 hour), cholesterol (on admission), blood glucose (serial) and C-reactive protein (serial)], the three hospitals that provided biochemistry data sent all tests conducted during the specified time frame. However, it was feasible to extract specific test results from the biochemistry data sets and identify specific medications from the medications data sets.

There were a number of issues with data that were provided by hospitals, such as the inclusion of 'test' patients at one hospital, discrepancies between hospitals on the format and naming of the fields (e.g. BCIS fields were provided as: 'yes/no', '1/2' or '1. yes/2. no') and the delay in receiving extracts. Once identified, 'test' patients were removed at source and discrepancies between formatting and naming of fields were addressed by hardcoding.

Cardiovascular magnetic resonance exposure

Cardiovascular magnetic resonance reports were submitted for all consented patients who received CMR in hospitals A and B. Like the ECHO data, CMR data were in free-text format; the hospital that provided linked data (hospital B) extracted the CMR variables of interest from the free-text reports. Information about whether or not a CMR was ordered for clinical need or research purposes (i.e. patient participating in another research study) was not recorded routinely. From information provided by hospital A, the proportion ordered for clinical need was 67%.

Data linkage with Hospital Episode Statistics and Patient Episode Database Wales

Hospital Episode Statistics, ONS and PEDW data were provided from the first recruitment date across all hospitals (May 2013) up to 30 September 2014 (Swansea), 31 March 2015 (Bristol and Leeds) and 30 April 2015 (Cardiff). Data linkage with HES, PEDW and vital status was achieved for 1655 out of 1670 (99%) patients across all hospitals. The linkage for each HES or PEDW data set is shown in *Table 11*. No data were supplied for patients for whom the NHS number was not recorded.

A further review of the linked data demonstrated that it was possible to identify an admission that matched the index admission for 1554 (93%) patients; this increased to 1612 (97%) patients when the dates of admissions recorded in hospital episode data and the date of the index admission recorded in HISs

TABLE 11 Data linkage for each HES and PEDW data set, by hospital

		Patients with, *n* (%)			
Site	Consented (*n*)	Any admissions data	Any outpatient data	Any A&E data	Admissions, outpatient or A&E data
Hospital A[a]	763	757 (99)	743 (97)	583 (76)	758 (99)
Hospital B	272	272 (100)	269 (99)	196 (72)	272 (100)
Hospital C[b]	320	311 (97)	266 (83)	264 (83)	316 (99)
Hospital D[c]	315	309 (98)	292 (93)	191 (61)	309 (98)
Total	1670	1649 (99)	1570 (94)	1234 (74)	1655 (99)

a No NHS number for five patients.
b No NHS number for one patient.
c No NHS number for six patients; no event date for 17 patients.

were allowed to differ by 1 day. For some patients ($n = 22$, hospital D), it was not possible to identify the index admission in HES because the event date was not recorded in the HIS. This also meant that it was not possible to identify admissions, outpatient appointments or A&E visits in the year after the index admission for these patients. Data availability is shown in *Table 12*.

Identifying the eligible study cohort and cardiovascular magnetic resonance exposure in hospital episode data

We identified 98% (range 92–100% across hospitals) of patients who underwent PPCI and 85% (range 46–99% across hospitals) of patients who had an emergency angiogram but no PCI in hospital episode data.

We could not identify all CMR exposure in HES. Admissions including the date of the CMR were identified for 109 of the 189 patients with CMR recorded in HISs (57%) and a record of CMR was found in the hospital episode data for 49 of these 109 (45%) patients. Patients who had a CMR dated after discharge, based on the HIS, were assumed to have had the CMR as an outpatient ($n = 81$); only 7 (9%) of these patients had a matching outpatient date in the hospital episode data. None of these seven outpatient episodes included any code for CMR (procedure codes are not well recorded in the HES outpatients' data set). Data availability is shown in *Table 13* and the details of CMR identification in the hospital episode data are shown in *Figure 9*.

Summary of main findings

Identifying the eligible population

Patients who activated the PPCI pathway and received PCI were easy to identify from catheter laboratory databases, since consistent terminology was used to define these patients. A proportion of these patients recruited in the study were identified independently of these databases. Patients who activated the PPCI pathway but did not receive PPCI were not consistently defined in catheter laboratory databases; these patients required further manual checks by catheter laboratory staff who assisted the research nurses in identifying eligible patients. Some of these patients were screened out, possibly because of (1) misunderstanding by catheter laboratory staff or research nurses over eligibility (especially at the beginning of the study) and (2) the lack of consistent terminology used to describe these patients in catheter laboratory databases, leading to confusion about whether or not to include them.

TABLE 12 Data linkage for each HES and PEDW data set, by hospital

		n (%)			
Site	Consented (*N*)	Admission matching index admission date (± 1 day)	Any APC data in year after index admission	Any outpatient data in year after index admission	Any A&E data in year after index admission
Hospital A[a]	763	756 (99)	342 (45)	720 (94)	315 (41)
Hospital B	272	269 (99)	115 (42)	258 (95)	116 (43)
Hospital C[b]	320	295 (92)	130 (41)	234 (73)	119 (37)
Hospital D[c]	315	292 (93)	86 (27)	284 (90)	89 (28)
Total	1670	1612 (97)	673 (40)	1496 (90)	639 (38)

APC, admitted patient care (inpatient).
a No NHS number for five patients.
b No NHS number for one patient.
c No NHS number for six patients; no event date for 17 patients.

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TABLE 13 Consented patients who underwent PPCI and emergency angiography without PCI, identified in hospital episode data

		n (%)					
Site	**Consented (*N*)**	**Number (out of *N*) consented and matched for PPCI index date (CRF and hospital electronic record)**	**Number (and %) of those in the left adjacent column also identified in national routine data sets (HES/PEDW)**	**Number (out of *N*) consented and matched for emergency angiography but without PPCI (CRF and hospital electronic record)**	**Number (and %) of those in the left adjacent column also identified in national routine data sets (HES/PEDW)**	**Number (out of *N*) consented and matched for CMR (CRF and hospital electronic record)**	**Number (and %) of those in the left adjacent column also identified in national routine data sets (HES/PEDW)**
Hospital A	763	655	649 (99)	108	107 (99)	151	49 (32)
Hospital B	272	246	246 (100)	26	23 (88)	38	6 (16)
Hospital C	320	295	273 (92)	25	22 (88)	–	–
Hospital D	315	280	274 (98)	35	16 (46)	–	–
Total	1670	1476	1444 (98)	194	168 (85)	189	55 (29)

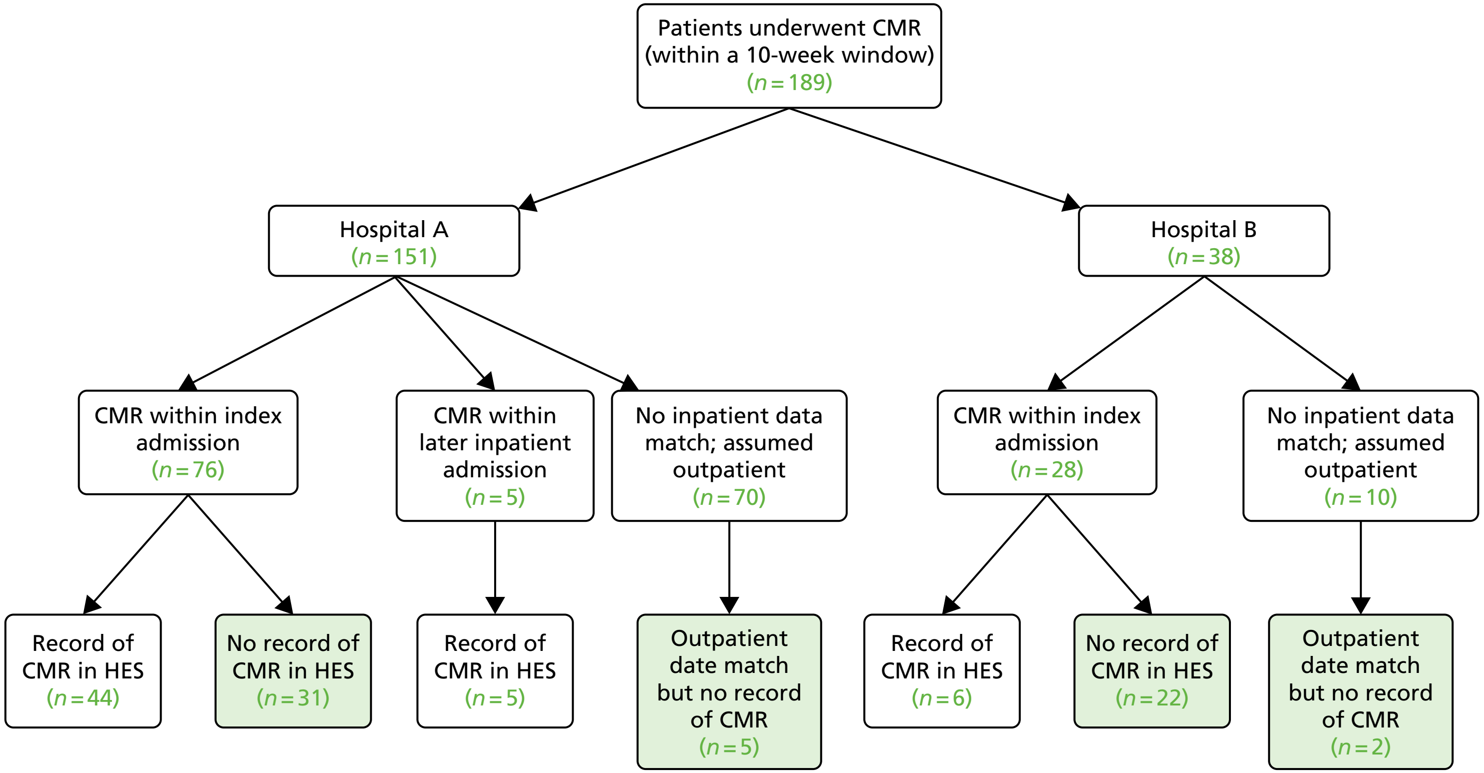
Patients underwent CMR (within a 10-week window) (n = 189)
Hospital A (n = 151)
Hospital B (n = 38)
CMR within index admission (n = 76)
CMR within later inpatient admission (n = 5)
No inpatient data match; assumed outpatient (n = 70)
CMR within index admission (n = 28)
No inpatient data match; assumed outpatient (n = 10)
Record of CMR in HES (n = 44)
No record of CMR in HES (n = 31)
Record of CMR in HES (n = 5)
Outpatient date match but no record of CMR (n = 5)
Record of CMR in HES (n = 6)
No record of CMR in HES (n = 22)
Outpatient date match but no record of CMR (n = 2)

FIGURE 9 Details of CMR recording in HES/PEDW data.

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Implementing consent

We asked all participating hospitals to implement a conventional system of written consent so that we could establish a consent rate and ensure that we had consent to obtain follow-up data from HES and PEDW. We met the feasibility objective of implementing conventional prospective consent at all hospitals. Consent rates ranged from 59% to 74%[27] with respect to numbers considered eligible to participate, and from 22% to 86% with respect to approximate BCIS volume in the period of recruitment; these percentages were lower for some hospitals than we had anticipated for a study in which participants have no active involvement. The main reason for the lower than expected consent rate, and the variation between hospitals, was that many patients identified as eligible were missed; PPCI patients are asleep immediately following the procedure, rarely confined to bed after the first 4–6 hours and many are discharged within 24 hours or transferred to referring hospitals. Some of the missed patients activated the PPCI pathway at the weekend, when research nurses were not always available. In some centres, patients did not get admitted to the critical care ward or general ward after the PPCI procedure. We implemented postal consent to invite identified eligible patients who were not approached in hospital, but return rates were low. Some patients were unable to cope with the emergency nature of their condition and the large amount of new information they were given as part of their care; for some, the request to participate in a research study seemed to be yet another thing to think about and it was easier for them to decline to take part.

Data linkage and extraction across hospitals

We did not meet the feasibility criterion for data linkage and extraction from HISs for all of the requested data sets. We prespecified that, for each participating hospital, the data items requested should be available (i.e. extracted from sources and linked) for > 90% of patients. Only one hospital provided all of the requested data sets (anonymised, clinical, ECHO, biochemistry and medication on discharge) for > 80% of eligible (for the anonymised data set) and consented patients. Some hospitals had entire data sets missing: medications on discharge were not available from hospitals B, C and D; information about ECHO tests was not available from hospital B; and biochemistry data were not available from hospital D. There were several reasons for missing data, for example:

- Some hospitals were unable to extract data from local stand-alone databases that were designed for a specific purpose, for example logging biochemistry requests or storing and presenting test results.[27] Such local databases were typically old and did not have an interface for data extraction; data would have had to be retrieved manually for each patient in turn, rather than submitting a 'batch' query. The study was not resourced for this activity. Moreover, obtaining data in this way was considered infeasible for a national registry (as well as time consuming) and hospitals were not requested to do so.
- Some data (e.g. medications on discharge, bedside ECHO) were not recorded electronically and were available only in paper form (sometimes scanned but not coded/searchable).
- Non-bedside imaging tests (ECHO and CMR) were available electronically but as free-text reports rather than coded data; variables of interest were impossible to extract from these reports by conventional text-searching methods because of the variability with which the information was recorded.[27]

Cardiovascular magnetic resonance exposure

We were able to obtain CMR reports for all consented patients, although imaging reports were largely in free-text format, so individual CMR parameters would have had to be extracted manually. We concluded that this would not be feasible for an extended registry.

Follow-up/outcome data

It would be feasible to obtain 12 months' follow-up data after the index admission through HES in an extended registry. Admissions (inpatient data set), outpatient appointments and A&E data could be identified for all patients for whom a NHS number was available and who had a date recorded for their index admission. Because we obtained hospital episode data only for patients who we believed to be eligible, we cannot comment on the risk that eligible patients might not have been identified.

Compiling the registry from Hospital Episode Statistics

It is not currently feasible to compile the registry from HES data rather than multiple HISs. Although we could identify the eligible population and obtain follow-up data, we could not identify the CMR exposure within 10 weeks of the index admission. This was mainly because the CMR is often performed at an outpatient clinic and the HES outpatient data quality, particularly for clinical information, is poor (i.e. lack of data on diagnoses or procedures).

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Chapter 5 Results for aim B: cohort characteristics, exposure and outcomes, and resource use/cost-effectiveness

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Aim B: to estimate the proportion of the target population who have cardiovascular magnetic resonance at two centres with dedicated cardiovascular magnetic resonance facilities and describe resource use and associated costs of having cardiovascular magnetic resonance after primary percutaneous coronary intervention

- Objective B1: to estimate the proportion of the target population who undergo a CMR following PPCI pathway activation.
- Objective B2: to describe resource use and associated costs of having CMR after PPCI pathway activation, including cost-effectiveness models.

In *Chapter 4*, we reported on the feasibility aspects of the study with respect to identifying the eligible population, implementing consent, and data linkage and extraction across sites and with hospital episode data. In this chapter, we report on the quantitative characteristics of the cohort with respect to index admission (baseline) data, follow-up data and the health economic analysis we conducted for this study.

A series of economic decision models were developed to identify the key drivers of cost-effectiveness. As uncertainty surrounds the performance of CMR imaging in practice and its benefit to patients in terms of more optimal treatment, a flexible framework was required to facilitate the assessment of uncertainty around parameter estimates. Models are a simplification of the real world and will never capture every possible scenario associated with an intervention, but the key consequences need to be included when models are conceptualised and structured.[64] It is helpful if there are clinical events driving the models to define branches in the decision trees and associated event probabilities. The models were developed in consultation with clinical experts on the study team.

Two subgroups of patients who activated the PPCI pathway were chosen for the economic decision models: (1) patients with multivessel disease and (2) patients with unobstructed coronary arteries. Both subgroups were identified by formal consensus (see *Chapter 6*, *Patient subgroups*) as potentially benefiting from CMR. Patients with multivessel disease are the largest subgroup of patients in the population that activates the PPCI pathway (40–60%), and there is clinical uncertainty about how to treat this subgroup. Patients with normal coronary arteries are a distinct group which, at the outset, the research team expected to benefit most from CMR.

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Characteristics of consented versus non-consented patients

Table 14 shows the baseline characteristics of consented and non-consented patients. The IMD and WIMD scores were higher among those who consented than those who did not (SMDs 0.31 and 0.27, respectively). The percentage of patients who underwent PPCI was also higher among those who consented than those who did not (90% vs. 65%, respectively; SMD 0.70). This imbalance arose primarily from hospital A.

Characteristics of participants by hospital

Table 15 shows the characteristics of participants by hospital. Participants from the four hospitals were similar with respect to demographics, comorbidities and previous cardiac interventions, although rates of hypertension were lower in patients from hospital B than in patients from hospitals A, C and D (18% vs. 41–52%).

A CMR scan was performed (within 10 weeks of the index admission) for 20% of consented patients in one CMR centre and for 14% of consented patients in the second CMR centre. CMR data from hospital A were submitted as free-text reports; individual CMR parameters were difficult to extract electronically from these. Hospital B extracted CMR parameters of interest from the free-text reports manually. The baseline characteristics of patients who did and patients who did not receive CMR are shown in *Table 16*. Patients referred for CMR were slightly younger than those who did not have CMR. No other differences were noted.

TABLE 14 Baseline characteristics of consenting and non-consenting patients (for whom data were available)

Characteristic	Consenting patients (*n* = 1649)	Non-consenting patients (*n* = 705)	SMD[a]
Age (years), mean (SD)[b]	64 (12.7)	65 (14.2)	0.06
Male sex, *n*/*N* (%)	1159/1516 (76)	481/677 (71)	0.12
Current smoker, *n*/*N* (%)	478/1473 (32)	240/602 (40)	0.16
IMD score, median (IQR)[c]	13.4 (7.7–25.8)	19.9 (10.4–34.9)	0.31
WIMD rank, median (IQR)[d]	891 (459–1370)	671 (268–1221)	0.27
Diabetes, *n*/*N* (%)	231/1536 (15)	134/645 (21)	0.15
Hypertension, *n*/*N* (%)	601/1455 (41)	263/663 (40)	0.03
Previous PCI, *n*/*N* (%)	157/1552 (10)	73/652 (11)	0.04
Previous CABG, *n*/*N* (%)	37/1540 (2)	25/654 (4)	0.09
Previous MI, *n*/*N* (%)	193/1547 (12)	101/650 (16)	0.09
PPCI, *n*/*N* (%)	1307/1452 (90)	429/664 (65)	0.70
Length of stay (days), median (IQR)[e]	3 (2–4)	2 (1–4)	0.13

a SMDs can be interpreted as follows: values of 0.20 are 'small' in magnitude, those around 0.50 are 'medium' and those around or above 0.80 are 'large'.[65]
b Missing data (consented patients, non-consented patients): (8, 5).
c Missing data (consented patients, non-consented patients): (179, 15).
d Missing data (consented patients, non-consented patients): (92, 47).
e Missing data (consented patients, non-consented patients): (250, 78).

Note

Values are numbers (percentages) unless otherwise stated.[27]

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TABLE 15 Baseline characteristics of participants, by hospital

Characteristic	Hospital A (*n* = 762)	Hospital B (*n* = 272)	Hospital C (*n* = 315)	Hospital D (*n* = 300)
Age (years), mean (SD)[a]	65.1 (12.7)	62.9 (12.5)	63.8 (12.4)	63.4 (13.0)
Male sex, *n*/*N* (%)	512/655 (78)	183/246 (74)	238/315 (76)	226/300 (75)
Current smoker, *n*/*N* (%)	191/660 (29)	95/240 (40)	95/300 (32)	97/273 (36)
IMD score, median (IQR)[b]	12.2 (7.1–21.7)	20.5 (10.1–39.2)	–	–
WIMD rank, median (IQR)[c]	–	–	817 (334–1478)	902 (553–1314.5)
Diabetes, *n*/*N* (%)	91/700 (13)	33/243 (14)	70/310 (23)	37/283 (13)
Hypertension, *n*/*N* (%)	275/663 (41)	42/238 (18)	143/282 (51)	141/272 (52)
Previous PCI, *n*/*N* (%)	71/701 (10)	35/242 (14)	27/310 (9)	24/299 (8)
Previous CABG, *n*/*N* (%)	21/704 (3)	7/243 (3)	5/308 (2)	4/285 (1)
Previous MI, *n*/*N* (%)	88/707 (12)	40/240 (17)	33/312 (11)	32/288 (11)
PPCI, *n*/*N* (%)	597/655 (91)	220/243 (91)	267/295 (91)	223/259 (86)
Length of stay (days), median (IQR)[d]	3 (2–4)	2 (1–3)	3 (1–4)	2 (1–4)

[a] Missing data by hospital (hospital A, hospital B, hospital C, hospital D): 8 patients (1, 0, 0, 7).
[b] Missing data by hospital (hospital A, hospital B, hospital C, hospital D): 179 patients (169, 10, not collected for hospitals C or D).
[c] Data missing for 92 patients (not collected for hospitals A and B, 80, 12).
[d] Data missing for 250 patients (109, 2, 17, 122). Proportion of eligible population receiving CMR and characteristics of patients who did/did not receive CMR.

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TABLE 16 Baseline and CMR characteristics of patients who did and patients who did not have CMR in hospitals A and B

Characteristic	Patients who had CMR (*n* = 189)	Patients who did not have CMR (*n* = 846)	SMD[a]
Age (years), mean (SD)[b]	61.8 (11.7)	65.1 (12.8)	0.26
Male sex, *n*/*N* (%)	121/154 (79)	574/747 (77)	0.04
Current smoker, *n*/*N* (%)	52/168 (31)	234/732 (32)	0.02
IMD score, median (IQR)[c]	12.4 (7.5–23.5)	13.5 (7.8–26.3)	0.08
Diabetes, *n*/*N* (%)	19/176 (11)	105/767 (14)	0.09
Hypertension, *n*/*N* (%)	63/166 (38)	254/735 (35)	0.07
Previous PCI, *n*/*N* (%)	18/176 (10)	88/767 (11)	0.04
Previous CABG, *n*/*N* (%)	3/176 (2)	25/771 (3)	0.09
Previous MI, *n*/*N* (%)	20/174 (11)	108/773 (14)	0.07

continued

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TABLE 16 Baseline and CMR characteristics of patients who did and patients who did not have CMR in hospitals A and B (*continued*)

Characteristic	Patients who had CMR (n = 189)	Patients who did not have CMR (n = 846)	SMD[a]
PPCI, n/N (%)	140/154 (91)	677/744 (91)	0.003
Length of stay (days), median (IQR)[d]	2 (2–3)	3 (2–3)	0.11

a SMDs can be interpreted as follows: values of 0.20 are 'small' in magnitude, those around 0.50 are 'medium' and those around or above 0.80 are 'large'.[65]
b Missing data (patients who had CMR, patients who did not have CMR): 2 patients (1, 1).
c Missing data (patients who had CMR, patients who did not have CMR): 180 patients (43, 137).
d Missing data (patients who had CMR, patients who did not have CMR): 112 patients (32, 80).

Note

Values are numbers (percentages) unless otherwise stated.[27]

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Participant follow-up

Table 17 shows the cardiac-related events in the 12 months following the index admission in the entire cohort. Overall, 55 out of 1670 (3%) patients died during follow-up (median age 73 years, IQR 66–82 years). MACE rate in this cohort was 13% (219/1670).

The recorded causes of death for patients who died within 1 year of admission are shown in *Appendix 6*. Only 32 out of 54 (59%) patients died from causes closely associated with ischaemic heart disease; an additional 2 (4%) died from other heart conditions and 8 out of 54 (15%) patients died of cancer.

TABLE 17 Rates of death and cardiac-related events in the 12 months following the index admission in the entire cohort

Event	Number of events, n/N (%)	Person-years of observation	Events per 1000 person-years (95% CI)
Death	55/1638 (3)	1536.33	35.8 (27.0 to 46.6)
MI	74/1638 (5)	1376.04	53.8 (42.2 to 67.5)
Stroke	2/1638 (0.1)	1427.12	1.4 (0.02 to 5.1)
Repeat PCI	117/1638 (7)	1347.76	86.8 (71.8 to 104.0)
CABG	20/1638 (1)	1417.25	14.1 (8.6 to 21.8)
MACE (death, MI, revascularisation)	219/1638 (13)	1311.44	167.0 (145.6 to 190.6)

Note

The denominator is 1638 because the date of index admission was missing for 22 patients and HES/PEDW data were unavailable for 10 patients.

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Cost-effectiveness models

Multivessel disease

The expected costs and QALYs gained under each of the ischaemia testing options are shown in *Table 18* together with the cost-effectiveness results for CMR and pressure wire, each compared with stress ECHO. Comparisons are made with stress ECHO because this was the ischaemia test in use at the time of the study (and is considered the 'existing' comparator) and also because CMR and pressure wire were assumed to be equally effective; these strategies differ only in terms of their costs. Based on the point estimates, CMR was slightly less costly and more effective than stress ECHO and, therefore, dominated stress ECHO. Pressure wire was more costly and more effective than stress ECHO: the ICER is considerably higher than the accepted cost-effectiveness threshold of £20,000–30,000 per QALY, and, therefore, would not be considered cost-effective relative to stress ECHO. Pressure wire is convenient for cardiologists if the test identifies the fact that a patient needs revascularisation, as the patient can be treated immediately while in the catheter laboratory, and the cost of the pressure wire in addition to the revascularisation is modest. In the base-case analysis, 35% of patients having ischaemia testing were assumed to truly have ischaemia; the majority of patients are, therefore, having an expensive test without needing further treatment. If a greater proportion of patients undergoing ischaemia testing required revascularisation, it is likely that the estimated cost of a pressure-wire strategy would reduce. It would be possible to use a pressure wire on other vessels at the time of the index angiography and PCI, but it was beyond the scope of this work to consider the likely costs and consequences of such a strategy. Based on the point estimates, pressure wire is dominated by CMR, because CMR is less costly and equally as effective. Cost and QALY differences are small relative to the mean values under each strategy, and none of the differences in costs or QALYs is close to being statistically significant; indeed, the differences in QALYs were tiny. There is considerable uncertainty around these base-case results; however, as is clear from the plots of 1000 simulated cost and QALY differences from the PSA for CMR and pressure wire (each compared with stress ECHO) in *Figures 10* and *11*. In each figure, there are a large number of points in two or three quadrants of the cost-effectiveness plane. The black dot is the point estimate of the cost and QALY difference, and, in each figure, it is close to the origin.

For this feasibility study, it is not the cost-effectiveness results per se that are of interest, but rather the way in which they change in response to sensitivity analyses that helps us to determine the key drivers of cost-effectiveness. *Table 19* reports the results of the sensitivity analyses around this model. Sensitivity analysis one, around the probabilities of ischaemia testing or a decision to revascularise a second vessel (or not) directly from the index angiography, affects the mean costs and QALYs under each strategy but does not alter the cost-effectiveness results, because these probabilities are the same under each strategy. Sensitivity analyses two and three, around the diagnostic accuracy of CMR and pressure wire, had the

TABLE 18 Base-case results from the cost-effectiveness model for multivessel disease

Ischaemia testing option	Costs (£), mean (SE)	QALYs, mean (SE)	Difference in costs to stress ECHO, mean (95% CI)	Difference in QALYs, compared with stress ECHO, mean (95% CI)	ICER (£), compared with stress ECHO
Stress ECHO	5495 (556)	0.7564 (0.0545)			
CMR	5431 (560)	0.7576 (0.0551)	–64 (–232 to 187)	0.0012 (–0.0076 to 0.0093)	CMR dominant (–53,563)
Pressure wire	5855 (539)	0.7576 (0.0551)	360 (–116 to 844)	0.0012 (–0.0076 to 0.0093)	300,216

Note

All costs and ICERs are rounded to the nearest pound.

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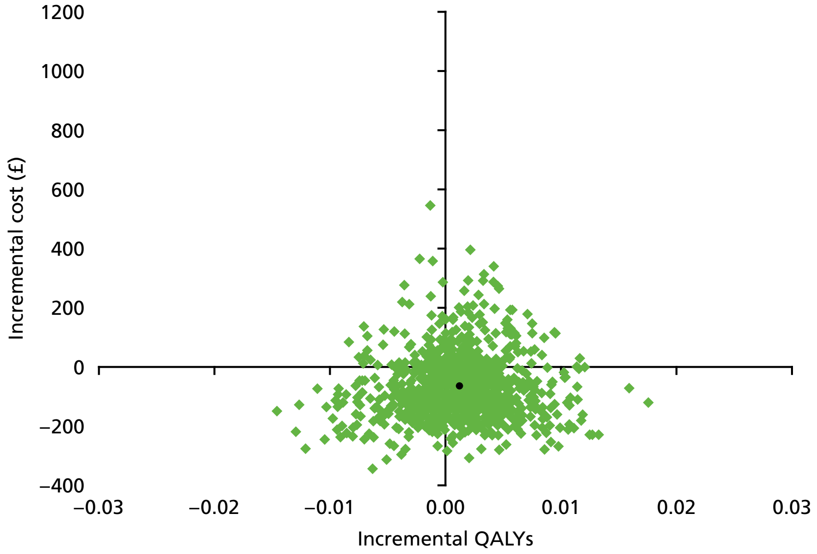

FIGURE 10 A plot of the 1000 simulated cost and QALY differences from the PSA for CMR vs. stress ECHO.

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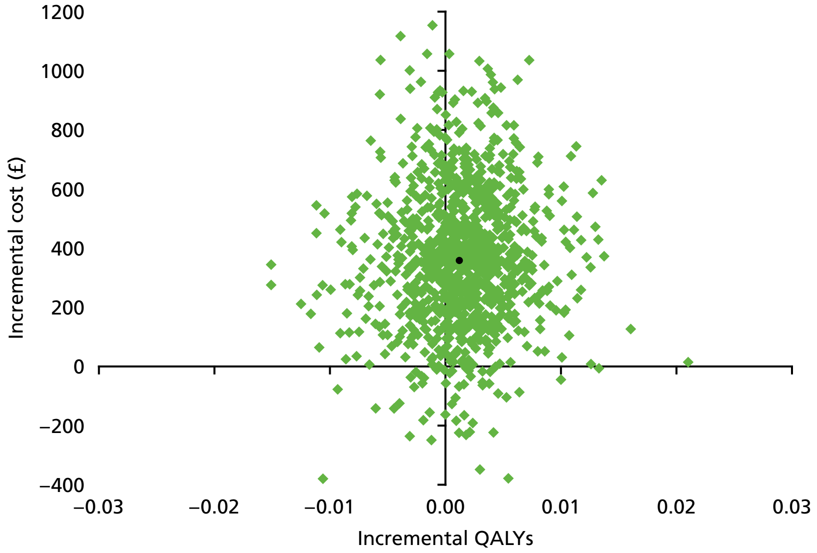

FIGURE 11 A plot of the 1000 simulated cost and QALY differences from the PSA for pressure wire vs. stress ECHO.

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most effect on results. When the sensitivity and specificity of CMR were reduced to 80%, CMR became more costly than stress ECHO, rather than dominant, and, at accepted cost-effectiveness thresholds, would not be considered cost-effective relative to stress ECHO. When the sensitivity and specificity of pressure wire were reduced to 80%, conclusions did not alter: pressure wire was still more costly and slightly more effective than stress ECHO, but the ICER quadrupled. The diagnostic accuracy of the ischaemia tests, in particular CMR, are key drivers of cost-effectiveness. Varying the costs of CMR, angiography and pressure wire, and varying QALYs for patients with MACE and those without MACE, did cause cost-effectiveness results to vary, but did not alter cost-effectiveness conclusions.

TABLE 19 Results of the sensitivity analyses around the cost-effectiveness model for multivessel disease

SA	Ischaemia testing option	Costs (£), mean (SE)	QALYs, mean (SE)	Difference in costs, compared with stress ECHO, mean (95% CI)	Difference in QALYs, compared with stress ECHO, mean (95% CI)	ICER (£), compared with stress ECHO
Base case	Stress ECHO	5495 (556)	0.7564 (0.0545)			
	CMR	5431 (560)	0.7576 (0.0551)	–64 (–232 to 187)	0.0012 (–0.0076 to 0.0093)	CMR dominant (–53,563)
	Pressure wire	5855 (539)	0.7576 (0.0551)	360 (–116 to 844)	0.0012 (–0.0076 to 0.0093)	300,216
1. Decision from angiography	Stress ECHO	4575 (449)	0.7537 (0.0654)			
	CMR	4558 (500)	0.7540 (0.0661)	–17 (–62 to 45)	0.0003 (–0.0022 to 0.0026)	CMR dominant (–53,563)
	Pressure wire	4667 (500)	0.7540 (0.0661)	93 (–21 to 214)	0.0003 (–0.0022 to 0.0026)	300,216
2. CMR test accuracy	Stress ECHO	5495 (556)	0.7564 (0.0545)			
	CMR	5558 (600)	0.7567 (0.0572)	63 (–202 to 390)	0.0004 (–0.0119 to 0.0108)	168,453
3. PW test accuracy	Stress ECHO	5495 (556)	0.7564 (0.0545)			
	Pressure wire	5944 (568)	0.7567 (0.0572)	449 (–18 to 947)	0.0004 (–0.0119 to 0.0108)	1,207,875
4. ECHO test accuracy	Stress ECHO	5431 (553)	0.7568 (0.0555)			
	CMR	5431 (560)	0.7576 (0.0551)	+0 (–128 to 253)	0.0008 (–0.0022 to 0.0036)	201
	Pressure wire	5855 (539)	0.7576 (0.0551)	424 (18 to 888)	0.0008 (–0.0022 to 0.0036)	529,193
5. MACE +0.05	Stress ECHO	5674 (586)	0.7520 (0.0566)			
	CMR	5610 (580)	0.7533 (0.0574)	–65 (–233 to 164)	0.0012 (–0.0078 to 0.0087)	CMR dominant (–53,434)
	Pressure wire	6033 (575)	0.7533 (0.0574)	359 (–85 to 831)	0.0012 (–0.0078 to 0.0087)	296,587
5. MACE –0.05	Stress ECHO	5317 (564)	0.7607 (0.0589)			
	CMR	5252 (565)	0.7619 (0.0595)	–65 (–244 to 192)	0.0012 (–0.0081 to 0.0097)	CMR dominant (–53,463)
	Pressure wire	5676 (533)	0.7619 (0.0595)	359 (–112 to 830)	0.0012 (–0.0081 to 0.0097)	297,408
6. CMR cost +20%	Stress ECHO	5495 (556)	0.7564 (0.0545)			
	CMR	5463 (556)	0.7576 (0.0551)	–32 (–218 to 187)	0.0012 (–0.0076 to 0.0093)	CMR dominant (–27,021)
6. CMR cost –20%	Stress ECHO	5495 (556)	0.7564 (0.0545)			
	CMR	5399 (551)	0.7576 (0.0551)	–96 (–268 to 159)	0.0012 (–0.0076 to 0.0093)	CMR dominant (–80,104)

continued

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TABLE 19 Results of the sensitivity analyses around the cost-effectiveness model for multivessel disease (*continued*)

SA	Ischaemia testing option	Costs (£), mean (SE)	QALYs, mean (SE)	Difference in costs, compared with stress ECHO, mean (95% CI)	Difference in QALYs, compared with stress ECHO, mean (95% CI)	ICER (£), compared with stress ECHO
7. PW cost +20%	Stress ECHO	5495 (556)	0.7564 (0.0545)			
	Pressure wire	6015 (560)	0.7576 (0.0551)	521 (78 to 992)	0.0012 (–0.0076 to 0.0093)	434,425
7. PW cost –20%	Stress ECHO	5495 (556)	0.7564 (0.0545)			
	Pressure wire	5694 (537)	0.7576 (0.0551)	199 (–240 to 622)	0.0012 (–0.0076 to 0.0093)	166,007
8. QALYs for MACE –0.2	Stress ECHO	5495 (556)	0.7306 (0.0559)			
	CMR	5431 (560)	0.7346 (0.0565)	–64 (–232 to 187)	0.0040 (–0.0057 to 0.0117)	CMR dominant (–16,041)
	Pressure wire	5855 (539)	0.7346 (0.0565)	360 (–116 to 844)	0.0040 (–0.0057 to 0.0117)	89,907
9. QALYs for no MACE +0.2	Stress ECHO	5495 (556)	0.9306 (0.0576)			
	CMR	5431 (560)	0.9346 (0.0587)	–64 (–232 to 187)	0.0040 (–0.0071 to 0.0104)	CMR dominant (–16,041)
	Pressure wire	5855 (539)	0.9346 (0.0587)	360 (–116 to 844)	0.0040 (–0.0071 to 0.0104)	89,907

PW, angiography and pressure wire; SA, sensitivity analysis.

Note

All costs and ICERs are rounded to the nearest pound.

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An alternative way of assessing the sensitivity of results to the cost of an ischaemia test is to consider how the cost of the test would need to alter for the costs of alternative strategies to be estimated to be equal. In the base-case analyses, the cost of CMR was £264, and a CMR strategy was less costly than a stress ECHO strategy. Threshold analyses around the cost of CMR identified that if the cost rose to £371, there was no difference in the costs between a CMR and a stress ECHO strategy. In the base-case analyses, the cost of angiography and pressure wire was £1340, and a pressure-wire strategy was more expensive than a CMR or stress ECHO strategy. Threshold analyses identified that the cost of angiography and pressure wire would need to reduce to just £250 for there to be no difference in costs between a CMR and a pressure-wire strategy, and to £415 for there to be no difference between the cost of a stress ECHO and a pressure-wire strategy.

Normal (unobstructed) coronary arteries

The expected costs, QALYs and cost-effectiveness results under standard ECHO and CMR compared with standard ECHO alone for patients with normal coronaries are shown in *Table 20*. The reduction in costs associated with treating fewer patients for MI with the introduction of CMR testing compensated only partially for the additional cost of the CMR test. Mean costs and QALYs gained were higher with standard ECHO and CMR than with standard ECHO alone, and the ICER would not be considered cost-effective at accepted thresholds. There is considerable uncertainty around these base-case results, however, as is clear from the plot of the simulated cost and QALY differences from the PSA in *Figure 12*. There are a large number of points in three quadrants of the cost-effectiveness plane.

TABLE 20 Base-case results from the cost-effectiveness model for normal coronaries

Ischaemia testing option	Costs (£), mean (SE)	QALYs, mean (SE)	Difference in costs, mean (95% CI)	Difference in QALYs, mean (95% CI)	ICER (£)
Standard ECHO	3032 (564)	0.7615 (0.0837)			
Standard ECHO and CMR	3130 (589)	0.7620 (0.0844)	98 (–199 to 488)	0.0005 (–0.0050 to 0.0077)	190,114

Note

All costs and ICERs are rounded to the nearest pound.

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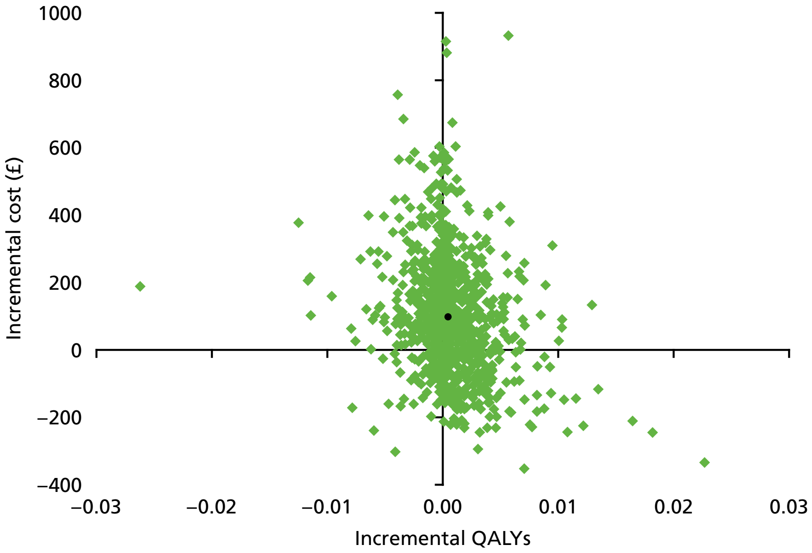

FIGURE 12 A plot of the 1000 simulated cost and QALY differences from the PSA for standard ECHO and CMR vs. standard ECHO.

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Table 21 reports the results of the sensitivity analyses around this model, designed to help identify the key drivers of cost-effectiveness. Sensitivity analysis one (reducing the diagnostic accuracy of CMR) and sensitivity analysis six (increasing the cost of CMR) had the greatest impact on the mean cost difference between standard ECHO and CMR and standard ECHO alone. Threshold analyses around the cost of CMR (£264 in the base-case analyses) identified that, if the cost reduced to £166, there was no difference in the costs between standard ECHO and CMR and a standard ECHO alone strategy. Sensitivity analyses 8–10, which all directly varied QALYs, had the greatest impact on the difference in QALYs between the arms. However, in all cases, standard ECHO and CMR remained both more costly and more effective than standard ECHO alone, and in none of the sensitivity analyses would standard ECHO and CMR be considered cost-effective at accepted thresholds. These sensitivity analyses suggest that the diagnostic accuracy of CMR is again a key driver of cost-effectiveness. Results are also influenced by the cost of CMR, and the difference between utility values assigned to MACE and no MACE, and the proportion of patients who have MACE, who are assumed to die.

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TABLE 21 Results of the sensitivity analyses around the cost-effectiveness model for normal coronaries

SA	Ischaemia testing option	Costs (£), mean (SE)	QALYs, mean (SE)	Difference in costs, mean (95% CI)	Difference in QALYs, mean (95% CI)	ICER (£)
Base case	Standard ECHO	3032 (564)	0.7615 (0.0837)			
	Standard ECHO and CMR	3130 (589)	0.7620 (0.0844)	98 (–199 to 488)	0.0005 (–0.0050 to 0.0077)	190,114
1. CMR test accuracy	Standard ECHO	3032 (564)	0.7615 (0.0837)			
	Standard ECHO and CMR	3183 (591)	0.7618 (0.0850)	151 (–105 to 523)	0.0003 (–0.0026 to 0.0053)	469,998
2. ECHO test accuracy	Standard ECHO	2945 (561)	0.7617 (0.0863)			
	Standard ECHO and CMR	3130 (589)	0.7620 (0.0844)	185 (–59 to 581)	0.0003 (–0.0027 to 0.0042)	631,744
3. MACE (ratio = 4)	Standard ECHO	3067 (541)	0.7608 (0.0826)			
	Standard ECHO and CMR	3165 (559)	0.7614 (0.0830)	98 (–192 to 465)	0.0005 (–0.0043 to 0.0069)	190,154
4. MACE (ratio = 2)	Standard ECHO	3043 (573)	0.7613 (0.0829)			
	Standard ECHO and CMR	3146 (606)	0.7617 (0.0834)	104 (–162 to 498)	0.0004 (–0.0051 to 0.0063)	250,905
5. MACE (ratio = 1)	Standard ECHO	3046 (579)	0.7612 (0.0847)			
	Standard ECHO and CMR	3161 (596)	0.7614 (0.0850)	115 (–168 to 492)	0.0002 (–0.0051 to 0.0069)	554,609
6. CMR cost +20%	Standard ECHO	3032 (564)	0.7615 (0.0837)			
	Standard ECHO and CMR	3183 (579)	0.7620 (0.0844)	151 (–133 to 532)	0.0005 (–0.0050 to 0.0077)	292,836
6. CMR cost –20%	Standard ECHO	3032 (564)	0.7615 (0.0837)			
	Standard ECHO and CMR	3077 (572)	0.7620 (0.0844)	45 (–229 to 476)	0.0005 (–0.0050 to 0.0077)	87,391
7. Reduce MACE costs	Standard ECHO	2974 (548)	0.7615 (0.0837)			
	Standard ECHO and CMR	3077 (574)	0.7620 (0.0844)	103 (–159 to 502)	0.0005 (–0.0050 to 0.0077)	198,992
8. QALYs for MACE –0.2	Standard ECHO	3032 (564)	0.7457 (0.0879)			
	Standard ECHO and CMR	3130 (589)	0.7474 (0.0886)	98 (–199 to 488)	0.0018 (–0.0091 to 0.0139)	55,281
9. QALYs for no MACE +0.2	Standard ECHO	3032 (564)	0.9457 (0.0905)			
	Standard ECHO and CMR	3130 (589)	0.9474 (0.0911)	98 (–199 to 488)	0.0018 (–0.0094 to 0.0134)	55,281

TABLE 21 Results of the sensitivity analyses around the cost-effectiveness model for normal coronaries (*continued*)

SA	Ischaemia testing option	Costs (£), mean (SE)	QALYs, mean (SE)	Difference in costs, mean (95% CI)	Difference in QALYs, mean (95% CI)	ICER (£)
10. QALYs for MACE (50% die)	Standard ECHO	2994 (516)	0.7488 (0.0859)			
	Standard ECHO and CMR	3095 (542)	0.7503 (0.0864)	101 (–180 to 464)	0.0015 (–0.0090 to 0.0133)	66,040

SA, sensitivity analysis.

Note

All costs and ICERs are rounded to the nearest pound.

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Summary of main findings

Cohort characteristics and follow-up

Baseline characteristics were reasonably well balanced between participants who consented and those who did not consent in the study, but suggested that patients living in less deprived residential areas were, on average, less willing to take part. Characteristics were better balanced across participants recruited by the four hospitals, and participants who did and those who did not receive a CMR scan. Data completeness was good for most variables. Follow-up data were available for the entire follow-up period (12 months) for only 729 out of 1035 (70%) participants in England and 287 out of 635 (45%) participants in Wales. This is because data were requested soon after recruitment finished and the Welsh data were provided rapidly. The data for English hospitals took much longer to be released, resulting in a longer follow-up period. The limited follow-up was a result of this process being part of the testing feasibility for a full registry; in the context of a registry, the request for these data would be made at an appropriate stage of the study to achieve the desired duration of follow-up.

The proportion of the target population that gets cardiovascular magnetic resonance after activating the primary percutaneous coronary intervention pathway

Although > 10% of patients in hospitals with a dedicated CMR facility were referred for CMR, many of these referrals were for research (patient participating in a research study) rather than clinical purposes. It is not clear whether or not this reflects practice in other hospitals with dedicated CMR facilities. Referral for non-clinical reasons (unless the findings are used to change clinical management) would dilute any observed effect of CMR on outcomes in an extended registry. It was not possible to determine how many CMRs that were done for research purposes were subsequently reviewed by the treating clinician and resulted in changes in patient management.

Cost-effectiveness models

For each of the base-case models, the differences in QALYs between strategies were tiny; therefore, the results are driven largely by the differences in costs, although these were also modest. Sensitivity analyses around the two models identified the diagnostic accuracy of the ischaemia tests as the key driver of cost-effectiveness. In the model for patients with multivessel disease, the costs of ischaemia testing and the QALYs associated with MACE and no MACE exerted an influence on cost-effectiveness results, but not to the same extent as the diagnostic accuracy of CMR and pressure wire. Similarly, in the model for patients with normal coronaries, the cost of CMR, the difference between QALYs associated with MACE and no MACE, and the proportion of patients who have MACE who are assumed to die, exerted an influence on the results.

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Chapter 6 Results for aim C: formal consensus to identify clinically important changes in management resulting from cardiovascular magnetic resonance patients who activate the primary percutaneous coronary intervention pathway

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Aim C: to identify an outcome measure representing a definitive change in clinical management, conditional on having had cardiovascular magnetic resonance, that would be credible to cardiologists and other stakeholders as a measure of the 'value-added' by doing cardiovascular magnetic resonance

- Objective C1: to define, using formal consensus methods, a treatment/process outcome that will constitute a definitive change in clinical management arising from having CMR.
- Objective C2: to identify patient subgroups in whom CMR use is indicated, using formal consensus methods and illustrative data from the registry.
- Objective C3: to determine whether or not hospital episode data adequately capture the main changes in clinical management identified using formal consensus.
- Objective C4: to pilot the implementation of a primary outcome based on the changes in management for which consensus was achieved using hospital episode data.

We used a formal consensus method based on the modified nominal group technique[66] to identify important changes in management that can be used to define the composite outcome. Formal consensus is a method that combines both research evidence and expert opinion. We used this approach because we knew from a preliminary scoping of the literature that there were few studies that reported the impact of CMR on patient management.[4]

We used clinical expertise to define 'clinical events' that captured the important changes in management and a clinical coder to identify collaborated with codes (ICD-10[31] and the OPCS Classification of Intervention and Procedures[32]) corresponding to these clinical events. We then searched for these codes in hospital episode data for participants in the cohort study during the 12 months following the index admission (PPCI pathway activation).

Literature review

We initially examined a small number of key reports, reviews and primary studies to determine the extent of the literature reporting how CMR influences patient management. There were few studies that directly reported the impact of CMR on patient management, and none of these related to our population of interest. *Figure 13* shows the flow diagram of the systematic review and the different types of studies identified. We identified a total of 171 studies reporting the use of CMR in patients with acute MI who

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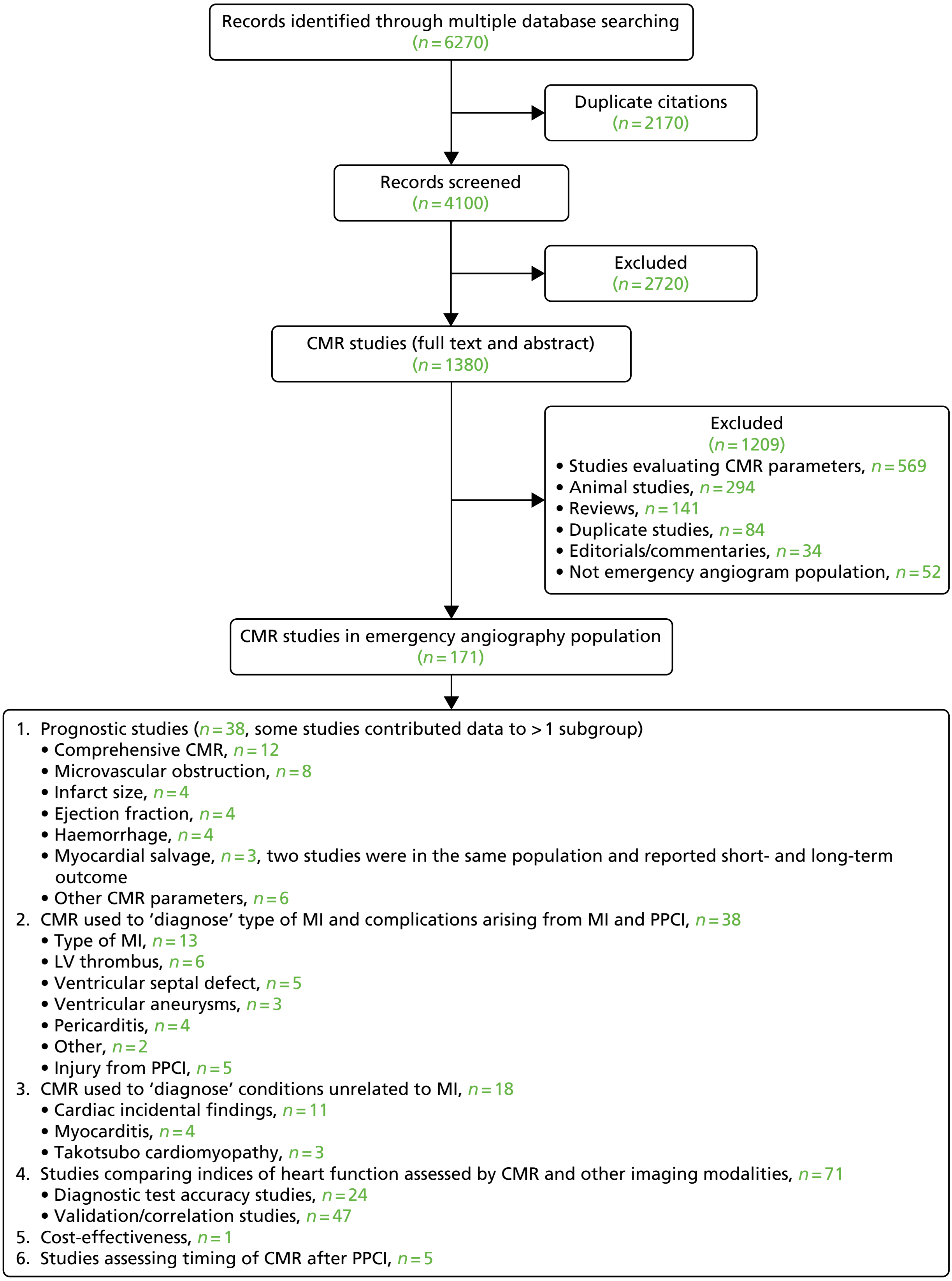
Records identified through multiple database searching
(n = 6270)
Duplicate citations
(n = 2170)
Records screened
(n = 4100)
Excluded
(n = 2720)
CMR studies (full text and abstract)
(n = 1380)
Excluded
(n = 1209)
• Studies evaluating CMR parameters, n = 569
• Animal studies, n = 294
• Reviews, n = 141
• Duplicate studies, n = 84
• Editorials/commentaries, n = 34
• Not emergency angiogram population, n = 52
CMR studies in emergency angiography population
(n = 171)

1. Prognostic studies (*n* = 38, some studies contributed data to > 1 subgroup)
   - Comprehensive CMR, *n* = 12
   - Microvascular obstruction, *n* = 8
   - Infarct size, *n* = 4
   - Ejection fraction, *n* = 4
   - Haemorrhage, *n* = 4
   - Myocardial salvage, *n* = 3, two studies were in the same population and reported short- and long-term outcome
   - Other CMR parameters, *n* = 6
2. CMR used to 'diagnose' type of MI and complications arising from MI and PPCI, *n* = 38
   - Type of MI, *n* = 13
   - LV thrombus, *n* = 6
   - Ventricular septal defect, *n* = 5
   - Ventricular aneurysms, *n* = 3
   - Pericarditis, *n* = 4
   - Other, *n* = 2
   - Injury from PPCI, *n* = 5
3. CMR used to 'diagnose' conditions unrelated to MI, *n* = 18
   - Cardiac incidental findings, *n* = 11
   - Myocarditis, *n* = 4
   - Takotsubo cardiomyopathy, *n* = 3
4. Studies comparing indices of heart function assessed by CMR and other imaging modalities, *n* = 71
   - Diagnostic test accuracy studies, *n* = 24
   - Validation/correlation studies, *n* = 47
5. Cost-effectiveness, *n* = 1
6. Studies assessing timing of CMR after PPCI, *n* = 5

FIGURE 13 Flow diagram of the study selection process and types of studies identified.

activated the PPCI pathway. There were no studies that directly compared groups of patients having CMR or not with respect to patient management or clinical outcomes in this population.

There were 38 prognostic studies assessing the value of CMR in predicting MACEs; 12 did not distinguish the contributing CMR markers, and 26 assessed individual CMR markers of myocardial damage [e.g. microvascular obstruction (MVO), infarct size (IS), LV ejection fraction (EF), myocardial salvage, intramyocardial haemorrhage] as predictors of MACE. These studies did not all evaluate the prognostic value of CMR indices in addition to indices available from alternative imaging modalities; most were small (20–1217 patients, median 257), single centre and heterogeneous in terms of the CMR parameters reported and how these were assessed. Nevertheless, they showed that CMR markers (particularly MVO, IS and myocardial salvage) were consistently associated with MACEs in STEMI patients.

There were 38 studies of the role of CMR in 'diagnosing' a specific feature of the index MI or complications arising from the index MI or procedure. CMR was used to investigate the type of MI (i.e. acute, chronic, aborted) in 13 studies, to detect complications of MI [e.g. LV thrombus, ventricular septal defect (VSD) ventricular aneurysms and pericarditis] in 19 studies and to detect injury from PPCI in five studies. Many of these were case reports, some were diagnostic test accuracy studies comparing CMR with ECHO as the reference standard (e.g. diagnosis of thrombus) and some also followed up patients and assessed the prognostic implications of the CMR findings (e.g. aborted MI).

There were 18 studies in which CMR was used to 'diagnose' conditions other than MI (e.g. myocarditis and Takotsubo cardiomyopathy in patients with unobstructed arteries on angiography) and incidental cardiac findings. All but two of these were case reports. There were 71 studies in which CMR was compared with one or more other imaging modalities [i.e. ECHO, SPECT, computed tomography (CT), angiography or with standard coronary angiography with respect to indices of heart function (e.g. myocardial viability, necrosis, perfusion, myocardium at risk, ischaemia)]. Twenty-four of these were diagnostic test accuracy studies (those that included a reference standard and provided statistics of test performance, i.e. sensitivity, specificity, positive or negative predictive values, receiver operating characteristic curves) and 47 were validation or correlation studies. Most focused on infarct characteristics and myocardial viability, but the definitions and techniques assessing viability were highly variable for both CMR and the comparator, making it difficult to compare studies.

Formulation of consensus statements

Thirty-seven draft statements were generated by the three cardiologists and one methodologist (see *Appendix 7*, *Table 31*). Examples of draft statements, categorised by patient subgroup, are shown in *Appendix 7*, *Table 32*. Statements relating to the same patient subgroup/condition (e.g. patients at risk of complications after PPCI who develop LV thrombus) were condensed into one statement. This reduced the number of statements from 37 to 16. All statements were then reworded to standardise their format. Examples of reworded statements are shown in *Appendix 7*, *Table 32*. The 16 statements were discussed in turn at the internal group meeting and the following changes were made:

- The total number of statements was reduced from 16 to 12. Two statements relating to device implantation were condensed into one, three statements were removed because it was felt that their content was covered adequately by other statements and one statement was removed because it was felt that it did not relate to a change in patient management.
- A supporting paragraph was drafted to put the statement into context, summarise the research evidence and include any key references. These references were chosen to reflect the best available evidence; although, for several statements, the cited studies were small prognostic studies or case series (i.e. the only available evidence).
- The statements were reworded to clarify the care pathway compared with which the additional benefit of CMR was anticipated (e.g. alternative imaging modalities such as ECHO or SPECT).

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The final 12 statements are shown in *Table 22* and examples of supporting paragraphs are shown in *Appendix 7*, *Table 33*. These 12 statements describe changes in management relating to six patient subgroups:

1. Patients with a poor prognosis or at risk of complications after PPCI [e.g. those who develop LV thrombus, those with low EF who require an implantable cardioverter defibrillator (ICD), those at risk of impending cardiac rupture] whose treatment could potentially be optimised (statements 1, 4, 6, 7 and 9).
2. Patients with a good prognosis after PPCI who could be discharged earlier and followed up less often (statement 2).
3. Patients with multivessel disease, in whom revascularisation for the additional diseased arteries could be optimised (statements 8 and 10).
4. Patients with unobstructed arteries on angiography [who may have had a heart attack that resolved spontaneously (e.g. MI with spontaneous recanalisation/embolic MI) or another condition, such as myocarditis or cardiomyopathy] for whom treatment planning could be optimised based on a definitive diagnosis (statement 5).
5. Patients with an out-of-hospital-cardiac arrest (OHCA) in whom the cause could be definitively identified, leading to appropriate treatment (statement 3).
6. Patients with incidental cardiac (e.g. mitral regurgitation, pericardial effusion, valve disease, papillary rupture, congenital cardiac anomalies) and extra-cardiac findings (e.g. pleural effusion, lung mass, mediastinal lymph adenopathy), in whom appropriate treatment could be started (statements 11 and 12).

TABLE 22 Final statements following the expert group meeting

Statement number	Statement	Patient subgroup
1	Compared with ECHO, CMR after PPCI allows patients with CMR markers that indicate a poor prognosis (e.g. impaired LV function, large infarct size, MVO) to be followed up more appropriately and undergo more aggressive medical therapy for secondary prevention	Poor prognosis/risk of complications after PPCI
2	Compared with ECHO, CMR after PPCI allows patients with CMR markers that indicate a good prognosis (e.g. normal LV function, high myocardial salvage, no MVO, no residual ischaemia) to be discharged earlier and followed up less frequently	Good prognosis after PPCI
3	Compared with ECHO, CMR better identifies the cause of OHCA (e.g. large MI, arrhythmogenic right ventricular cardiomyopathy, aberrant coronary arteries, hypertrophic cardiomyopathy) to optimise further treatment for the patient (e.g. defibrillator for primary arrhythmia or PCI) or family members	Out-of-hospital cardiac arrest
4	CMR after PPCI identifies patients at high risk of having a ventricular septal defect or impending cardiac rupture, who may require a ventricular patch or other urgent cardiac surgery, and guides the optimal management of these patients	Poor prognosis/risk of complications after PPCI
5	In patients with a ‘normal’ (unobstructed) coronary angiogram, CMR can differentiate patients who have had a MI with spontaneous reperfusion or distal embolisation from patients with a non-ischaemic diagnosis (e.g. myocarditis, Takotsubo cardiomyopathy, aortic dissection), resulting in a patient treatment plan appropriate for the definitive diagnosis	Unobstructed arteries on angiogram

TABLE 22 Final statements following the expert group meeting (*continued*)

Statement number	Statement	Patient subgroup
6	Compared with ECHO, CMR after PPCI better identifies patients at high risk of sudden cardiac death who would benefit most from an implantable cardiac device (e.g. ICD or CRT)	Poor prognosis/risk of complications after PPCI
7	Compared with ECHO, CMR after PPCI better identifies patients who would not benefit from cardiac resynchronisation therapy	Poor prognosis/risk of complications after PPCI
8	Compared with stress ECHO or SPECT, CMR after PPCI in patients with multivessel disease better assesses ischaemia and viability of the myocardium to optimise the revascularisation strategy for the patient and avoid additional diagnostic tests	Multivessel disease
9	Compared with ECHO, CMR after PPCI better identifies patients with LV thrombus for treatment with anticoagulation therapy	Poor prognosis/risk of complications after PPCI
10	Compared with other imaging modalities, in patients with multivessel disease, CMR after PPCI better identifies the artery that caused the MI and guides the subsequent treatment plan in relation to additional revascularisation (e.g. PCI or coronary artery bypass graft surgery)	Multivessel disease
11	Compared with ECHO, CMR after PPCI better identifies incidental cardiac findings that may need further investigation and treatment	Incidental cardiac findings
12	Compared with ECHO, CMR after PPCI identifies significant incidental non-cardiac findings (e.g. oesophageal and lung tumours, pulmonary embolus, aortic aneurysm) that may need further investigation and treatment	Incidental non-cardiac findings

CRT, cardiac resynchronisation therapy.

The expert panel

Nineteen consultant cardiologists were invited to participate in the consensus process. Seven cardiologists (37%) agreed to participate. Of these, two had CMR, three had interventional, one had ECHO and one had heart failure expertise. All seven cardiologists completed the first survey independently.

First survey

Figure 14 shows the distribution of responses for the first survey. There was consensus for three of the 12 statements (25%) regarding the change in management being clinically important: statement 3, relating to the ability of CMR to identify the cause of OHCA and, therefore, optimise treatment for the patient; statement 5, relating to the ability of CMR to provide a definitive diagnosis in patients found to have unobstructed arteries on angiography; and statement 9, relating to the ability of CMR to identify patients with LV thrombus and initiate treatment with anticoagulation therapy. There was no consensus for any statement that the change in management was not clinically important.

Examples of respondents' comments to the first survey regarding individual statements are shown in *Appendix 7*, *Table 34*. Consensus was sought on the importance of the change in management and most respondents commented on this issue. However, some respondents also considered other factors when rating statements, for example the quality of the supporting evidence, the proportion of patients likely to benefit, the ability of the NHS to provide a service in line with the statement and whether or not the cost of CMR justified the perceived benefit.[4]

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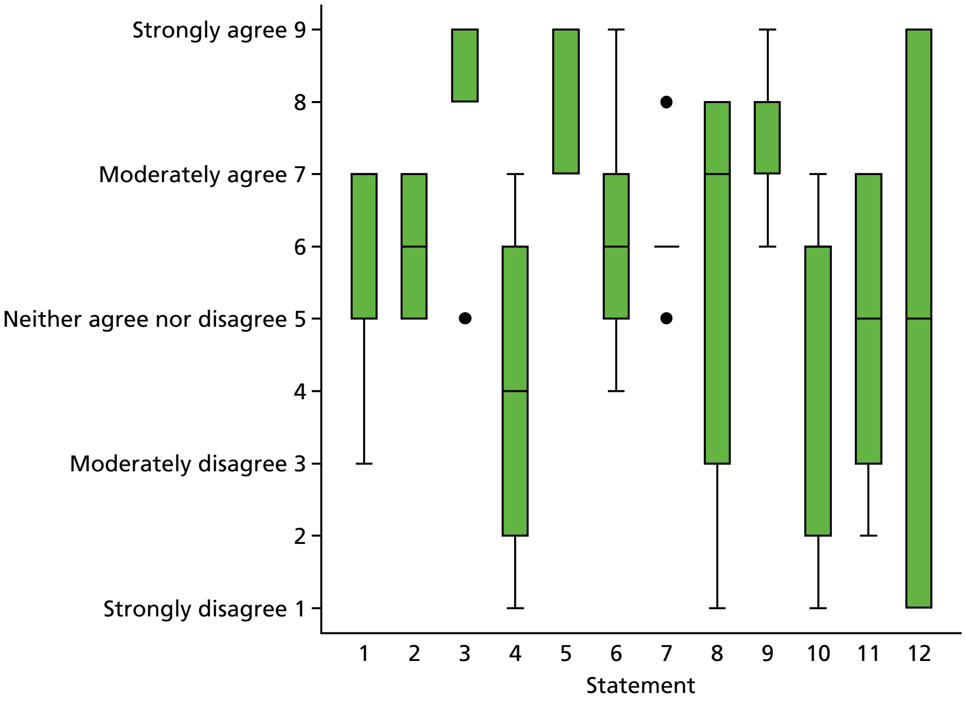

FIGURE 14 Median and IQR for the 12 statements in the first survey ($n = 7$). Boxes represent the median and IQR and the whiskers represent the upper and lower adjacent values (upper quartile + 1.5*IQR, and lower quartile – 1.5*IQR).[67] Dots represent extreme values. Statements 3, 5 and 9 were considered to be in consensus (median score ≥ 7 and IQR 6–9).

Face-to-face meeting

The face-to-face meeting was attended by six of the seven cardiologists and three non-clinical members of the initial working group. As a result of the face-to-face meeting, the survey was modified as follows:

- The number of statements was reduced from 12 to 10. Statement 10 (relating to patients with multivessel disease) was removed because cardiologists felt that this statement overlapped significantly with statement 8. Statements 11 and 12 (relating to incidental cardiac and non-cardiac findings) were combined into one statement.
- Respondents were asked to rate five aspects of each statement, organised hierarchically – (1) whether or not CMR is better than the comparator (e.g. ECHO), (2) whether or not the information from CMR leads to a change in management, (3) whether or not the change in management is clinically important (i.e. likely to reduce risk of MACEs in the long term), (4) whether or not the change in management is likely to reduce NHS costs in the long term and (5) whether or not the anticipated benefit was sufficiently large to make CMR cost-effective among the patients in whom it would be indicated. Consensus was based on the distribution of responses to questions 1–3 of each statement (i.e. median ≥ 7 and IQR 6–9 for clinically important changes in management, and median ≤ 3 and IQR 1–3 for questions 1, 2 and 3). Responses to questions 1–3 were used because question 1 was constructed to interrogate the respondent's appraisal of the evidence, question 2 was constructed to determine whether or not the respondent believed the NHS service delivery changed as a result of CMR and question 3 was constructed to determine whether or not the respondent believed that any change recognised in the response to question 2 was clinically important. Discussions in the meeting revealed that consideration of costs and cost-effectiveness for the NHS influenced some panel members' responses to the initial survey. Questions 4 and 5 were added to isolate these aspects of consideration and separate them from the question of change in management, which was the aim of the consensus process.
- The free-text box in which respondents could justify their score was removed.

The modified survey is shown in *Table 23*.

TABLE 23 Consensus statements (modified survey)

Statement number	Statement
1	The following statements relate to the ability of CMR to identify patients who have a poor prognosis after PPCI: • CMR markers (e.g. impaired LV function, large infarct size, MVO) better identify patients with a poor prognosis after PPCI than markers based on ECHO • Better identification of patients with a poor prognosis after PPCI allows these patients to be followed up more appropriately and treated more aggressively • More appropriate follow-up and more aggressive treatment in these patients is expected to lead to a reduced risk of MACEs in the long term
2	The following statements relate to the ability of CMR to identify patients who have a good prognosis after PPCI: • CMR markers (e.g. normal LV function, high myocardial salvage, no MVO, no residual ischaemia) better identify patients with a good prognosis after PPCI than markers based on ECHO • Better identification of patients with a good prognosis after PPCI allows these patients to be followed up less frequently • Less frequent follow-up in these patients is expected to lead to less NHS resource use in the long term
3	The following statements relate to the ability of CMR to identify the causes of OHCA in patients who undergo an emergency angiogram: • CMR better identifies the cause of OHCA (e.g. large MI, ARVC, aberrant coronary arteries, HCM) than ECHO • Better identification of the cause of OHCA allows treatment to be optimised for these patients (e.g. defibrillator for primary arrhythmia or PCI) or their family members (e.g. genetic screening and counselling, primary prevention) • The ability to optimise treatment for these patients or family members is expected to lead to a reduced risk of MACEs in the long term
4	The following statements relate to the ability of CMR to identify patients with VSD after MI: • CMR identifies the location and characteristics of post-infarct VSD better than ECHO • Better identification of the location and characteristics of post-infarct VSD guides the optimal management of these patients • Optimal management of patients with post-infarct VSD is expected to lead to a reduced risk of MACEs in the long term
5	The following statements relate to the ability of CMR to differentiate MI from other diagnoses in patients found to have unobstructed coronary arteries on emergency angiography: • Unlike ECHO, CMR can provide a definitive ischaemic diagnosis (e.g. MI with spontaneous reperfusion or distal embolisation) or a non-ischaemic diagnosis (e.g. myocarditis, Takotsubo cardiomyopathy, aortic dissection) in patients with unobstructed coronary arteries on angiography • A definitive diagnosis results in a patient treatment plan appropriate for that diagnosis • A treatment plan appropriate for the diagnosis is expected to lead to a reduced risk of MACEs in the long term
6	The following statements relate to the ability of CMR to identify patients at high risk of sudden cardiac death after PPCI who would benefit most from an ICD: • CMR identifies PPCI patients who are at high risk of sudden cardiac death better than ECHO • Better identification of PPCI patients at high risk of sudden cardiac death allows optimal patient selection for an implantable cardiac device (ICD or CRT) • Optimal patient selection for an ICD is expected to lead to a reduced risk of MACEs in these patients in the long term
7	The following statements relate to the ability of CMR to identify patients who would not benefit from CRT after PPCI: • CMR identifies patients who would not benefit from CRT better than echocardiography • The ability to identify patients who would not benefit from CRT would reduce CRT use in patients who do not need it • Reducing CRT use in patients who do not need it is expected to lead to reduced risk of MACEs in these patients in the long term

continued

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TABLE 23 Consensus statements (modified survey) (*continued*)

Statement number	Statement
8	The following statements relate to the ability of CMR to assess ischaemia and viability in patients with multivessel disease: • CMR assesses ischaemia and viability of the myocardium better than ECHO • Better assessment of ischaemia and viability of the myocardium optimises the revascularisation strategy for patients with multivessel disease and avoids additional diagnostic tests • The ability to optimise the revascularisation strategy for patients with multivessel disease is expected to lead to a reduced risk of MACEs in the long term
9	The following statements relate to the ability of CMR to identify patients with post-infarct LV thrombus: • CMR identifies post-infarct LV thrombus better than ECHO • Better detection of post-infarct LV thrombus in PPCI patients allows more affected patients to be treated with anticoagulation therapy • Treatment with anticoagulation therapy in patients with post-infarct LV thrombus is expected to lead to a reduced risk of MACEs in the long term
10	The following statements relate to the ability of CMR to detect incidental cardiac and non-cardiac findings if offered routinely to patients who undergo an emergency angiogram: • CMR identifies more incidental cardiac/non-cardiac findings than ECHO • Improved detection of potentially significant incidental findings allows affected patients to be investigated further and/or treated • Further investigation and treatment is expected to reduce the risk of MACE/increase overall survival in affected patients in the long term

ARVC, arrhythmogenic right ventricular cardiomyopathy; CRT, cardiac resynchronisation therapy; HCM, hypertrophic cardiomyopathy; VSD, ventricular septal defect.
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Modified survey

Fifty-four cardiologists (including five of the cardiologists who attended the formal consensus meeting) completed the survey. There was consensus that five of the 10 statements (50%) described clinically important changes in management (*Figure 15*). These were statements 3, 5 and 9 (which were in consensus in the first survey) and two additional statements: statement 1, relating to the ability of CMR to identify patients who have a poor prognosis after PPCI, and statement 8, relating to the ability of CMR to assess ischaemia and viability in patients with multivessel disease. There was no consensus that any of the other statements described a change in management that was not clinically important.[4] The final statements from the modified survey are in *Appendix 8*.

Implementation of a primary outcome based on the changes in management for which consensus was achieved

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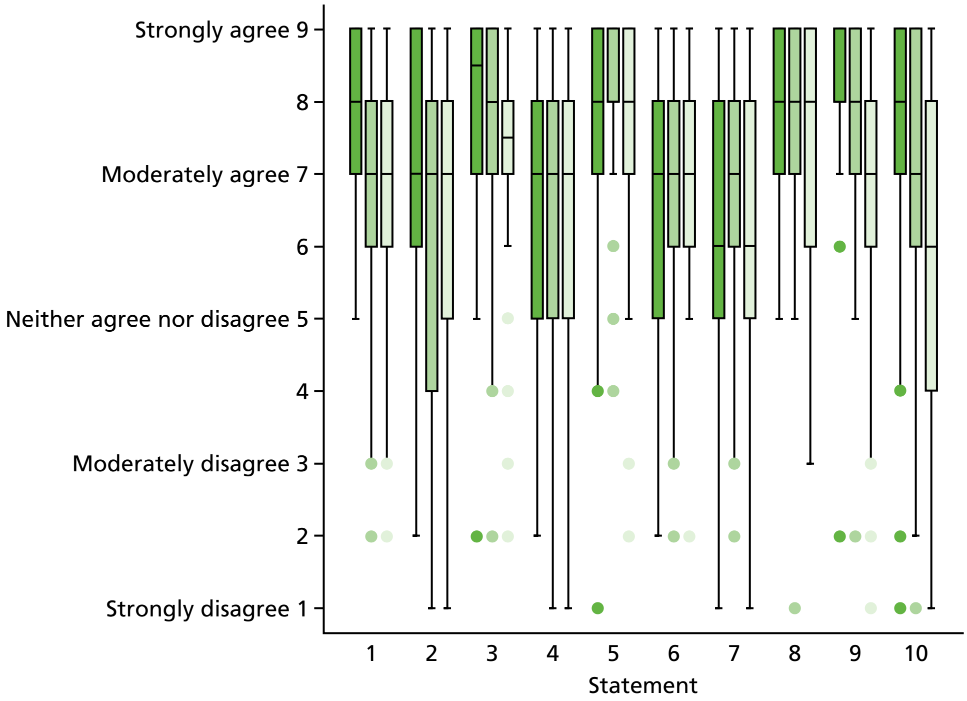

FIGURE 15 Median and IQR for the 10 statements in the modified survey ($n = 54$). Boxes represent the median and IQR and the whiskers represent the upper and lower adjacent values (upper quartile + 1.5*IQR, and lower quartile – 1.5*IQR).[67] Dots represent extreme values.

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Patient subgroups

We identified five patient subgroups (*Table 24*) for which there was consensus that CMR changed management in a clinically important way, either from HISs or from HES/PEDW.

- Patients who underwent PPCI could be identified both from HISs and from HES/PEDW.
- Patients with unobstructed arteries could not be directly identified from either HIS or HES, but they were indirectly identified from HIS (consented into study and underwent angiography but had no data in BCIS) and from HES/PEDW (had a record for angiography but no record for PCI).
- Patients with multivessel disease could only be identified reliably from HISs; the presence of disease in multiple vessels is not coded by ICD-10 but might be inferred from multiple procedure codes in HES/PEDW for coronary revascularisation (PCI or CABG).
- Patients who experienced OHCA, and PPCI patients who went on to develop LV thrombus, could be identified only from HES/PEDW.

The proportions of patients in each subgroup (across all hospitals and by hospital) are shown in *Table 25*. Across all hospitals, 89% of patients underwent PPCI, 11% were found to have unobstructed coronary arteries and 44% of patients had multivessel disease. The proportions of patients in each subgroup were similar between hospitals, except for patients with multivessel disease (19% in hospital D vs. 48%, 51% and 53% in hospitals A, B and C, respectively).

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TABLE 24 Data sources and definitions used for identifying subgroups of patients

Subgroup	Data source	Definition
PPCI	BCIS	BCIS data recorded at site
Multivessel disease	BCIS	Two or more vessels with > 50% stenosis (pre PCI)
Unobstructed coronary arteries	BCIS	BCIS data not recorded
OHCA	HES/PEDW	Index admission includes HES/PEDW diagnosis I46 'Cardiac arrest'
LV thrombus	HES/PEDW	Index admission includes HES/PEDW diagnosis I23.6 'Thrombosis of atrium, auricular appendage and ventricle as current complications following acute myocardial infarction'

TABLE 25 Frequency of patient subgroups by hospital

	Hospital, *n* (%)				
Patient subgroup	A (*N* = 758)	B (*N* = 272)	C (*N* = 316)	D (*N* = 309)	Total (*N* = 1655), *n* (%)
PPCI	651 (86)	246 (90)	291 (92)	279 (90)	1467 (89)
Multivessel disease	361 (48)	138 (51)	169 (53)	58 (19)	726 (44)
LV thrombus after PPCI	1 (0.1)	0 (0)	0 (0)	0 (0)	1 (0.1)
Unobstructed coronary arteries	107 (14)	26 (10)	25 (8)	30 (10)	188 (11)
OHCA	57 (8)	22 (8)	16 (5)	14 (5)	109 (7)

Note

Percentages do not add up to 100 because some patients were in more than one subgroup.

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Manual review of patient notes

We conducted a manual review of patient notes because of the uncertainty regarding the identification of the unobstructed coronary arteries subgroup from HISs. Only 38 out of 47 (81%) patients were identified as having unobstructed coronary arteries in the manual review of patient notes (see *Appendix 9*). Of the remaining nine patients, six had a culprit lesion identified (therefore, the likely reason for their emergency angiography was expected to be MI), and the reason for the coronary angiography in the other three patients was unknown.

We compared the diagnoses from the patient notes with the primary diagnoses recorded in HES for the index admission (see *Appendix 9*). Four of the 38 patients identified as having unobstructed coronary arteries in their medical notes had 'myocardial infraction' as a primary diagnosis in HES. Of the six patients who had a culprit lesion identified in their medical notes, only two had 'myocardial infraction' recorded as their primary diagnosis in HES; two had a diagnosis of 'chronic ischaemic heart disease', one had a diagnosis of 'pain in throat and chest' and one had a diagnosis of 'atrial fibrillation and flutter'.

Identifying changes in management in hospital episode data

The important changes in management identified from the statements in consensus, the patient subgroups these changes in management refer to, the HES/PEDW data sources used to identify them and the events identified from hospital episode data sources in the 12 months of follow-up after the index admission are shown in *Appendix 10*. Medication data are not available in hospital episode data; therefore, any changes in medication during follow-up could not be identified. This was particularly relevant for the LV thrombus after PPCI subgroup, for which the start of anticoagulation therapy was identified as the important change in management. All relevant non-ischaemic diagnoses were identifiable in hospital episode admissions data, as were procedures, such as implantation of devices, repeat revascularisation and additional diagnostic tests. In contrast, we could not identify these from the outpatient data set because ICD-10 and OPCS codes associated with each outpatient episode were missing for a large proportion of patients (25% of patients had missing diagnoses codes, 74% of patients had missing procedure codes and 74% of patients had 'unknown and unspecified causes of morbidity' as diagnosis). This will lead to an underestimation of diagnostic tests in the cohort, because most diagnostic tests are carried out on an outpatient basis. However, we could identify the frequency of outpatient appointments under the cardiology specialty.

Implementation of the consensus statements

The number of events representing changes in management in the relevant patient subgroups, identified in HES/PEDW up to 12 months after the index admission by CMR status are shown in *Table 26*. The frequency of events in patients who did and in those who did not have CMR was similar across all subgroups. Patients who had CMR had, on average, more outpatient appointments across all subgroups.

Table 27 shows the time to first event for each change in management and for all subgroups, by CMR status. Except for patients with unobstructed coronary arteries, patients in other subgroups who did not have CMR had an admission for an additional diagnostic test earlier than patients who had CMR. In the subgroup of patients with unobstructed coronary arteries, patients who did not have CMR had an admission related to a new non-ischaemic diagnosis earlier, and an admission for an additional diagnostic test and implantation of a device later than patients who did get CMR. In the PPCI/multivessel disease subgroups, time to first cardiology outpatient appointment was earlier for patients who did not have CMR than for patients who had CMR.

The frequency of events in CMR versus non-CMR hospitals is shown in *Table 28*. On average, patients in CMR centres had more outpatient appointments than patients in non-CMR centres. New diagnoses, additional diagnostic tests, implantation of devices and additional revascularisation in patients with multivessel disease were more frequent in CMR hospitals than in non-CMR hospitals. Time to the first event in CMR versus non-CMR centres for all events and by patient subgroup are shown in *Table 29*. In CMR centres, patients in most subgroups had an admission for an additional diagnostic test and implantation of a device later than patients in non-CMR centres. Time to first cardiology outpatient appointment was earlier for patients in CMR centres across all subgroups.

Cardiovascular magnetic resonance imaging questionnaire

The changes in management identified by the CMR questionnaire and from HES/PEDW data are shown in *Table 30*. Changes in management identified by the CMR questionnaire could also be identified in hospital episode data, although there were clearly some gaps in the data we had available to us, namely: (1) poor coding of outpatient hospital episode data (diagnoses), (2) failure to obtain medication data and (3) poor coding of diagnostic tests and investigations (both acute care and outpatient data sets).

Summary of main findings

We identified five subgroups of ACS patients who activate the PPCI pathway and for whom there was consensus that CMR changes patient management in a clinically important way: (1) patients who have an OHCA (≈7% of those who activate the PPCI pathway),[69] (2) patients who have a 'normal' (unobstructed) coronary angiogram (≈10% of those who activate the PPCI pathway),[15,16] (3) patients who develop LV thrombus (3% overall and 9% in patients with anterior STEMI),[70] (4) patients who have multivessel disease (between 40% and 65% of those who undergo PPCI)[7,10,71] and (5) patients in whom CMR markers indicate a poor prognosis (up to 60% of patients after STEMI).[2,72] There was consensus about

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TABLE 26 Events representing changes in management identified in HES/PEDW inpatient and outpatient data up to 12 months after the index admission, by CMR status

	n (%)					
Patient subgroup	**New diagnoses (non-ischaemic, Takotsubo, myocarditis, pericarditis, endocarditis, coronary spasm)**	**Changes in medication**	**Additional diagnostic tests (PET, ECHO, IVUS, pressure wire, radionuclide angiocardiography, CT, angiography)**	**Implantation of devices (CRT or ICD)**	**Revascularisation (PCI or CABG) within 3 months**	**Cardiology outpatient appointments, median (IQR)**
PPCI						
CMR (*N* = 152)	0 (0)	No data available	16 (11)	0 (0)	N/A	2 (1–3)
No CMR (*N* = 1312)	10 (1)	No data available	129 (10)	6 (0.5)	N/A	1 (1–2)
Multivessel disease						
CMR (*N* = 104)	0 (0)	No data available	11 (11)	0 (0)	11 (11)	2 (1–3)
No CMR (*N* = 622)	4 (1)	No data available	61 (10)	4 (1)	64 (10)	1 (1–2)
LV thrombus after PPCI						
CMR (*N* = 1)	0 (0)	No data available	0 (0)	0 (0)	N/A	3 (3–3)
No CMR (*N* = 0)	0 (0)	No data available	0 (0)	0 (0)	N/A	–
Unobstructed coronary arteries						
CMR (*N* = 35)	1 (3)	No data available	6 (17)	1 (3)	N/A	2 (1–3)
No CMR (*N* = 139)	1 (1)	No data available	12 (9)	3 (2)	N/A	1 (0–2)
OHCA						
CMR (*N* = 14)	0 (0)	No data available	2 (14)	0 (0)	N/A	1 (1–3)
No CMR (*N* = 95)	1 (1)	No data available	10 (11)	5 (5)	N/A	1 (1–2)

CRT, cardiac resynchronisation therapy; N/A, not available.

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TABLE 27 Time to first event representing a change in management in HES/PEDW up to 12 months after the index admission, by CMR status

Patient subgroup	Number of days until event after the index admission, median (IQR)					
	New diagnoses (non-ischaemic, Takotsubo, myocarditis, pericarditis, endocarditis, coronary spasm)	Changes in medication	Additional diagnostic tests (PET, ECHO, IVUS, pressure wire, radionuclide angiocardiography, CT, angiography)	Implantation of devices (CRT or ICD)	Revascularisation (PCI or CABG) within 3 months	Cardiology outpatient appointments
PPCI						
CMR (*N* = 152)	–	No data available	107 (50–240)	–	N/A	64 (34–99)
No CMR (*N* = 1312)	16 (8–20)	No data available	74 (27–171)	147 (48–171)	N/A	55 (33–95)
Multivessel disease						
CMR (*N* = 104)	–	No data available	85 (50–221)	–	99 (50–180)	76 (52–116)
No CMR (*N* = 622)	13 (8–110)	No data available	62 (24–130)	147 (84–169)	66 (39–122)	57 (33–95)
LV thrombus after PPCI						
CMR (*N* = 1)	–	No data available	–	–	N/A	66 (66–66)
No CMR (*N* = 0)	–	No data available	–	–	N/A	–
Unobstructed coronary arteries						
CMR (*N* = 35)	358 (358–358)	No data available	93 (58–140)	78 (78–78)	N/A	67 (52–121)
No CMR (*N* = 139)	180 (180–180)	No data available	123 (78–284)	245 (71–262)	N/A	67 (44–106)
OHCA						
CMR (*N* = 14)	–	No data available	110 (79–141)	–	N/A	65 (61–104)
No CMR (*N* = 95)	48 (48–48)	No data available	62 (48–93)	126 (71–167)	N/A	64 (41–99)

CRT, cardiac resynchronisation therapy; N/A, not available.

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TABLE 28 Events representing changes in management identified in HES/PEDW inpatient and outpatient data up to 12 months after the index admission in CMR vs. non-CMR centres (hospitals A and B vs. hospitals C and D, respectively)

	n (%)					
Patient subgroup	**New diagnoses (non-ischaemic, Takotsubo, myocarditis, pericarditis, endocarditis, coronary spasm)**	**Changes in medication**	**Additional diagnostic tests (PET, ECHO, IVUS, pressure wire, radionuclide angiocardiography, CT, angiography)**	**Implantation of devices (CRT or ICD)**	**Revascularisation (PCI or CABG) within 3 months**	**Cardiology outpatient appointments, median (IQR)**
PPCI						
CMR centres (*N* = 897)	6 (1)	No data available	112 (12)	5 (1)	N/A	2 (1–3)
Non-CMR centres (*N* = 567)	4 (1)	No data available	33 (6)	1 (0.2)	N/A	1 (0–1)
Multivessel disease						
CMR centres (*N* = 499)	4 (1)	No data available	61 (12)	4 (1)	53 (11)	2 (1–3)
Non-CMR centres (*N* = 227)	0	No data available	11 (5)	0	22 (10)	1 (0–1)
LV thrombus after PPCI						
CMR centres (*N* = 1)	0	No data available	0	0	N/A	3 (3–3)
Non-CMR centres (*N* = 0)	–	No data available	–	–	N/A	–
Unobstructed coronary arteries						
CMR centres (*N* = 133)	2 (2)	No data available	16 (12)	4 (3)	N/A	1 (0–2)
Non-CMR centres (*N* = 41)	0	No data available	2 (5)	0	N/A	0 (0–1)
OHCA						
CMR centres (*N* = 79)	0	No data available	9 (11)	4 (5)	N/A	2 (1–3)
Non-CMR centres (*N* = 30)	1 (3)	No data available	3 (10)	1 (3)	N/A	1 (0–1)

CRT, cardiac resynchronisation therapy; N/A, not available.

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TABLE 29 Time to first event representing a change in management in HES/PEDW up to 12 months after the index admission in CMR vs. non-CMR centres (hospitals A and B vs. hospitals C and D, respectively)

	Number of days until event after the index admission, median (IQR)					
Patient subgroup	New diagnoses (non-ischaemic, Takotsubo, myocarditis, pericarditis, endocarditis, coronary spasm)	Changes in medication	Additional diagnostic tests (PET, ECHO, IVUS, pressure wire, radionuclide angiocardiography, CT, angiography)	Implantation of devices (CRT or ICD)	Revascularisation (PCI or CABG) within 3 months	Cardiology outpatient appointments
PPCI						
CMR centres (*N* = 897)	14 (8–17)	No data available	79 (33–205)	167 (126–171)	N/A	46 (30–81)
Non-CMR centres (*N* = 567)	20 (14–34)	No data available	45 (24–116)	48 (48–48)	N/A	90 (57–126)
Multivessel disease						
CMR centres (*N* = 499)	13 (8–110)	No data available	69 (32–159)	147 (84–169)	71 (41–151)	52 (32–87)
Non-CMR centres (*N* = 227)	–	No data available	59 (15–122)	–	63 (43–88)	95 (68–136)
LV thrombus after PPCI						
CMR centres (*N* = 1)	–	No data available	0	0	N/A	66 (66–66)
Non-CMR centres (*N* = 0)	–	No data available	–	–	N/A	–
Unobstructed coronary arteries						
CMR centres (*N* = 133)	269 (180–358)	No data available	103 (68–205)	162 (75–254)	N/A	65 (46–103)
Non-CMR centres (*N* = 41)	–	No data available	184 (69–299)	–	N/A	89 (54–133)
OHCA						
CMR centres (*N* = 79)	–	No data available	79 (62–141)	147 (99–169)	N/A	63 (42–95)
Non-CMR centres (*N* = 30)	48 (48–48)	No data available	48 (5–74)	48 (48–48)	N/A	86 (52–105)

CRT, cardiac resynchronisation therapy; N/A, not available.

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TABLE 30 Changes in management in patients who received CMR, identified using the CMR questionnaire administered to cardiologists or HES/PEDW data

	n/*N* (%)	
Change in management	**CMR questionnaire ($n = 187$)**	**HIS or HES ($n = 185$)**
Risk stratification after PPCI		
Patients with markers of a good prognosis	102/160 (64)	Not possible to identify
Patients with markers of a poor prognosis	58/162 (36)	
Change in management?	55/123 (45)	Yes, potentially identifiable in HES by considering the frequency and timing of events representing changes in management
Patients with multivessel disease	121/165 (73)	104/185 (56)
Change in management (additional diagnostic tests)?	18/111 (16)	11/104 (11) Difficult to identify all diagnostic tests because procedure codes were not well recorded in HES/PEDW outpatient data
Change in management (did CMR optimise revascularisation)?	95/120 (79)	Yes, potentially identifiable in HES by considering timing of revascularisation and frequency of additional diagnostic tests
Patients with LV thrombus	9/187 (5)	2/185 (1)
Change in management (anticoagulation therapy)?	5/9 (60)	Not possible to identify in HES as medications not available Potentially possible to identify in HIS if medications on discharge data are provided
Patients with unobstructed arteries	19/183 (10)	35/185 (19)
New diagnosis?	13/16 (81)	1/35 (3)
What were the diagnoses?	• Myocarditis ($n = 4$) • Takotsubo cardiomyopathy ($n = 5$) • Heart attack with spontaneous LCX/DS reperfusion and myocarditis ($n = 1$) • Spontaneous LAD reperfusion ($n = 1$) • Borderline low normal EF, possibly consistent with early DCM ($n = 1$) • Prior infarcts ($n = 1$)	• Acute MI ($n = 88$) • Acute MI AND cardiac arrest ($n = 1$) • Acute MI AND cardiomyopathy ($n = 1$) • Acute MI AND chronic ischaemic heart disease ($n = 2$) • Acute MI AND other diseases of the digestive system ($n = 1$) • Acute MI AND pain in throat and chest ($n = 1$) • Angina pectoris ($n = 1$) • Chronic ischaemic heart disease ($n = 4$) • Chronic ischaemic heart disease AND acute MI ($n = 2$) • Heart failure AND chronic ischaemic heart disease AND acute MI ($n = 1$) • Other acute ischaemic heart diseases ($n = 1$) • Other diseases of pericardium AND acute MI ($n = 1$)
Change in management?	15/19 (79)	Yes, potentially identifiable

TABLE 30 Changes in management in patients who received CMR, identified using the CMR questionnaire administered to cardiologists or HES/PEDW data (*continued*)

	n/*N* (%)	
Change in management	**CMR questionnaire (*n* = 187)**	**HIS or HES (*n* = 185)**
Patients with OHCA	24/180 (13)	14/185 (8)
Cause identified by CMR?	19/24 (79)	0/14 (new diagnosis recorded)
Change in management?	11/24 (46)	Yes, potentially identifiable

DCM, dilated cardiomyopathy; LAD, left anterior descending artery; LCX/DS, left circumflex artery/diameter stenosis.

Notes

HES/PEDW data were unavailable for two patients with CMR within 10 weeks of the index admission.

Denominators for the CMR questionnaire indicate the number of responses for each question, excluding missing responses.

the first three subgroups in both rounds of the survey, and consensus was reached about the remaining two subgroups in the modified survey. These results suggest that CMR benefits a large proportion of patients who activate the PPCI pathway.[4] The population investigated was generally representative of the population of patients who activate the PPCI pathway; 11% of patients did not undergo PPCI and were categorised as having unobstructed coronary arteries, 44% of patients had multivessel disease and 7% of patients had an OHCA. Fewer patients than reported in the literature were identified as having LV thrombus (0.3% in our data vs. 3% reported in PPCI populations).

Two subgroups, patients with OHCA and patients who developed LV thrombus after PPCI, could not be identified from HIS data submitted by hospitals but could be identified in the HES/PEDW admissions data relating to the index admission. We defined patients as having unobstructed coronary arteries if they had no BCIS data, because we did not have other information in our HIS data sets for positive identification of this subgroup. We conducted a manual review of these patients' medical notes because we were uncertain whether or not all patients identified as such truly had unobstructed coronary arteries. The majority of patients (81%) were defined as having unobstructed arteries from their medical notes, although 13% did have a culprit lesion identified, suggesting that the most likely reason that these patients activated the PPCI pathway was MI. We also compared the diagnosis from medical notes with the primary diagnosis in HES for all patients in the unobstructed coronary artery subgroup. Again, there were discrepancies, with some patients who were identified as having unobstructed coronary arteries in their medical notes having a primary diagnosis of MI. We conclude that some patients were incorrectly classified as having unobstructed coronary arteries from HIS, and that classification of this patient subgroup is likely to vary depending on the data source used (medical notes, HIS or hospital episode data).

Some important changes in management identified through the formal consensus (e.g. additional revascularisation in the multivessel disease group, implantation of devices) were readily identifiable in HES/PEDW admission data sets. Some changes in management (e.g. changes in medication) were unavailable because medications data are not available in HES/PEDW. Other changes in management (e.g. additional diagnostic tests) were likely to be underestimated because a large proportion of diagnostic tests are performed on an outpatient basis but procedure codes are not well recorded in outpatient data sets.

When implementing the consensus statements, we considered both the frequency of the events representing the important changes in management and time to the first event. This is because, for some changes in management (e.g. additional revascularisation for multivessel disease patients or a new diagnosis in patients with unobstructed coronary arteries), it is the timing to the event that represents the main change in management resulting from CMR. Although there were differences by CMR status in both the frequency and timing of events for all patient subgroups, we chose not to interpret these because of the small numbers involved and because our main objective was to test the feasibility of implementing the consensus statements using hospital episode data.

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The CMR questionnaire highlighted several gaps in hospital episode data (i.e. lack of medications data and poor coding of diagnostic tests and investigations). Without the former data, it would be difficult to characterise patients at baseline (index admission), which is important for identifying and controlling for, confounding, and without the latter data we would be unlikely to have reasonable sensitivity for important changes in management during follow-up in a registry.

Chapter 7 Discussion

Main findings: study results

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Feasibility of setting up a registry using hospital information system data

The outcome measures of the feasibility prospective cohort study were feasibility parameters to establish if (1) consent can be implemented at all four hospitals, (2) data linkage and extraction from multiple HISs can be achieved for $> 90\%$ of consented patients at all hospitals, (3) local data can be successfully linked with hospital episode data for $> 90\%$ of consented patients at all hospitals and (4) the proportion of patients activating the PPCI pathway who get a CMR scan is $\geq 10\%$ in hospitals with dedicated CMR facilities.

The results suggest that the registry is feasible with respect to points 1, 3 and 4, albeit with some caveats, but not point 2. We found that recruitment and consenting of the patient population (using conventional consent), and linkage of local HIS data with hospital episode/vital status data are feasible. However, we experienced problems with identifying and approaching all eligible patients across all sites and we could not obtain all of the requested data from all hospitals. We had envisaged that it would be relatively straightforward to identify patients meeting the eligibility criteria (i.e. patients who activated the PPCI pathway, including those who had an emergency angiogram but did not receive PCI) consecutively, given the emergency nature of PPCI pathway activation. Indeed, we chose this population for a national CMR registry using routinely collected data because, at the outset, we expected that this population would be easy to identify from hospital databases. Although patients who received PPCI were easy to identify from catheter laboratory databases, not all eligible patients were identified in this way and many were identified manually by the research nurses.

The numbers of PPCI patients identified as eligible and approached at each hospital were lower than the numbers of PPCIs reported to BCIS by each hospital over the recruiting period (varying from 22% to 86% across the four hospitals; see *Table 10*). Some PPCI patients were missed because they were quickly repatriated to their local referring hospital. Other patients who arrived at the PPCI centre via A&E were not always classified as PPCI (e.g. patients who experienced out-of-hospital cardiac arrest), resulting in many of them being missed.

Patients who activated the PPCI pathway but had an emergency angiogram without PPCI (i.e. those with unobstructed coronary arteries) were difficult to identify from catheter laboratory databases. Contrary to expectation, there was no data field in any database capturing emergency admission to the catheter laboratory. These patients were also not described consistently in HIS databases and there was misunderstanding over eligibility (especially at the beginning of the study) by catheter laboratory staff and research nurses. Therefore, it is unclear what proportion of these patients was identified at each site during the recruiting period and how the proportion may have changed over time.

We met the feasibility objective of implementing conventional prospective consent at all hospitals, although consent rates were lower than anticipated for a study in which participants have no active involvement. The main reason for this was that many patients identified as eligible were missed (because of short hospital stay, no nurse cover at weekends, quick repatriation to referring hospitals, mobile inpatient

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population, etc.). There was also the issue of competing studies in the hospitals, including the perception that interventional studies should be given priority over observational studies. We relied on postal consent to invite patients identified as eligible and who were not approached in hospital, but return rates were low and we did not have the resources to send reminders or make telephone calls.

We explored alternative methods of obtaining consent as part of the feasibility study. We considered applying for approval to recruit patients without consent ['presumed consent', section 251 (of the NHS Act 2006[76]) exemption] but concluded that this proposal would be unacceptable legally, given that, in principle, it is possible for patients to be asked to give consent for their data to be used for the study.[73] Exemptions are granted only on a temporary basis (pending implementation of consent) or when consent is impossible, not just infeasible. We considered the option of requesting consent at the same time as requesting procedural consent (e.g. by adding a paragraph to the standard NHS form, either opt-in or opt-out consent), although the emergency nature of the procedure means that written procedural consent is not always obtained and verbal assent is often recorded by hand in the patient notes.[27] Furthermore, we were unsuccessful previously when trying to introduce a research consent step into usual care; at the lead hospital, we could not get permission to alter the standard NHS consent form for one specialty and it was impossible to coordinate a change in the written procedural consent across all specialties. Although we were aware of at least one instance when a lead consultant had been able to integrate an opt-out consent model (to allow the use of routinely collected data for research) in the procedural consent form, this instance related to a diagnostic rather than an interventional context. The former setting has a more structured environment with fewer consultants and possibly less time pressure and we considered that an analogous process would be difficult to replicate in the PPCI environment, in which patients are critically ill and staff are under constant pressure to free beds for incoming patients.

Most prospective registries in the UK require explicit patient consent (e.g. National Joint Registry,[74] Inflammatory Bowel Disease registry[75]), using stand-alone consent forms either with/without an approved 'short text' for obtaining consent that can be added to local consent forms. Participating hospitals are responsible for obtaining and recording patient consent with their uploads. However, the issue of missing information on consent is recognised and the National Joint Registry, for example, has dispensation [section 251 (of the NHS Act 2006[76]) exemption] to record patient details when the indication for patient consent is 'not recorded', although this dispensation is granted on an annual review basis. Other registries, such as the cardiac audits under the umbrella of the National Institute for Cardiovascular Outcomes Research (NICOR) [which includes the Myocardial Ischaemia National Audit Project (MINAP) and the BCIS National Audit of Percutaneous Coronary Intervention (NAPCI)], have exemption under section 251 of the NHS Act 2006[76] to use patient information for medical research without consent. We cannot discern a rationale for the inconsistency in the consent arrangements for existing registries. Therefore, we are uncertain whether or not a future registry would be granted a section 251 (of the NHS Act 2006[76]) exemption, as it is manifestly possible to implement prospective consent, as evidenced by some but not all existing registries.

A possible solution to the challenge of obtaining consent in the usual care setting would be to implement changes in NHS information technology (IT) administrative systems (ideally at the national level) to allow a record of verbal patient consent to be recorded in patients' electronic notes (e.g. a 'consent module'). The use of a system embedded within the NHS administrative systems could be applied more broadly to all registry or similar projects seeking to exploit routinely collected data, so that patients could be easily identified as having given or not given consent, having withdrawn consent, or not having been asked for consent. It could also capture whether or not the patient consents to all data being used and if not, which data are specifically excluded from the consent. However, we are uncertain whether or not verbal patient consent recorded in this way would comply with NHS Digital's requirement for 'explicit' patient consent (the legal basis for accessing HES/ONS data).[27,77]

Although patients and the public are broadly supportive of the use of electronic patient data for research,[78–81] there are concerns about potential breaches of privacy and the misuse of health data.[82] The public response to the care.data public consulation[83] highlighted important challenges in terms of patient confidence and trust in how electronic health records are used in medical research.[84] Newer consent models have been proposed, including a dynamic consent model, which would allow patients to control consent electronically over time and receive information about the uses of their data and up-to-date lay summaries of research projects that have used their data.[85] However, such a model would require investment in and maintenance of an electronic infrastructure, which would be difficult in the current economic climate of the NHS. Others have called for more adaptive governance models depending on the particular circumstances of the proposed research.[86] It was beyond the scope of this study to explore these possibilities for obtaining consent.[27] The difficulties we experienced in identifying consecutive eligible patients and consenting those who were identified in the emergency setting of activating the PPCI pathway highlight that the conventional consent model that we successfully implemented would not be feasible for a national registry.

We did not meet the feasibility criterion for data linkage and extraction (the target was that this should be achieved for > 90% of patients at all four hospitals) from HIS for all the requested data sets. Reasons for missing data included the following: difficulties in extracting data from local stand-alone databases, some of which were old and did not have an interface for data extraction; some data (e.g. medications on discharge, bedside ECHO) were not recorded electronically; imaging data were available electronically but only as free-text reports, making individual parameters of interest difficult to extract. The main impacts for a registry of failing to obtain these HISs is the inability to characterise the registry population in detail, to adjust any comparisons for patients' characteristics and to describe changes in these data over time (potential indicators of the consequences of important changes in management).

We had initially envisaged establishing a data linkage and extraction model in one hospital and using this to guide data extraction at the other hospitals. We also envisaged that this model would be automated, with minimal IT support beyond the set-up phase. However, this was not possible because HIS for each data set differed across hospitals and different hospitals provided different levels of start-up IT support for the research project.[27] We budgeted for only a small amount of funding (£5000) to each hospital to help with this aspect of the study. Data linkage requires expertise in several areas, including knowledge of the databases to be linked and skills in creating linkage programmes. This expertise was variable across hospitals and in-depth knowledge was sometimes lacking; this was perhaps not surprising given the diversity of the databases involved, and the fact that some of these were old and were being phased out.[27] We relied on each hospital identifying key individuals to help with this aspect of the study. In addition, even in hospital A, the highest priority for the IT team was to maintain the integrity and functionality of the clinical care systems; in this context, it was difficult for them to prioritise our request to support this research project, even with the funding that was available.

The complexity of data retrieval from multiple HISs in secondary care in the NHS has been highlighted previously.[61] The government's vision for the NHS, outlined in the National Information Board's complex *Personalised Health and Care 2020* framework,[87] is that it will be an entirely digital organisation by 2020. Although such a system, if properly implemented, should provide benefits for research as well as patient care, it is an ambitious goal given the current financial and operational pressures within NHS organisations. The earlier (and equally ambitious) National Programme for IT, which aimed to create a single electronic care record for patients, connect primary and secondary care IT systems and provide a single IT platform for health professionals, was dismantled, mainly because IT companies could not provide solutions to match the ambition.[27,88] Despite such programmes, our experience from this study has highlighted the poor-quality electronic infrastructure in hospitals and the multitude of clinical databases that are not amenable to 'interoperability' (i.e. not needing extensive customisation or permission from the database vendor to provide data flow). Full interoperability for HISs across the majority of hospitals, therefore, still appears to be a distant goal.[89]

We met the feasibility criterion of having > 10% of our consented population being referred for CMR in hospitals with a dedicated CMR facility. However, many of these referrals were for research (patient participating in a research study) rather than clinical purposes. For example, in the lead hospital, 33%

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of all referrals were for research. It is not clear whether or not this reflects practice in other hospitals with dedicated CMR facilities. Referral for non-clinical reasons (unless the findings are used to change clinical management) would dilute any observed effect of CMR on outcomes in an extended registry. Another challenge was that imaging reports were largely in free-text format, so individual CMR parameters would have to be extracted manually, which would not be feasible for an extended registry. A registry assessing the prognostic value of CMR, including individual CMR parameters, such as contractile function, myocardial oedema, MVO, intracardiac thrombus, myocardial haemorrhage and myocardial scar, would allow for an assessment of the value added of each parameter on patient outcome. Similarly, ECHO reports were also in free-text format, and bedside ECHO reports were missing entirely from our data sets because these are not routinely uploaded to electronic databases.

We made the decision to obtain data about follow-up from hospital episode data rather than from the source data submitted by participating hospitals, which are used to compile the hospital episode data. Using hospital episode data has two advantages: (1) follow-up episodes of care can be linked to index admissions, wherever they occur (not just in the participating hospitals) and (2) the organisations compiling hospital episode data apply established data management processes to improve data quality. We met the feasibility objective with respect to linkage of index admission data with hospital episode data. Linkage was achieved for 99% of patients. We failed to achieve linkage for the remainder mainly because of missing identifiers (NHS numbers) in the data sets submitted by participating hospitals. We had originally envisaged collecting information from local HISs on outcomes in the 12 months following the index procedure. However, we would have been unable to capture these data on every patient included in the study because many patients were discharged to, and followed up in, different hospitals, and it would have been difficult to liaise with and obtain data from multiple sites.

Is it feasible to set up a national registry from hospital episode data?

We explored the feasibility of setting up the registry retrospectively entirely by using linked, routinely collected data sets [e.g. hospital episode data, NHS England's Diagnostic Imaging Dataset (DID) and national audits, such as the BCIS' NAPCI[90]]. Setting up the registry in this way would avoid the need to obtain patient consent. This would be deemed appropriate on the basis that all of the information made available would be anonymised.

We were able to identify patients who activate the PPCI pathway in hospital episode data using the relevant procedure codes. We identified 98% of patients in our cohort who underwent PPCI and 85% of patients who underwent emergency angiography without PPCI. We could not, however, identify the CMR exposure in hospital episode data for the majority of study participants who had a CMR scan. This is because CMR is carried out mainly as an outpatient investigation and the hospital episode outpatient data sets do not contain details of the exact nature of the outpatient visit (only the specialty), so the reason for outpatient visits coded under the cardiology specialty was unclear. One option to consider would be the use of NHS England's DID to identify CMR exposure. DID is a central collection of detailed information about diagnostic imaging tests carried out on NHS patients, extracted from local radiology information systems and submitted monthly to NHS England.[91] The main driver for the creation of the DID was to assess how the use of diagnostic imaging could contribute to the early diagnosis of cancer (in particular, GP direct access to these tests). As such, DID has already been linked to cancer registry data, but not other national audits, and there could be substantial difficulties/delays in applying for linkage permissions with, for example, the BCIS' NAPCI data set.[90] Although DID captures information about referral source and patient type, details of the test (e.g. type of test and body site), demographic information (e.g. GP-registered practice, patient postcode, ethnicity, gender and date of birth), plus items about waiting times for each diagnostic imaging event (it does not store the images themselves, the individual parameters measured by the test or the outcomes/diagnoses related to the test). DID could not, therefore, be used to assess the prognostic value of individual components of a CMR scan, or the extent to which a CMR scan altered patient management. Nevertheless, it should allow ascertainment of CMR exposure.

Economic evaluation

We developed a series of economic decision models to identify the key drivers of cost-effectiveness. To our knowledge, this is the first time the key drivers of the cost-effectiveness of introducing CMR have been considered. We chose two patient subgroups for our models: patients with multivessel disease and patients with unobstructed coronary arteries. Both of these subgroups were identified as potentially benefiting from CMR in the formal consensus study.

Our results showed that, for each of the base-case models, the differences in QALYs between strategies were very small and, therefore, the results were largely driven by the differences in costs, although mean differences in cost for different strategies were modest. Sensitivity analyses around the two models identified the diagnostic accuracy of the ischaemia tests as the key driver of cost-effectiveness. In the model for patients with multivessel disease, the costs of ischaemia testing and the QALYs associated with MACEs and no MACEs exerted an influence on cost-effectiveness results, but not to the same extent as the diagnostic accuracy of CMR and pressure wire. Similarly, in the model for patients with unobstructed coronary arteries, the cost of CMR, the difference between QALYs associated with MACEs and no MACEs, and the proportion of patients who have MACEs who are assumed to die exerted an influence on the results; however, the better diagnostic accuracy of CMR and standard ECHO combined (the reference standard in the base case) compared with standard ECHO only was more important.

The key drivers of cost-effectiveness highlighted by each model are similar, and, therefore, it is likely that if CMR was introduced for our entire eligible population (patients who activate the PPCI pathway), it would be these parameters that would need to be measured accurately in any future study. This work highlights the importance of having accurate information about the diagnostic accuracy of different tests, as estimates for these parameters are such key determinants of cost-effectiveness. We have identified some of the key unknowns in terms of costs and outcomes in the population of patients who activate the PPCI pathway, which can inform future studies to ensure that important variables are captured in sufficient detail.

Identifying important changes in management resulting from cardiovascular magnetic resonance and the subgroups of patients to which these refer

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A key objective of our feasibility study was to define a primary composite outcome, acceptable to cardiologists and other stakeholders (e.g. clinical commissioners) as representing a clinically important change in management (e.g. expected to prevent future MACEs) as a result of an eligible patient having had CMR, that could be used for the registry in the medium term. Although such a primary outcome is not typical, it would allow evidence to be obtained more quickly to inform decisions about implementing CMR than would be possible for an evaluation based on MACEs. In the long term, we envisaged that the primary outcome for the registry would be MACEs, but addressing relevant research questions using the registry would need data for a large number of patients. For example, in order to have 90% power to detect a 1.2% difference in MACEs (4.8% vs. 6.0%) between those having CMR and those not, at the 5% level of statistical significance, and assuming 10% of patients who activate the PPCI pathway receive CMR and 90% do not, the registry would require > 37,000 patients. This represents 20 hospitals, with an average of 500 patients giving consent per year per site for > 3.5 years. We expected that important changes in management would be much more frequent than MACEs, allowing the effectiveness of CMR with respect to this outcome to be evaluated more quickly with data from fewer patients.

We used a formal consensus approach because there were no studies in the literature that reported the impact of CMR in our study population, reflecting the fact that changes in clinical management are difficult to use as end points in trials. This is because some important changes in clinical management are not easily observed[92] and the causal relationship between changes in management and improved

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outcomes is not well defined. Imaging has been identified as one of the key drivers of increased health-care costs; therefore, the adoption of an imaging modality in a new clinical context should be supported by evidence of its benefit to specific patient groups or clinical scenarios. Such evidence is difficult to obtain in practice.

We identified five subgroups of ACS patients who activate the PPCI pathway for whom there was consensus that CMR changes patient management in a clinically important way: (1) patients who have an OHCA (≈7% of those who activate the PPCI pathway),[69] (2) patients who have a 'normal' (unobstructed) coronary angiogram (≈10% of those who activate the PPCI pathway),[15,16] (3) patients who develop LV thrombus (3% overall and 9% in patients with anterior STEMI),[70] (4) patients who have multivessel disease (between 40% and 65% of those who undergo PPCI)[7,10,71] and (5) patients in whom CMR markers indicate a poor prognosis (up to 60% of patients after STEMI).[2,72] There was consensus about the first three subgroups in both rounds of the survey, whereas consensus was reached about the other two subgroups in the modified survey. These results suggest that CMR benefits a large proportion of patients who activate the PPCI pathway.

Cardiologists who participated in our research agreed that CMR is superior to ECHO in establishing a diagnosis in patients who survive an OHCA, which has implications for treatment and prognosis. Despite this view, there are few studies that have reported the role of CMR in managing these patients. A retrospective case series of 54 OHCA survivors showed that CMR diagnosed the cause (ischaemic or non-ischaemic cardiomyopathy) in 40 (74%) of the survivors.[93]

The cardiologists also agreed that CMR can provide a definitive diagnosis (e.g. acute MI, acute myocarditis and cardiomyopathy, especially Takotsubo cardiomyopathy) in patients with ACS and unobstructed coronary arteries. Evidence for the role of CMR in patients with ACS and unobstructed coronary arteries also comes from small retrospective case series. These suggest that CMR provides a definitive diagnosis in 80–90% of these patients.[20,23,94] Without access to CMR, the management of these patients is variable in clinical practice, which may have long-term implications. A 2015 systematic review[50] showed that the overall all-cause mortality in patients presenting with suspected MI and unobstructed coronary arteries was ≈5% at 12 months.

The cardiologists agreed that CMR identifies LV thrombus better than ECHO, which allows more patients to be identified and treated appropriately. Accurate identification of a LV thrombus is important because it often directs subsequent anticoagulation therapy to prevent embolic events. A 2015 systematic review,[95] published after we conducted the formal consensus study, showed that late gadolinium enhancement (LGE) CMR is the most accurate modality for detecting LV thrombus, with 88% sensitivity and 99% specificity (compared with standard ECHO, which had 24–33% sensitivity and 94–95% specificity, and contrast ECHO, which had 23–61% sensitivity and 96–99% specificity), although most of the included studies in this review did not use a pathological or surgical gold standard for the detection of LV thrombus.

There was agreement among cardiologists that CMR-based testing of ischaemia after PPCI would be likely to optimise the revascularisation strategy for patients with multivessel coronary disease, although they acknowledged that there is no evidence to support the view that a CMR-based revascularisation strategy would improve outcomes. Patients with multivessel disease have a two-fold increase in MACEs compared with patients with single-vessel disease.[96] There is continuing debate about the benefits of complete versus single lesion revascularisation during the index PPCI admission.[97] Despite recent evidence from randomised controlled trials (RCTs) showing improved clinical outcomes when complete revascularisation is undertaken at PPCI,[98] current American[99] and European[100] revascularisation guidelines for acute MI recommend revascularisation only of the infarct-related artery at PPCI in patients with multivessel disease.

There was considerable debate about using CMR to identify patients with a poor prognosis after PPCI. Although there was agreement that CMR parameters of cardiac function (e.g. impaired LV function, large infarct size, MVO) are useful for risk stratification after STEMI, there was disagreement about whether or not this would lead to a management change. Some cardiologists felt that there would be no changes to prescribing for secondary prevention because all patients should receive aggressive secondary prevention in accordance with guidelines. It was acknowledged, however, that CMR markers are prognostic for outcome;[4] two recent meta-analyses of prognostic studies (conducted after this formal consensus study) showed an increased risk of MACE, by 13–15% for every 10% decrease in EF assessed by CMR,[2] and in patients with MVO assessed by CMR [odds ratio (OR) 2.60, 95% CI 1.68 to 4.02 and OR 4.30, 95% CI 2.19 to 8.43, depending on the method of MVO assessment].[3]

We could not identify all patient subgroups from HIS data sets. Patients with LV thrombus and OHCA were identifiable only in hospital episode data, from ICD-10 codes for these diagnoses assigned to the index admission. Patients with unobstructed arteries could not be positively identified from HIS; we identified them by their exclusion from the hospital BCIS' NAPCI data sets (as only patients who have a stent inserted, i.e. have PPCI, or have had an attempt to have a stent inserted, are included in BCIS' NAPCI). Given the uncertainty we faced when trying to identify this population prospectively (see *Feasibility of setting up a registry using hospital information system data*) and the initial confusion over eligibility at the beginning of our recruitment period, we decided to review the medical notes (representing the reference standard) for a subset of these patients to determine the proportion classified correctly according to our definition of 'unobstructed coronary arteries' (exclusion from BCIS' NAPCI). Although we classified 81% of patients correctly, some patients we identified as having unobstructed arteries were identified as having a culprit lesion in the manual review of patients' notes. Furthermore, there was also a degree of disagreement between medical notes and the primary diagnosis recorded in hospital episode data for the index admission of these patients, with 11% of patients who were identified as having unobstructed coronary arteries in their medical notes having a primary diagnosis of MI in HES. Our investigation using medical notes highlights a degree of misclassification of this subgroup of patients, although this is not surprising given the uncertainty in diagnosis during the index admission.

Implementation of a primary outcome based on the changes in management for which consensus was achieved using hospital episode data

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There was consensus that CMR changes patient management in a clinically important way for five subgroups of ACS patients. For each group, we listed 'activities' (e.g. new diagnoses or procedures, additional diagnostic tests, changes in medication, outpatient appointments) that reflected a change in management. Activities were identified from the relevant consensus statements and by looking at care pathways, when available, to confirm that we captured all aspects of patient management in these activities. We then compiled a list of the relevant ICD-10 diagnosis codes and OPCS procedure codes (with help from clinicians on the study team and a dedicated HES coder). We identified these codes in hospital episode data for participants up to 12 months following the index procedure.

We were able to identify all of the activities that we identified as representing changes in management in the hospital episode data. Therefore, we conclude that it would be feasible to look for differences between patients who have and those who do not have CMR within ACS subgroups in terms of frequency and time to first event for some of the activities. We recognise that some events that were listed as representing a change in management (e.g. cardiology outpatient appointment, changes in medication) are not immediately amenable to inclusion in a composite outcome for a time-to-event model.

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This approach to constructing a proxy outcome reflects our original concept and appears to be feasible when the important changes in management are hypothesised to cause a change in the same direction in all events/activities included in a composite outcome for a subgroup. However, through the consensus process, it became apparent that some of the hypothesised changes in management arising from CMR will not necessarily result in a unidirectional change in the frequency or rate of an activity. In several instances, an important change in management was more appropriate targeting of a treatment activity to the patients who were likely to benefit most, without necessarily any change in the overall frequency of the activity. For example, in patients with multivessel disease, CMR may result in better (i.e. more cost-effective) targeting of additional revascularisation. In these situations, a simple evaluation of the frequency or rate of a proxy outcome would not detect any value of CMR to patients and the NHS.

We were unable to identify some important changes in management that could have arisen from CMR. There are no medication records in hospital episode data, so changes in drug therapy could not be identified. Initiation, withdrawal or changes in medication represented an important change in management for all of our patient subgroups and, in particular, patients with LV thrombus, for whom anticoagulation therapy is the main change in management. A potential solution to this problem is the linkage of HIS and hospital episode data with data from the Clinical Practice Research Datalink (CPRD), a primary care data set that has detailed prescription information. However, because not all general practices contribute data to CPRD, medications data would be available for only a proportion of patients in a registry.

We were also unable to identify additional tests or procedures carried out in the outpatient department because most outpatient episodes in the HES outpatient data set do not have diagnostic/procedure codes assigned to them. We are uncertain about the extent to which DID, recently added to the HES portfolio of data sets, may improve this situation. Finally, hospital episode data alone may not capture all activity related to changes in management as some patients will be seen multiple times by their GP or in private facilities. However, as the extent of after care in private facilities in the UK is minimal, it is unlikely to invalidate a future comparison in a registry.

Patient and public involvement and engagement

The chairperson of the Study Steering Committee (SSC) was a patient representative. We also included on the SSC a representative from the British Heart Foundation (the Area Development Manager). We felt that it was particularly important to have members of the public and a previous patient on the SSC because one of the main objectives of the feasibility study was to investigate the feasibility of consenting patients into a registry.

We sought the views of both of our lay members about various aspects of the study at all stages. For example, at the first meeting, we explored the issue of consent. Both our lay members suggested exploring the possibility of not having consent for the study and confirmed that they did not think using 'assumed consent' would be a problem if it was implemented in routine practice. We did this (as described in *Feasibility of setting up a registry using hospital information system data*) but concluded that this viewpoint, although prevalent among patients and the public, is not currently consistent with the data protection law.[101] When implementing our conventional consent method, we also asked patients who had been in a similar position to review the patient information leaflet and consent form to ensure that the information was not excessive but covered all the points that patients would want to know. This input was very useful and helped to guide some changes during the finalisation of these documents for the Research Ethics Committee submission.

We had planned to hold a focus group with patients and the public to engage with them about developing the primary outcome as part of the formal consensus process. The lay representatives on the SSC were consulted at length about this, including reviewing questionnaires that had been drafted for the consensus meetings. They concluded that, to form an opinion about the importance of the changes in management for which consensus was obtained, lay people would require an understanding in terms of technical knowledge and recent experience and, therefore, it was not reasonable to expect lay people to comment on or refine the outputs from the consensus process. Throughout the project, the lay representatives on the SSC (and, in particular, the SSC chairperson) expressed dismay about the lack of availability of HIS and hospital episode data and the delays this caused to the study. Accepting that our application for these data was held up by the one-off event of the moratorium in processing applications at NHS Digital (see *Chapter 2*, *Major delays with the study*), lay representatives were surprised that the plan for implementing new governance processes did not appear to have considered how applications in progress should be handled. The ruling from NHS Digital and ONS that the wording of the patient information leaflet was not compliant with the new guidance, after we had completed recruitment, seemed Kafkaesque[102] from the perspective of the researcher team.

Strengths and limitations of the study

Feasibility prospective cohort study

We established a successful collaboration among four hospitals and exceeded the recruitment target for the study of 1600 patients. We also identified the main challenges to establishing a prospective registry in the way we had envisaged: identifying the eligible population is difficult to do from local HISs; the conventional consent model fails to capture a sizeable proportion of the eligible population and would be costly to implement; and, most importantly, the required local data from HISs are not uniformly available/exportable.[27]

We did not identify or test a more efficient method to obtain consent. The methods used by hospitals for the study are almost certainly not feasible to implement in the long term for a registry, and are likely to result in varying completeness across hospitals. However, the barriers to any form of ‘presumed consent’ or ‘opt out’ seemed insurmountable without a long-term plan for implementing consent.

We are aware that CMR may benefit other groups of ACS patients (e.g. those with NSTEMI). However, we considered at the outset that it would be impossible to identify consecutive patients presenting with a broader diagnosis of ACS but not requiring emergency coronary angiography; being able to define and ascertain the entire eligible population is a key requirement of a high-quality database. This was a particularly important consideration given that the proposed registry was based on the premise of linking information collected in the course of usual care, avoiding the time and cost burden of primary data collection.[27] Even so, we still encountered difficulties in identifying from electronic records the group of patients with unobstructed coronary arteries in our eligible population.

We concluded that we could identify our eligible population in hospital episode data, based on the fact that we identified the index admission for most patients recruited into our study. However, because we had only hospital episode data for patients in the cohort, we cannot comment on or quantify the risk that an algorithm designed to identify such patients from hospital episode data could also identify some patients who would have been ineligible for the registry. Our impression from exploring codes assigned to hospital episode data for index admissions is that this risk is low and is likely to reduce as the quality of hospital episode data improves. The only way to quantify the risk would have been to request anonymised linkage of all HISs and hospital episode data for all cardiology admissions during the study period, with identification of the study cohort participants as a subgroup.

A major limitation is the length of time it took to complete the study. The main reason for this was because our application for HES data coincided with the moratorium on data requests by NHS Digital (formerly known as the Health and Social Care Information Centre), which resulted in a delay of 23 months in processing our application. This meant that the study took > 4.5 years to complete, whereas we had projected 1.5 years for completion. During this time, it is likely that data availability and the quality of the data will have changed/improved, given the rapidly evolving NHS IT systems/platforms. During this time, new diagnostic tests for detecting ischaemia (e.g. pressure wire), directly competing with CMR, were introduced and rapidly adopted by some cardiologists. These changes highlight the need for new research questions; therefore, it is likely that the aims and objectives for a national registry now would be different

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from those we proposed when we set up this study. For example, it may be more relevant to compare ischaemia testing using pressure wire with CMR, rather than to compare CMR with no CMR, which we proposed for our registry. We have tried to adapt the study to the current circumstances, for example with respect to the cost-effectiveness models, but have been unable to do anything about the changes in practice or the historic nature of the data collected.

Economic evaluation

There is considerable uncertainty around the majority of parameter estimates in both models. In the model for patients with unobstructed coronary arteries, the probability of patients truly having a MI was obtained from the results of a systematic review,[50] but all other probability estimates in both models are based on single papers, often on small or modest sample sizes. There was only sparse evidence found in the literature for many of the probability estimates required. This was particularly true for the probabilities of MACEs for patients who truly did and those who did not have a MI (and had appropriate treatment or not), in the model for patients with unobstructed coronary arteries. Members of the study team were concerned that the estimated ratio of MACEs in MI patients compared with non-MI patients (in patients with unobstructed coronary arteries) found in Pathik *et al.*[52] was very high; this is why we investigated this parameter in the sensitivity analyses.

Even when papers reported on the correct patient group and outcomes, studies may have been conducted in other countries, where practices may differ from those in the UK. For example, Smits *et al.*[38] specifically reported numbers that could be used to estimate the probability of a MACE by 1 year for those truly with ischaemia separately for those who were and those who were not revascularised (see *Figures 1* and *2*, and *Chapter 5*, *Cost-effectiveness models*); however, this study was conducted in Europe and Asia, with no UK centres included. Occasionally, estimates from a different patient group were the only estimates available. For example, in the model for patients with multivessel disease, the diagnostic accuracy of stress ECHO (its sensitivity and specificity) was taken from a paper considering the diagnosis of significant coronary artery disease, rather than a PPCI population, and estimates are based on the number of vessels rather than the number of patients.[39]

In the base-case analyses for multivessel disease, CMR and pressure wire were treated as reference standards, and both were assumed to have 100% sensitivity and specificity. There are suggestions in the literature that this is reasonable; for example, Emrich *et al.*[103] found that CMR correctly identified all 20 out of 125 patients with MI in their study. The assumption of equal diagnostic accuracy is critical, because the sensitivity analyses showed how diagnostic accuracy of the ischaemia tests was the key driver of cost-effectiveness. Similarly for the unobstructed coronary arteries model, reducing the diagnostic accuracy of CMR plus standard ECHO compared with standard ECHO alone (sensitivity analysis 1) doubled the ICER.

Individual patient data on resource use were not available from hospital episode data in time to be used in these analyses; resource use associated with each of the patient pathways was, therefore, estimated based on discussions with the PIPA study team and costs were largely obtained from NHS Reference Costs.[40] These methods have allowed standard care pathways to be costed but will have underestimated the variability between individual patients and their actual patient pathways.

As well as the costs of initial ischaemia testing (if applicable), and any revascularisation, we included the costs of follow-up outpatient appointments, medications and rehabilitation over the first year. We also included additional health-care costs to 1 year based on the Office of Health Economics' estimate of the annual cost per person of NHS care.[43] It is recognised that there will be an element of double counting here, as the costs of ischaemia testing, revascularisation and subsequent costs will overlap with these annual costs, but this will be the same for all strategies and should not affect the comparison of costs between strategies. These annual costs were included to account for differences in costs for patients who died; these costs were halved for patients with a MACE who died by 1 year.

Utility estimates for a PPCI population were found in the literature, but there was uncertainty around the utility decrement for patients with MACEs compared with those without MACEs. A decrement of 0.05 was assumed for patients with a MACE compared with those without a MACE.[48] Although this decrement has been used by others, the original reference for this decrement implies that it was a sensitivity analysis, and was not based on any primary data.[104] Utility estimates for patients with unobstructed coronary arteries were not found in the Tufts Cost-effectiveness Analysis Registry,[46] and a recent paper measuring quality of life in patients with MI with unobstructed coronary arteries reported that no studies measuring quality of life in these patients have previously been conducted.[105] This study measured quality of life using the SF-36 at 3 months post acute event and found similar findings in patients with unobstructed coronary arteries and a control group of MI patients with coronary heart disease, suggesting that the estimates used in our model for patients with unobstructed coronary arteries are reasonable.

Formal consensus study

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A key strength of the study was the use of a formal consensus approach, based on a systematic search of the literature as well as expert opinion. The nominal group technique is one of the four well-established methodologies for formal consensus [the other three are (1) the Delphi method, (2) the Research ANd Development Corporation (RAND)/University of California, Los Angeles Appropriateness Method (RAM) and (3) the National Institutes' of Health consensus development conference methodology].[4,106,107] Our literature review included all study designs to determine the size and nature of the evidence base and highlight research gaps. The search was systematic and extensive, including five databases and published abstracts. Four cardiologists contributed expert opinion. Two are UK/European CMR experts. The process provided evidence for the content validity of each statement. All cardiologists who drafted the statements proposed the same patient subgroups as potentially benefiting from CMR. There was generally good agreement between draft statements generated by cardiologists and the non-clinical reviewer.

There were no disagreements in the group meeting regarding the potential management change in each of the patient subgroups identified. Similarly, the studies identified in our literature review (both prognostic and diagnostic) were consistent in their findings. The majority of prognostic studies reported that CMR markers such as EF, MVO and haemorrhage were associated with MACEs, although most did not evaluate the prognostic value of CMR indices in addition to indices available from alternative imaging modalities. The evidence supporting many of the statements came from small, retrospective case series. There were no prospective studies in the literature that reported the impact of CMR on clinical management in our population or whether or not any changes in management affected patient outcomes.

The main features of a formal consensus method are anonymity (i.e. statements were rated free from peer-group pressure) and iterative feedback (i.e. participants could adjust their initial rating based on the feedback of the group rating). We described the supporting evidence for each statement, identified via the literature review, and fed back qualitative (i.e. panel members' comments) and quantitative (i.e. group median ratings of each statement) information at the face-to-face meeting. We also included a varied group of cardiologists from different specialties in order to encompass diverse perspectives.[4]

A potential limitation of this study is that we did not perform any formal quality assessment of primary studies. We made this decision for two reasons. First, the purpose of the review was to identify the evidence base in order to inform the consensus process, not to use the literature to quantify the effectiveness of CMR or its diagnostic or prognostic value. Second, no single assessment tool would have been appropriate for the diverse studies that were identified, hence assessments would not have been comparable. Therefore, we have not referred to our overall review as being 'systematic' (only the search), although its conduct closely reflected established guidelines for systematic reviews and we believe that other researchers following the same steps would replicate its findings.

The number of panel members in our study was lower than the recommended 8–12 members for a consensus panel.[107] Nevertheless, smaller groups are preferable to larger ones because, although having more group members increases the reliability of group judgement, large groups reduce the ability to elicit potentially important contributions from every member of the panel.[107] To overcome any criticism of the number of panel members in the study and to prevent the possibility of introducing bias (given the self-selected nature of the panel), we extended the survey to UK cardiologists who did not participate in the formal consensus process. Apart from one statement (statement 1, relating to the ability of CMR to identify patients with a poor prognosis after PPCI), the same statements were in consensus when the survey was completed by cardiologists external to the consensus process. This indicates that the process was robust and the survey statements were clear and unambiguous.

A further limitation of the study was that we did not include other stakeholders (e.g. GPs and patient representatives) in the consensus process.[108] Although we had originally planned to do so (see *Patient and public involvement and engagement*), we decided that the specialised nature of the statements would not be easily understood by those without cardiology expertise.[4] We did, however, hold a separate meeting (outside the consensus process) with a GP commissioner and the director of the Southwest Cardiac and Stroke Network. The conclusion of the meeting was that, given that the cohort is an emergency population and the consensus process identified that a large proportion of the population would potentially benefit from scanning, it would be better to offer CMR to the whole population rather than complicating the patient management strategy by scanning only subsets of patients.

Lessons for the future

Future studies attempting to answer research questions through linkage of routinely collected data sets (at the local and national level) should consider the following:

- Timeliness – a study must be reported within a reasonable time frame given the rapidly changing environment (e.g. NHS IT systems, introduction of new diagnostic tests).
- Data availability in hospitals – the HIS available at each hospital and the level of IT support available to provide the data need to be investigated thoroughly; funding is likely to be required to support data extraction.
- Data sources in hospitals – the relevant data sources at each hospital need to be identified before starting a study. For example, we decided to use BCIS/MINAP submission data sets instead of catheter laboratory databases after the study started; this caused considerable confusion and difficulties over patient eligibility, given that BCIS/MINAP could provide data only for patients who had STEMI/received PPCI and not patients with unobstructed coronary arteries.
- Hospital episode data – these data are made available (after 'cleaning') by NHS Digital (or Information Services Division Scotland, PEDW or Northern Ireland Department of Health) for whole financial years. Our failure to appreciate this meant that only ≈67% of patients had a whole 1 year of follow-up.

Implications for practice

Our experience highlights the need to assess 'feasibility' before attempting to set up a new registry. Although some of the pitfalls we experienced may, in hindsight, be viewed as resulting from a lack of 'preparedness', our experience is not unique. Registries (e.g. national audits) that have managed to overcome issues with data collection and quality have achieved this through a lengthy process, necessitating many iterations (and a feedback loop) before attaining any quality targets. This process requires considerable investment, infrastructure and commitment at the national level, which would be difficult to achieve in a research setting.[4] The process also has drawbacks; for example, iterations add to the complexity of creating a data set that is consistent over time and that takes into account changes in the methods of collecting data, which may result in concomitant inadvertent changes in definitions of the data.

We consider the following as desirable developments to make it more feasible to construct a registry from routinely collected data:

- More uniform implementation of IT across acute NHS trusts (e.g. a shortlist of 'approved' database suppliers with compatible features, including features to facilitate data extraction for secondary purposes).
- Lighter touch governance when anonymisation is done centrally. Access to patient data is likely to remain a challenge, particularly with the introduction of the General Data Protection Regulation (GDPR).[109,110] The lack of clarity over the safe and ethical secondary use of routinely collected data is currently a major barrier preventing access to routine data for research.
- A method for obtaining consent that is practicable to implement in the busy setting of the NHS. For example, this could involve an opt-out model of consent or presumed consent, combined with a national publicity campaign promoting the benefits of using routine data in research. Opt-out models of consent are currently very difficult to implement because of the specific, and changing, nature of the instructions for informing affected people. The apparent failure to make provision for analyses of historic and ongoing data sets, when data collection started before changes in law, is particularly wasteful and frustrating for researchers.
- Efficient provision of routine data by data guardians, for example NHS Digital.

Future research recommendations

The present study highlighted the difficulties of implementing a conventional consent process for a registry that recruits patients who undergo an emergency procedure and have a short hospital stay. An important area of future research should, therefore, be to identify and test a more efficient method of obtaining consent for similar studies in similar settings that need to link data sources. This issue should be approached at a national rather than a local level, and involve detailed discussions with all relevant stakeholders. Critically, clarification is required about whether or not it is possible, given the recent debates about data sharing and the changes to information governance policies at NHS Digital,[111] to obtain approval (under section 251 of the NHS Act 2006[76]) to use patient information for medical research and link national data sets without consent. Currently, there is discrepancy between UK national registries, with many implementing prospective consent,[74,75] whereas others, such as the national cardiac audits managed by NICOR, operate on the basis of section 251[76] exemptions.

Alternatively, we need to test the feasibility of conducting the study using linked, anonymised national data sets (e.g. hospital episode data, BCIS NAPCI, DID, CPRD for medications). This would avoid the need for obtaining individual patient consent or section 251[76] exemption, as data are anonymised when made available to researchers. Such a linked data set would be able to capture all the eligible population and could use MACEs as an outcome, although there may still be regulatory hurdles in obtaining permission to link these data sets and CPRD captures data for only a small proportion of the UK population.

There has been a rapid adoption of pressure-wire testing for detecting ischaemia during this study despite a lack of evidence of benefit over CMR. Our cost-effectiveness models have highlighted that the diagnostic accuracies of the CMR versus pressure-wire ischaemia tests are key drivers of the relative cost-effectiveness of management strategies based on these tests, compared with stress ECHO or each other. Therefore, future research is needed to quantify the relative diagnostic accuracy of CMR and pressure wire versus stress ECHO, and versus each other, for ischaemia testing. The fact that both CMR and pressure-wire testing are regarded as reference standards in clinical practice and no superior standard is recognised may mean that the cost-effectiveness of CMR versus pressure wire can be tested with respect to effectiveness only in a large RCT.

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Chapter 8 Conclusion

We conclude that it is not currently feasible to set up a multicentre registry in the way that we had envisaged. We did not identify all patients who were eligible for the study: patients with unobstructed arteries (i.e. those that had an emergency angiogram but did not receive PPCI) were difficult to identify from catheter laboratory databases. We successfully consented patients but obtaining individual, opt-in consent would not be feasible for a national registry. We explored several consent models (e.g. opt-out on procedural consent form and standard consent at discharge) but none was implemented because of logistic difficulties. Linkage of data from HISs with hospital episode data was feasible, but data from HISs are not uniformly available/exportable. Information about whether or not participants had had CMR in CMR hospitals was obtained successfully from HISs, although some referrals for CMR were for research rather than clinical purposes.[27]

In the cost-effectiveness models, the differences in QALYs between strategies were very small, and the results were driven largely by the differences in costs. Sensitivity analyses around the two models identified the diagnostic accuracy of the ischaemia tests as the key driver of cost-effectiveness.

We defined five subgroups of patients who activate the PPCI pathway for whom there was consensus that CMR changes patient management in a clinically important way.[4] All subgroups could be identified in either the local HIS data set, hospital episode data or both. It is feasible to identify some, but not all, important changes in management in follow-up hospital episode data. The main constraints on identifying important changes in management were as follows: (1) outpatient hospital episode data were poorly coded with respect to diagnosis, (2) medication data were not available at baseline or follow-up (preventing inspection of prescription of/changes in medication after the index event) and (3) data about diagnostic investigations were poorly coded in both acute care and outpatient data sets. More research would be needed to develop a specific composite outcome for a patient subgroup.[68]

Any multicentre registry set up in this patient population would need to be able to capture new and emerging diagnostic/interventional technologies. During the study, priority for CMR decreased because of the introduction of pressure-wire testing for diagnosing ischaemia in patients with multivessel disease. However, it is not clear whether or not pressure-wire testing is the optimal management strategy from the perspective of health services. This question could potentially be answered in a national registry, given that the use of pressure wire is (currently) driven largely by the preferences of interventional cardiologists rather than patient characteristics. However, we are uncertain whether or not CMR is used sufficiently to allow this question to be addressed.

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Contributions of authors

Jessica M Harris undertook the data handling, linkage and analysis, and prepared the tables and figures for the report.

Rachel C Brierley conducted the study and conceived some aspects of data collection from participating hospitals.

Maria Pufulete designed and conducted the study, determined the structure of the consensus process, conducted the literature review and wrote the report.

Chiara Bucciarelli-Ducci conceived the original research question and provided clinical and CMR expertise.

Elizabeth A Stokes carried out the health economic analyses and wrote the health economics sections of the report.

John P Greenwood was principal investigator at one of the recruiting hospitals, provided cardiology and CMR expertise and was a member of the working group in the consensus process.

Stephen H Dorman was principal investigator at one of the recruiting hospitals, provided cardiology expertise and was a member of the working group in the consensus process.

Richard A Anderson was principal investigator at one of the recruiting hospitals, provided cardiology expertise and was a member of the working group in the consensus process.

Chris A Rogers provided guidance with respect to statistics and study design.

Sarah Wordsworth provided guidance and oversaw the health economics analysis.

Sunita Berry was a member of the working group in the consensus process and provided expertise with respect to NHS commissioning of services.

Barnaby C Reeves was chief investigator with overall responsibility for the study, designed the study and provided strategic direction with the interpretation of study results.

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Publications

Pufulete M, Brierley RC, Bucciarelli-Ducci C, Greenwood JP, Dorman S, Anderson RA, *et al.* Formal consensus to identify clinically important changes in management resulting from the use of cardiovascular magnetic resonance (CMR) in patients who activate the primary percutaneous coronary intervention (PPCI) pathway. *BMJ Open* 2017;**7**:e014627.

Brierley RC, Pufulete M, Harris J, Bucciarelli-Ducci C, Greenwood JP, Dorman S, *et al.* Developing a UK registry to investigate the role of cardiovascular magnetic resonance (CMR) in patients who activate the primary percutaneous coronary intervention (PPCI) pathway: a multicentre, feasibility study linking routinely collected electronic patient data. *BMJ Open* 2018;**8**:e018987.

Stokes A, Doble B, Pufulete M, Reeves BC, Bucciarelli-Ducci C, Dorman S, *et al.* Cardiovascular magnetic resonance in emergency patients with multi-vessel disease or unobstructed coronary arteries: a cost-effectiveness analysis in the UK. *BMJ Open* 2019;**9**:e025700.

Pufulete M, Harris J, Dorman S, Cook L, Bucciarelli-Ducci C, Greenwood JP, *et al.* Feasibility of identifying important changes in care management resulting from cardiovascular magnetic resonance (CMR) using Hospital Episode Statistics data. *BMC Med Res Methodol* 2019; in press.

Data-sharing statement

Anonymised individual patient data (excluding hospital episode/vital status linked data) may be available for secondary research, conditional on assurance from the secondary researcher that the proposed use of the data is compliant with the Medical Research Council Policy on Data Preservation and Sharing regarding scientific quality, ethics requirements and value for money. All data requests should be submitted to the corresponding author for consideration and access may be granted following review. The hospital episode data/vital status data cannot be shared further due to conditions imposed by NHS Digital in the original data-sharing agreement that covered initial data release.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

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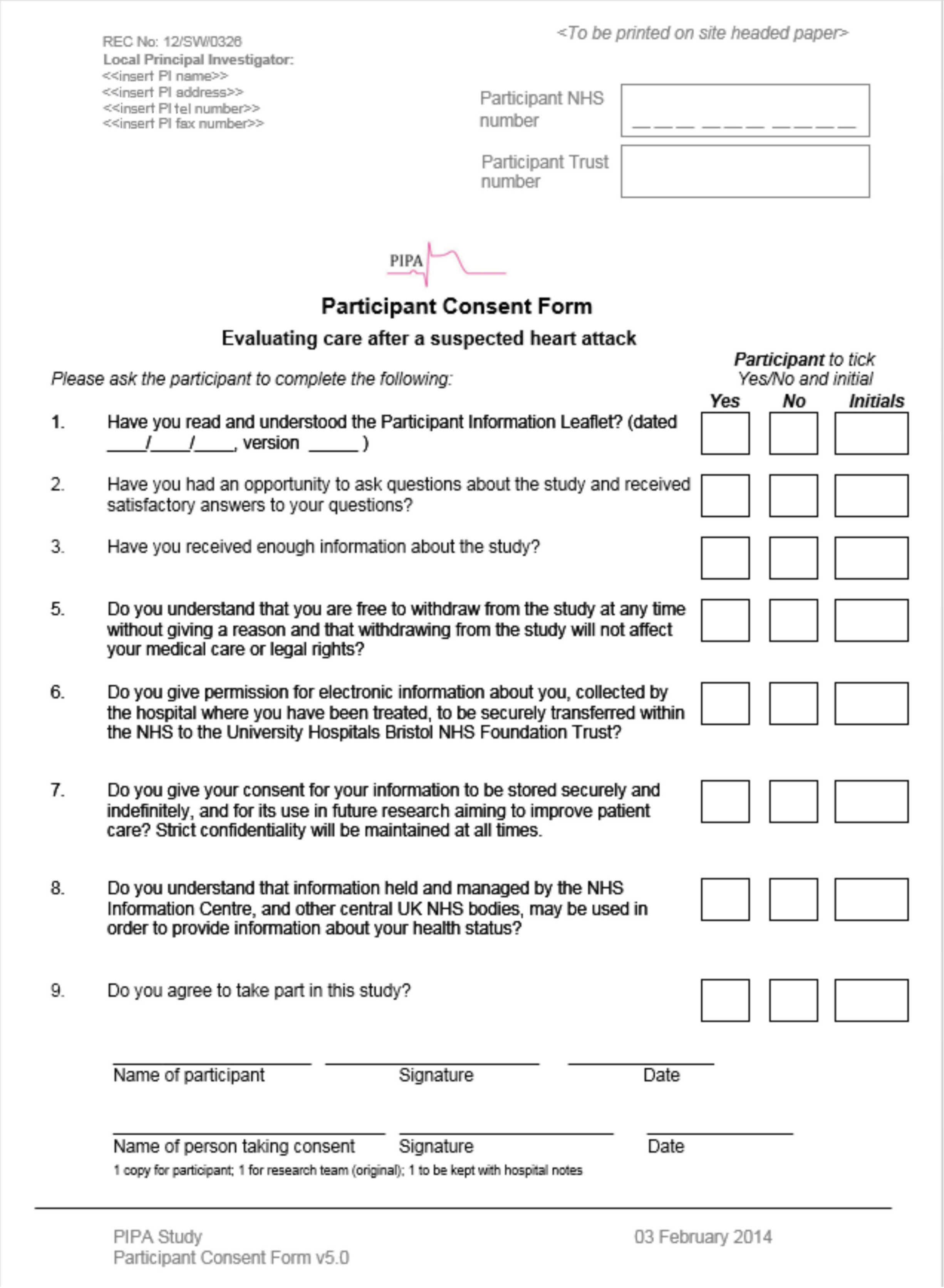
Appendix 1 Participant consent form



REC No: 12/SW/0326
Local Principal Investigator:
<<insert PI name>>
<<insert PI address>>
<<insert PI tel number>>
<<insert PI fax number>>

<To be printed on site headed paper>

Participant NHS number	___ ___ ___ ___ ___ ___ ___ ___ ___ ___
Participant Trust number	

PIPA

Participant Consent Form

Evaluating care after a suspected heart attack

Please ask the participant to complete the following:

***Participant** to tick Yes/No and initial*

		Yes	***No***	***Initials***
1.	Have you read and understood the Participant Information Leaflet? (dated ____/____/____, version _____)	☐	☐	☐
2.	Have you had an opportunity to ask questions about the study and received satisfactory answers to your questions?	☐	☐	☐
3.	Have you received enough information about the study?	☐	☐	☐
5.	Do you understand that you are free to withdraw from the study at any time without giving a reason and that withdrawing from the study will not affect your medical care or legal rights?	☐	☐	☐
6.	Do you give permission for electronic information about you, collected by the hospital where you have been treated, to be securely transferred within the NHS to the University Hospitals Bristol NHS Foundation Trust?	☐	☐	☐
7.	Do you give your consent for your information to be stored securely and indefinitely, and for its use in future research aiming to improve patient care? Strict confidentiality will be maintained at all times.	☐	☐	☐
8.	Do you understand that information held and managed by the NHS Information Centre, and other central UK NHS bodies, may be used in order to provide information about your health status?	☐	☐	☐
9.	Do you agree to take part in this study?	☐	☐	☐

________________ ________________ ________________
Name of participant Signature Date

________________ ________________ ________________
Name of person taking consent Signature Date

1 copy for participant; 1 for research team (original); 1 to be kept with hospital notes

---

PIPA Study
Participant Consent Form v5.0

03 February 2014

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Appendix 2 Office of Population Censuses and Surveys and *International Classification of Diseases*, Tenth Edition, codes list

OPCS procedure codes	
CMR	
U10.3	Cardiac magnetic resonance imaging
PCI	
K49	Transluminal balloon angioplasty of coronary artery
K50	Other therapeutic transluminal operations on coronary artery
K75	Percutaneous transluminal balloon angioplasty and insertion of stent into coronary artery
CABG	
K40	Saphenous vein graft replacement of coronary artery
K41	Other autograft replacement of coronary artery
K42	Allograft replacement of coronary artery
K43	Prosthetic replacement of coronary artery
K44	Other replacement of coronary artery
K45	Connection of thoracic artery to coronary artery
K46	Other bypass of coronary artery
Angiography, no PCI	
K63.3	Angiocardiography of left side of heart NEC
K63.5	Coronary arteriography using single catheter
K63.6	Coronary arteriography NEC
PET	
U10.4	Myocardial positron emission tomography
U21.3	Positron emission tomography NEC
U36.2	Positron emission tomography with computed tomography NEC
ECHO	
K58.5	Transluminal intracardiac echocardiography
U20.1	Transthoracic echocardiography
U20.2	Transoesophageal echocardiography
U20.3	Intravascular echocardiography
U20.4	Epicardial echocardiography
U20.5	Stress echocardiography
IVUS	
K51.2	Intravascular ultrasound of coronary artery
L726	Intravascular ultrasound of artery NEC

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OPCS procedure codes	
Pressure wire	
K63.4- K63.6 ***AND***	Coronary arteriography
K51.8 ***AND***	Other specified diagnostic transluminal operations on coronary artery
Y44.2 ***AND***	Monitoring of pressure in organ NOC
Y53.-	Approach to organ under image control
Radionuclide angiocardiography	
U10.5	Radionuclide angiocardiography
Computed tomography angiography	
U10.2	Cardiac computed tomography angiography
Single photon emission computed tomography	
U21.4	Single photon emission computed tomography NEC
Implantation of ICD	
K59	Cardioverter defibrillator introduced through the vein
K72	Other cardioverter defibrillator
Implantation of CRT	
K60.7	Implantation of intravenous biventricular cardiac pacemaker system
K61.7	Implantation of biventricular cardiac pacemaker system
K59.6	Implantation of cardioverter defibrillator using three electrode leads
ICD-10 diagnosis codes	
OHCA	
I46	Cardiac arrest
LV thrombus	
I23.6	Thrombosis of atrium, auricular appendage and ventricle as current complications following acute myocardial infarction
STEMI	
I21.0	Acute transmural myocardial infarction of anterior wall
I21.1	Acute transmural myocardial infarction of inferior wall
I21.2	Acute transmural myocardial infarction of other sites
I21.3	Acute transmural myocardial infarction of unspecified site
Takotsubo cardiomyopathy	
I42.8 ***AND***	Other cardiomyopathies
F43.8	Other reactions to severe stress
Myocarditis	
I51.4	Myocarditis, unspecified
Pericarditis	
I30	Acute pericarditis
I31.0	Chronic adhesive pericarditis
I31.1	Chronic constrictive pericarditis
I31.9	Disease of pericardium, unspecified
I32.0	Pericarditis in bacterial diseases classified elsewhere

ICD-10 diagnosis codes	
I32.1	Pericarditis in other infectious and parasitic diseases classified elsewhere
I32.8	Pericarditis in other diseases classified elsewhere
I01.0	Acute rheumatic pericarditis
I02.0	Rheumatic chorea with heart involvement
I09.2	Chronic rheumatic pericarditis
Endocarditis	
I33.9	Acute endocarditis, unspecified
Coronary spasm	
I20.1	Angina pectoris with documented spasm
MI	
I21	Acute myocardial infarction
Stroke	
I64	Stroke, not specified as haemorrhage or infarction

CRT, cardiac resynchronisation therapy; NEC, not elsewhere classified; NOC, not otherwise classified.

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Appendix 3 Literature search

MEDLINE (via OvidSP)

Date range searched: 1950 to 16 January 2014.

Date searched: 16 January 2014.

Search strategy

1. exp Myocardial Infarction/ (142,973)
2. myocardial infarct$.tw. (134,547)
3. heart attack$.tw. (3601)
4. MI.tw. (25,881)
5. ami.tw. (12,166)
6. stemi.tw. (3663)
7. heart infarct$.tw. (705)
8. Acute Coronary Syndrome/ (6784)
9. acute coronary syndrome$.tw. (15,521)
10. ACS.tw. (9320)
11. or/1-10 (210,783)
12. exp angioplasty/ (53,568)
13. angioplasty.tw. (34,003)
14. percutaneous coronary intervention$.tw. (14,406)
15. exp Percutaneous Coronary Intervention/ (34,668)
16. PCI.tw. (11,157)
17. PPCI.tw. (366)
18. exp Stents/ (50,784)
19. stent$.tw. (56,427)
20. Myocardial Revascularization/ (9079)
21. revasculari$.tw. (37,853)
22. reperfused.tw. (5688)
23. reperfusion.tw. (55,775)
24. or/12-23 (191,056)
25. exp Magnetic Resonance Imaging/ (295,774)
26. Magnetic resonance imag$.tw. (122,420)
27. Cardiovascular magnetic resonance.tw. (1765)
28. cardiac magnetic resonance.tw. (3179)
29. MRI.tw. (121,901)
30. CMR.tw. (3035)
31. or/25-30 (344,849)
32. 24 and 31 (5713)
33. 11 and 32 (1318)
34. exp animals/ not humans/ (3,863,199)
35. 33 not 34 (1051)

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EMBASE

Date range searched: 1980 to 16 January 2014.

Date searched: 16 January 2014.

Search strategy

1. exp heart infarction/ (261,299)
2. myocardial infarct$.tw. (185,732)
3. heart attack$.tw. (4991)
4. MI.tw. (45,694)
5. ami.tw. (19,697)
6. stemi.tw. (10,463)
7. heart infarct$.tw. (1450)
8. exp Acute Coronary Syndrome/ (26,244)
9. acute coronary syndrome$.tw. (28,004)
10. ACS.tw. (17,708)
11. or/1-10 (337,561)
12. exp angioplasty/ (67,762)
13. angioplasty.tw. (47,179)
14. percutaneous coronary intervention$.tw. (27,203)
15. exp Percutaneous Coronary Intervention/ (59,160)
16. PCI.tw. (26,664)
17. PPCI.tw. (1281)
18. Stent/ (64,591)
19. exp cardiovascular stent/ (34,380)
20. stent$.tw. (94,492)
21. heart muscle revascularization/ (21,848)
22. revasculari$.tw. (56,445)
23. reperfused.tw. (7304)
24. reperfusion.tw. (77,453)
25. or/12-24 (298,341)
26. exp nuclear magnetic resonance imaging/ (524,106)
27. Magnetic resonance imag$.tw. (164,672)
28. Cardiovascular magnetic resonance.tw. (3414)
29. cardiac magnetic resonance.tw. (6341)
30. MRI.tw. (203,793)
31. CMR.tw. (7673)
32. or/26-31 (563,445)
33. 25 and 32 (13,408)
34. 11 and 33 (3451)
35. (exp animal/ or nonhuman/) not exp humans/ (5,173,875)
36. 34 not 35 (3048)
37. limit 36 to embase (2864)

The Cochrane Library

Date range searched: 1950 to 16 January 2014.

Date searched: 16 January 2014.

Search strategy

#1 MeSH descriptor: [Myocardial Infarction] explode all trees
#2 MeSH descriptor: [Acute Coronary Syndrome] explode all trees
#3 myocardial next infarct*
#4 heart next attack*
#5 MI
#6 AMI
#7 STEMI
#8 heart next infarct*
#9 'acute coronary syndrome*'
#10 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9
#11 MeSH descriptor: [Angioplasty] explode all trees
#12 MeSH descriptor: [Percutaneous Coronary Intervention] explode all trees
#13 MeSH descriptor: [Stents] explode all trees
#14 MeSH descriptor: [Myocardial Revascularization] this term only
#15 angioplasty
#16 'percutaneous coronary intervention*'
#17 PCI or PPCI
#18 stent*
#19 revasculari*
#20 reperfused
#21 reperfusion
#22 #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21
#23 MeSH descriptor: [Magnetic Resonance Imaging] explode all trees
#24 'Magnetic resonance imag*'
#25 'Cardiovascular magnetic resonance'
#26 'cardiac magnetic resonance'
#27 MRI or CMR
#28 #23 or #24 or #25 or #26 or #27
#29 #11 and #22 and #28

Web of Science

Date range searched: 1950 to 16 January 2014.

Date searched: 16 January 2014.

Search strategy

# 4 1,351 #3 AND #2 AND #1
# 3 218,389 TOPIC: (Angioplasty or "percutaneous coronary intervention*" or PCI or PPCI or stent* or revasulari* or reperfused or reperfusion)
# 2 257,465 TOPIC: ("Magnetic Resonance Imag*" or "Cardiovascular magnetic resonance" or " cardiac magnetic resonance" or MRI or CMR)
# 1 273,481 TOPIC: ("myocardial infarct*" or "heart attack*" or "heart infarct*" or "acute coronary syndrome*" or MI or AMI or STEMI or ACS)

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Bioscience Information Service (BIOSIS)

Date range searched: 1950 to 16 January 2014.

Date searched: 16 January 2014.

Search strategy

# 6 873 #5 AND #4
# 5 TAXONOMIC DATA: (human not (animal* not human))
# 4 #3 AND #2 AND #1
# 3 TOPIC: (Angioplasty or "percutaneous coronary intervention*" or PCI or PPCI or stent* or revasulari* or reperfused or reperfusion)
# 2 TOPIC: ("Magnetic Resonance Imag*" or "Cardiovascular magnetic resonance" or " cardiac magnetic resonance" or MRI or CMR)
# 1 TOPIC: ("myocardial infarct*" or "heart attack*" or "heart infarct*" or "acute coronary syndrome*" or MI or AMI or STEMI or ACS)

Appendix 4 First survey (statements, supporting paragraphs and references)

Benefit to patients and the NHS of cardiac magnetic resonance imaging after primary percutaneous coronary intervention pathway activation

Thank you for agreeing to complete this survey. We expect the survey to take about 20 minutes of your time. You are asked to read and rate 12 statements relating to the potential impact of CMR in changing the management of patients in a clinically important way. The patient population under consideration includes all patients who activate the PPCI pathway. Please rate your agreement with each statement on the scale provided. Each statement has a supporting paragraph that provides background information and links to full-text references. We believe that we have used the best available evidence but we are aware that the evidence is of variable quality.

In order to progress through the survey, please use the following navigation buttons:

Click the Next button to go to the next page.

Click the Previous button to return to the previous page.

Click the Number buttons in the text to access the full references.

Click the Submit button to submit the survey at the end.

Statement 1. Compared with echocardiography, cardiovascular magnetic resonance after primary percutaneous coronary a intervention allows patients with cardiovascular magnetic resonance markers that indicate a poor prognosis (e.g. impaired left ventricular function, large infarct size, microvascular obstruction) to be followed up more appropriately and undergo more aggressive medical therapy for secondary prevention

Accurate assessment of infarct characteristics is important for risk stratification after PPCI. CMR can quantify in a single scan all cardiac markers relevant to PPCI outcomes, with high reproducibility and accuracy. CMR has high spatial and temporal resolution and is superior to ECHO for measuring LV volumes and EF.[112] Additionally, CMR markers, such as infarct size, MVO and myocardial salvage, have been shown to have long-term prognostic value.[113–115] LGE CMR has added prognostic value over ECHO.[116]

Statement 2. Compared with echocardiography, cardiovascular magnetic resonance after primary percutaneous coronary intervention allows patients with cardiovascular magnetic resonance markers that indicate a good prognosis (e.g. normal left ventricular function, high myocardial salvage, no microvascular obstruction, no residual ischaemia) to be discharged earlier and followed up less frequently

Cardiovascular magnetic resonance measures several markers (i.e. infarct size, myocardial salvage index, MVO, myocardial oedema and haemorrhage) that cannot be measured by ECHO. These markers can be used to predict cardiac remodelling and prognosis after MI,[113–115] determine the optimal therapeutic pathway for each patient and prevent over- and under-treatment.

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Statement 3. Compared with echocardiography, cardiovascular magnetic resonance better identifies the cause of out-of-hospital cardiac arrest (e.g. large myocardial infarction, arrhythmogenic right ventricular cardiomyopathy, aberrant coronary arteries, hypertrophic cardiomyopathy) to optimise further treatment for the patient (e.g. defibrillator for primary arrhythmia or percutaneous coronary intervention) or family members

Out-of-hospital cardiac arrest affects about 60,000 people in the UK each year. Currently, hospital survival is about 32%. Early identification of the cause is essential to improve survival. Causes of OHCA include MI (40–90%) and inherited cardiomyopathies, such as arrhythmogenic right ventricular cardiomyopathy (ARVC) and hypertrophic cardiomyopathy (HCM). Unlike ECHO, CMR allows in vivo tissue characterisation, which differentiates scarring resulting from MI from other causes of focal fibrosis (e.g. observed in non-ischaemic cardiomyopathies such as ARVC and HCM).[117] LGE on CMR can predict serious cardiac complications in patients with HCM (e.g. all-cause death, cardiac death and death from heart failure),[118] and identifies patients who may need more aggressive medical and device therapy (e.g. renin-aldosterone system inhibition for prevention of heart failure or ICD placement for primary prevention of sudden cardiac death).

Statement 4. Cardiovascular magnetic resonance after primary percutaneous coronary intervention identifies patients at high risk of having ventricular septal defect or impending cardiac rupture, who may require ventricular patch or other urgent cardiac surgery, and guides the optimal management of these patients

Ventricular septal defect (VSD) and LV free wall rupture are rare complications of MI, occurring in < 1% of PPCI patients, usually within 1 week of the infarct. Mortality ranges between 50% and 80%. Diagnosis can be difficult to make and usually requires multimodality imaging (e.g. ECHO, ventriculography, CT, CMR) before surgical repair. Because of its high spatial resolution, CMR can be used to clarify the detailed structure of these lesions. CMR accurately identifies the location, size and tissue margins of VSD and is useful for detecting apical defects, which are not easily identified by ECHO. CMR measurements may also be used to determine the size of the ventricular patch required to close the VSD, which avoids the inflation of a sizing balloon in friable infarcted tissue.[119] These features, together with other CMR markers of damage (e.g. infarct size, MVO, LV dysfunction) are useful for guiding optimal management of patients with post-infarct VSD. Similarly, CMR can differentiate between the different types of impending free wall rupture (i.e. acute, subacute and chronic), which may be helpful in planning surgical management.[119]

Statement 5. In patients with a 'normal' (unobstructed) coronary angiogram, cardiovascular magnetic resonance can differentiate patients who have had a myocardial infarction with spontaneous reperfusion or distal embolisation from patients with a non-ischaemic diagnosis (e.g. myocarditis, Takotsubo cardiomyopathy, aortic dissection), resulting in a patient treatment plan appropriate for the definitive diagnosis

The incidence of unobstructed coronary angiogram in patients who activate the PPCI pathway is between 5% and 12%. In these patients, the lack of an accurate diagnosis may result in inappropriate or unnecessary treatment and/or follow-up and a poorer prognosis.[19] CMR facilitates differential diagnosis in the context of an unobstructed coronary angiogram, providing a definitive diagnosis (e.g. myocardial infarction, myocarditis, Takotsubo cardiomyopathy) in 65–90% of these patients.[20,23] In patients with myocarditis, LGE on CMR may predict long-term adverse outcomes.[26] In the context of MI without an angiographic lesion, CMR can locate the culprit infarct-related artery in patients with spontaneous reperfusion or with distal embolisation.

Statement 6. Compared with echocardiography, cardiovascular magnetic resonance after primary percutaneous coronary intervention better identifies patients at high risk of sudden cardiac death who would benefit most from an implantable cardiac device (e.g. implantable cardiac defibrillator, cardiac resynchronisation therapy)

About 6% of heart attack patients subsequently die suddenly from a presumed cardiac cause. Current guidelines recommend the use of ICD to prevent sudden cardiac death in patients who have a low LV EF after a heart attack. EF is used in clinical practice to make decisions about ICD implantation, but it has a low predictive value and many patients with an ICD will never benefit from it.[120] EF is most commonly measured by ECHO, but CMR is now considered the gold standard for EF measurement because it is more reproducible than ECHO.[112] CMR has been shown to be better than ECHO for selecting patients for ICD implantation when strict EF thresholds are used to guide implantation.[121] The extent of myocardial scar characterised by LGE CMR may also be used to predict whether or not ICD implantation is appropriate in this patient group.[122] Furthermore, LGE CMR can guide placement of the LV lead away from scarred myocardium, which results in a better clinical outcome after cardiac resynchronisation therapy (CRT).[123]

Statement 7. Compared with echocardiography, cardiovascular magnetic resonance after primary percutaneous coronary intervention better identifies patients who would not benefit from cardiac resynchronisation therapy

Cardiac resynchronisation therapy (or biventricular pacing) uses a specialised pacemaker to resynchronise the beating of the two ventricles by pacing both simultaneously, which improves the contraction of the left ventricle and the overall efficiency of the heart. It is used in patients with systolic ventricular dysfunction and heart failure. However, about 30% of patients who meet the inclusion criteria for CRT do not respond to it.[124] CMR assessment of mechanical dyssynchrony and myocardial scar provides additional value over ECHO for identifying responsive patients.[125,126] Myocardial scar is an important feature of non-response to CRT[127,128] and LGE CMR accurately differentiates between transmural, mid-myocardial, epicardial and subendocardial scar.

Statement 8. Compared with stress echocardiography or single-photon emission computed tomography, cardiovascular magnetic resonance after primary percutaneous coronary intervention in patients with multivessel disease better assesses ischaemia and viability of the myocardium to optimise the revascularisation strategy for the patient and avoid additional diagnostic tests

Between 40% and 65% of the patients who activate the PPCI pathway have multivessel disease. Adequate assessment of residual ischaemia in non-culprit arteries post PPCI is important for effective management because this patient group has an adverse prognosis. Various techniques are currently used to assess the need for additional revascularisation, including stress ECHO, SPECT and stress-perfusion CMR. Stress CMR has excellent prognostic value[129] and better diagnostic accuracy than SPECT[130,131] or stress ECHO[132] for detecting angiographically significant coronary artery disease.

Statement 9. Compared with echocardiography, cardiovascular magnetic resonance after primary percutaneous coronary intervention better identifies patients with left ventricular thrombus for treatment with anticoagulation therapy

Left ventricular thrombus is a serious complication of acute MI. It increases the risk of thromboembolic events, particularly stroke. LV thrombus develops in up to 10% of patients with anterior wall infarctions after PPCI. Although ECHO is most commonly used to detect LV thrombus and to assess its shape and size, between 10% and 46% of echocardiograms are inconclusive.[133] LGE CMR is considered the gold standard for detecting LV thrombus, because it detects thrombus based on tissue characteristics rather than anatomic appearance. Fewer thrombi are detected by contrast-ECHO than by LGE CMR.[134] CMR has a higher sensitivity (88%) than contrast (61%) and non-contrast (< 33%) ECHO.[134,135]

Statement 10. Compared with other imaging modalities, in patients with multivessel disease, cardiovascular magnetic resonance after primary percutaneous coronary intervention better identifies the artery that caused the myocardial infarction and guides the subsequent treatment plan in relation to additional revascularisation (percutaneous coronary intervention or coronary artery bypass graft surgery)

In patients with multivessel disease presenting with acute MI, the culprit artery is not always easy to identify as more than one artery could be responsible. CMR has higher spatial resolution than SPECT, allowing easy identification of the infarct-related artery and non-culprit territory stenosis in PPCI patients,[136] and, hence, appropriate risk-stratification of patients with multivessel disease for planning their future treatment.[137]

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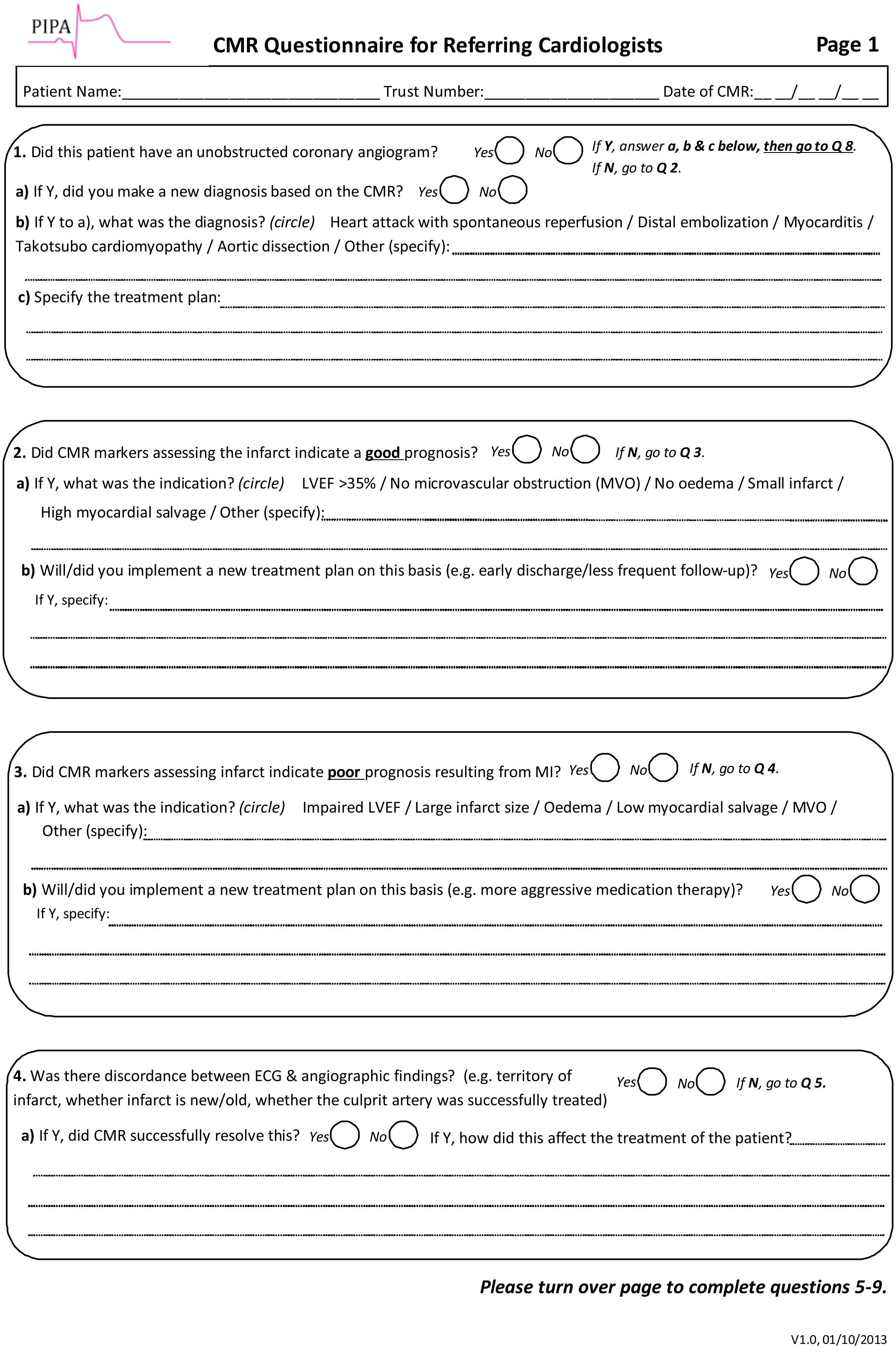
Statement 11. Compared with echocardiography, cardiovascular magnetic resonance after primary percutaneous coronary intervention better identifies incidental cardiac findings that may need further investigation and treatment

Compared with ECHO, CMR provides versatile imaging planes, superior tissue contrast and advanced tissue characterisation, allowing a comprehensive assessment of cardiac anatomy, function and flow, and imaging of the great vessels (including venous return), the pericardium and suspected cardiac tumours.[138] As such, CMR can identify congenital coronary anomalies, cardiac masses, coronary artery aneurysms, valvular heart disease, thoracic aortic disease, and so forth. CMR can adequately differentiate benign from malignant tumours in the heart.[139]

Statement 12. Compared with echocardiography, cardiovascular magnetic resonance after primary percutaneous coronary intervention identifies significant incidental non-cardiac findings (e.g. oesophageal and lung tumours, pulmonary embolus, aortic aneurysm) that may need further investigation and treatment

Unlike ECHO, which provides limited imaging of mediastinal and extra-cardiac structures, CMR images a substantial part of the thorax and abdomen in the field of view, which may potentially contain non-cardiac abnormalities. The prevalence of non-cardiac findings on CMR is up to 80% (with up to 30% of these representing potentially significant findings), depending on the characteristics of the population examined.[140–142]

Appendix 5 Cardiovascular magnetic resonance questionnaire for cardiologists



PIPA

CMR Questionnaire for Referring Cardiologists **Page 1**

Patient Name:______________________________ Trust Number:____________________ Date of CMR:__ __/__ __/__ __

1. Did this patient have an unobstructed coronary angiogram? *Yes* ○ *No* ○ *If* ***Y****, answer* ***a, b & c below, then go to Q 8****.*
If ***N****, go to* ***Q 2****.*

a) If Y, did you make a new diagnosis based on the CMR? *Yes* ○ *No* ○

b) If Y to a), what was the diagnosis? *(circle)* Heart attack with spontaneous reperfusion / Distal embolization / Myocarditis / Takotsubo cardiomyopathy / Aortic dissection / Other (specify):

c) Specify the treatment plan:

2. Did CMR markers assessing the infarct indicate a **good** prognosis? *Yes* ○ *No* ○ *If* ***N****, go to* ***Q 3****.*

a) If Y, what was the indication? *(circle)* LVEF >35% / No microvascular obstruction (MVO) / No oedema / Small infarct / High myocardial salvage / Other (specify):

b) Will/did you implement a new treatment plan on this basis (e.g. early discharge/less frequent follow-up)? *Yes* ○ *No* ○
If Y, specify:

3. Did CMR markers assessing infarct indicate **poor** prognosis resulting from MI? *Yes* ○ *No* ○ *If* ***N****, go to* ***Q 4****.*

a) If Y, what was the indication? *(circle)* Impaired LVEF / Large infarct size / Oedema / Low myocardial salvage / MVO / Other (specify):

b) Will/did you implement a new treatment plan on this basis (e.g. more aggressive medication therapy)? *Yes* ○ *No* ○
If Y, specify:

4. Was there discordance between ECG & angiographic findings? (e.g. territory of infarct, whether infarct is new/old, whether the culprit artery was successfully treated) *Yes* ○ *No* ○ *If* ***N****, go to* ***Q 5.***

a) If Y, did CMR successfully resolve this? *Yes* ○ *No* ○ If Y, how did this affect the treatment of the patient?

Please turn over page to complete questions 5-9.

V1.0, 01/10/2013

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PIPA

CMR Questionnaire for Referring Cardiologists **Page 2**

5. Did this patient have multi vessel disease? *Yes* ○ *No* ○ *If* ***N****, go to* ***Q 6****.*

a) If Y, did CMR help you to optimise the revascularisation strategy? *Yes* ○ *No* ○ If Y, explain how:

b) Was this patient referred for other diagnostic tests? *Yes* ○ *No* ○ If Y, which?

6. In this patient, did CMR identify a high risk of developing other conditions relating to the infarct? *Yes* ○ *No* ○ *If* ***N****, go to* ***Q 7****.*

a) If Y, what was the finding? *(circle)* VSD / Impending cardiac rupture / LV thrombus / Other (specify):

b) Will/did you implement a new treatment plan on this basis? *Yes* ○ *No* ○ If Y, what? *(circle)* Cardiac surgery; Implantable cardiac device; Anticoagulation therapy; Other (specify):

7. Did CMR identify that this patient would not benefit from an implantable cardiac device? *Yes* ○ *No* ○ *Go to* ***Q 8****.*

8. Did this patient have an out-of-hospital cardiac arrest? *Yes* ○ *No* ○ *If* ***N****, go to* ***Q 9****.*

a) If Y, did CMR identify the cause? *Yes* ○ *No* ○

b) If Y to a), did this guide further treatment of patient? *(circle)* Defibrillator for primary arrhythmia / PCI / Other (specify):

9. Did CMR identify any cardiac or non cardiac incidental findings? *Yes* ○ *No* ○

a) If Y, specify findings:

b) Did this change the treatment plan?

Any other comments:

Completed: Name ______________ Signature ______________ Date __ __/__ __/__ __
d d / m m / y y

Please return completed questionnaires to the Trial Manager [redacted]

[redacted]

V1.0, 01/10/2013

Appendix 6 Recorded causes of death for deaths within 1 year of index admission

Cause of death	*n* (%)
Acute MI, unspecified	14 (26)
Acute or chronic renal failure	1 (2)
Aortic (valve) stenosis	1 (2)
Atrial fibrillation and flutter	1 (2)
Bronchopneumonia	1 (2)
Cardiogenic shock	1 (2)
Chronic ischaemic heart disease, unspecified	5 (9)
Community-acquired pneumonia	1 (2)
Congestive cardiac failure	2 (4)
Heart failure	1 (2)
Intentional self-harm by hanging, strangulation and suffocation	1 (2)
Intentional self-harm by other specified means	1 (2)
Intercerebral bleed	1 (2)
Ischaemic bowel	1 (2)
Ischaemic cardiomyopathy	2 (4)
Ischaemic colitis	1 (2)
Ischaemic heart disease	2 (4)
Malignant neoplasm of bronchus and lung	3 (6)
Malignant neoplasm of other and unspecified parts of mouth	1 (2)
Metastatic adenocarcinoma of lung	1 (2)
Multiple myeloma	1 (2)
MI	4 (7)
Other interstitial pulmonary diseases with fibrosis	1 (2)
Pulmonary embolism	1 (2)
Pulmonary embolism without mention of acute cor pulmonale	1 (2)
Severe LV failure	1 (2)
Small-cell lung cancer	1 (2)
Squamous cell carcinoma of the lung	1 (2)
Urinary tract infection, site not specified	1 (2)
Total	54

Cause of death was unavailable for one participant.

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Appendix 7 Supporting tables for consensus process

TABLE 31 Original statements generated for consensus process

Number	Statement
Coronary artery disease positive	
1	Multivessel disease – CMR assessment of ischaemia and viability to guide further PCI either as inpatient or outpatient
2	Multivessel disease – CMR assessment of ischaemia and viability to guide CABG
3	PPCI with discordance between ECG and angiographic findings? New/old infarct? Territory of infarct? Was the culprit artery successfully treated?
4	Chronic multivessel disease with no clear culprit lesion? Clarify diagnosis/guide further therapy
5	Assess the significance of bystander coronary artery disease (which will influence the need of further elective PCI to other vessels)
6	CMR can differentiate between acute and chronic MI (important when the cause of cardiac dysfunction is unclear despite angiography or ultrasound)
7	In patients with multivessel disease in whom the culprit artery cannot be identified, CMR can identify the infarct-related artery and guide (1) targeted PCI and (2) viability of CABG
8	Assessment of LV function to guide AICD implantation (primary prevention)
9	CMR is more effective than ECHO at identifying STEMI patients who are at risk of sudden arrhythmic death (consequence: early implantation of a cardioverter defibrillator?)
10	OHCA with ambiguous anatomy? Primary arrhythmia or acute MI – defibrillation or revascularisation?
11	Assessment of LV thrombus to guide possible anticoagulation
12	CMR can accurately diagnose LV thrombus (unlike ECHO) (consequence: possible anti-coagulation therapy with vitamin K antagonist?)
13	Assessment of pericardial effusion
14	CMR markers: MVO, oedema, scar size, haemorrhage, etc. Good prognostic indicators but no/little current evidence that they are used to change patient management at the moment
15	Impact on the length of stay (if CMR does not show very poor EF, very large area of MVO, impending cardiac rupture)
16	CMR can accurately diagnose LV thrombus (consequence: possible anti-coagulation therapy with vitamin K antagonist?)
17	CMR can identify impending cardiac rupture (consequence: cardiac operation or ventricular patch if needed)
18	More aggressive medical treatment in those with large infarcts and large MVO?
19	Closer medical follow-ups in those with large infarcts and large MVO?
20	Potential to change/optimise/maximise pharmacological treatment
21	Assessment of LV function to guide more aggressive medical therapy/secondary prevention
22	CMR has prognostic importance – follow-up patients in clinic more or less often depending on how good or bad the CMR is. Secondary prevention needed?
23	Identify complications of acute MI (e.g. impending cardiac rupture and act on it, e.g. surgery)

continued

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TABLE 31 Original statements generated for consensus process (*continued*)

Number	Statement
Coronary artery disease negative	
24	In STEMI patients with atypical angiographic characteristics (in whom the culprit artery cannot be identified) CMR may identify the MI location and infarct-related artery (consequence: revascularisation of appropriate artery)
25	PPCI with 'normal' coronaries – is it infarct with spontaneous reperfusion?
26	PPCI with 'normal' coronaries – is it myopericarditis?
27	PPCI with 'normal' coronaries – is it cardiomyopathy (dilated, hypertrophic, Takotsubo, etc.)?
28	In patients with chest pain, elevated troponins and unobstructed coronary arteries, CMR can rule out any significant pathology (e.g. patients with spontaneous reperfusion) (consequence: early discharge? Any follow-up for these patients?)
29	Equivocal ST elevation and angiographic findings? Alternative diagnosis e.g. pulmonary emobolus, aortic dissection
30	PPCI with 'normal' coronaries – impact on the length of stay (early discharge)
31	PPCI with 'normal' coronaries – impact on medical treatment and no secondary prevention medications
32	PPCI with 'normal' coronaries – impact on the patients' quality of life (of having this diagnosis as opposed to the diagnosis of a MI) (impact on insurance, mortgage, etc.)
33	Impact on the length of hospital stay (shorter bed stay if CMR does not show major abnormalities)
Incidental findings	
34	Assessment of other incidental valvular heart disease findings
35	Assessment of mitral regurgitation – is it ischaemic, dilated annulus, native valve disease?
36	Incidental findings on CMR (e.g. valve disease, congenital anomalies) that will be subsequently treated/monitored?
37	Potential for CMR to be a 'one-stop shop' for imaging procedures

AICD, automated implantable cardioverter defibrillator; ECG, electrocardiogram.

TABLE 32 Examples of draft statements and reworded statements

Subgroup	Draft statements	Reworded statements
Unobstructed arteries on angiogram	PPCI with 'normal' coronaries – is it infarct with spontaneous reperfusion? Equivocal ST elevation and angiographic findings? Alternative diagnosis, for example pulmonary embolus, aortic dissection?	In patients with a normal coronary angiogram, CMR can identify a heart attack with spontaneous reperfusion or distal embolisation for treatment with medical therapy for secondary prevention
	PPCI with 'normal' coronaries – is it cardiomyopathy (e.g. dilated, hypertrophic, Takotsubo) PPCI with 'normal' coronaries – is it myopericarditis?	In patients with a normal coronary angiogram, CMR can provide a new diagnosis (e.g. myocarditis, Takotsubo cardiomyopathy, aortic dissection) resulting in a different patient treatment plan
Multivessel disease	Multivessel disease – CMR assessment of ischaemia and viability to guide further PCI either as inpatient or outpatient	In patients with multivessel disease, CMR after PPCI assesses ischaemia and viability of the heart tissue to optimise the treatment for the patient
	Assess the significance of bystander coronary artery disease (which will influence the need of further elective PCI to other vessels) Chronic multivessel disease with no clear culprit lesion? Clarify diagnosis/guide further therapy	In patients with multivessel disease, CMR after angiography identifies the artery that caused the heart attack, and guides the appropriate therapy (PCI or CABG surgery)
LV thrombus after MI	Assessment of LV thrombus to guide possible anticoagulation CMR can accurately diagnose LV thrombus (unlike ECHO)	CMR after PPCI clearly identifies patients with LV thrombus for treatment with anticoagulation therapy

TABLE 33 Examples of supporting paragraphs

Statement 5	The incidence of normal coronary angiogram in patients who activate the PPCI pathway is between 5% and 12%. In these patients, the lack of an accurate diagnosis may result in inappropriate or unnecessary treatment and/or follow-up and poorer prognosis.[19] CMR facilitates differential diagnosis in the context of a normal coronary angiogram, providing a definitive diagnosis (e.g. MI, myocarditis, Takotsubo cardiomyopathy) in 65–90% of these patients.[20,23] In patients with myocarditis, LGE on CMR may predict long-term adverse outcomes.[20,23] In the context of MI without an angiographic lesion, CMR can locate the culprit infarct-related artery in patients with spontaneous reperfusion or with distal embolisation
Statement 8	Between 40% and 65% of the patients who activate the PPCI pathway have multivessel disease. Adequate assessment of residual ischaemia in non-culprit arteries post PPCI is important for effective management because this patient group has an adverse prognosis. Various techniques are currently used to assess the need for additional revascularisation, including stress ECHO, SPECT and stress-perfusion CMR. Stress CMR has excellent prognostic value[129] and better diagnostic accuracy than SPECT[130,131] or stress ECHO[132] for detecting angiographically significant coronary artery disease
Statement 9	LV thrombus is a serious complication of acute MI. It increases risk of thromboembolic events, particularly stroke. LV thrombus develops in up to 10% of patients with anterior wall infarctions after PPCI. Although ECHO is most commonly used to detect LV thrombus and to assess its shape and size, between 10% and 46% of echocardiograms are inconclusive.[133] LGE CMR is considered the gold standard for detecting LV thrombus, because it detects thrombus based on tissue characteristics rather than anatomic appearance. Fewer thrombi are detected by contrast-ECHO than by LGE CMR.[134] CMR has a higher sensitivity (88%) than contrast (61%) and non-contrast (< 33%) ECHO[134,135]

TABLE 34 Examples of respondents' comments for the three statements in consensus (3, 5 and 9) and the three statements not in consensus (1, 2 and 8)[4]

Statement 3	Importance of management change *CMR differentiates causes of cardiomyopathy (IHD vs. not). We use it regularly in patients post OHCA* *I have seen many cases of OHCA in which the use of CMR has made a diagnosis or significantly altered the diagnosis. Diagnostic refinement in the light of CMR findings also frequently results in changes in drug or device treatment, and often highlights the need for family screening. The improved anatomical, morphological and tissue characterisation that CMR allows drives the benefit of CMR over ECHO and allows better identification of the cause of out-of-hospital arrest* Quality of supporting evidence *I don't think it has been proved that clinical outcomes are better with a CMR strategy* *CMR is unlikely to alter the immediate management of these patients. However, if the cause is unclear after ECHO and enzymes, then CMR is helpful but I am not aware of any studies specifically assessing this*
Statement 5	Importance of management change *Agree. Unobstructed coronaries with elevated troponin need diagnostic resolution and CMR is helpful* *These patients are difficult to manage and often given incorrect diagnosis and especially different theories by different doctors during same admission* *I have direct experience of the benefit of CMR in this area. Therefore, I strongly agree with statement 5. CMR with LGE is especially useful and I have seen many instances when CMR after acute MI with 'normal' coronary arteries has helped diagnosis, differentiating between distal vessel occlusion, LV clot, myocarditis and Takotsubo cardiomyopathy. The results of CMR in this patient group have also directly affected my management of this group of patients including drugs used and length of stay* *MRI is clinically useful in this situation in my experience and occasionally makes a very useful change to management* Quality of supporting evidence *Unfortunately, again no RCT to indicate benefit of CMR*

continued

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TABLE 34 Examples of respondents' comments for the three statements in consensus (3, 5 and 9) and the three statements not in consensus (1, 2 and 8)[4] (*continued*)

Statement 9	Importance of management change	
		Thrombus is poorly assessed by ECHO with many inconclusive reports in my experience locally
		I strongly agree with this statement as I have experience of many patients in which ECHO demonstrated no LV thrombus that was subsequently found on CMR. This personal experience correlates with the studies quoted in the text of the statement
	Quality of supporting evidence	
		This statement is true but whether this leads to better patient outcomes is uncertain
Statement 1	Importance of management change	
		All patients who have suffered an acute MI and subsequently undergone PPCI should receive aggressive secondary prevention. Thus, even though CMR can help refine prognosis, I do not feel that this additional information would lead to any significant changes to prescribing for secondary prevention. Enhanced confidence in CMR findings (compared to ECHO) and refinement of prognosis with respect to infarct size, MVO and MSI may help physicians discharge/follow up patients more appropriately
		All patients should have aggressive secondary prevention
	Quality of supporting evidence	
		Whilst I agree with the evidence presented, there is no evidence to support the assertion the CMR findings lead to better outcomes for patients, as there have been no trials assessing this
		I don't think it has been proved that CMR compared with ECHO leads to improved patient outcomes
		While MVO and MSI are markers of prognosis, LV systolic function remains the most important prognostic factor, which can be assessed with ECHO. We need interventions based on CMR parameters which improve prognosis
	Cost of CMR in relation to perceived benefit	
		Agree, but not sure current restricted availability and high cost and only modest anticipated change in clinical action justifies wholesale change from ECHO that also predicts risk well
Statement 2	Importance of management change	
		PPCI patients are already discharged early and often have little follow-up
		CMR has more reproducible results than ECHO for measuring cardiac function. When this reproducibility is combined with additional measurements that can further indicate good prognosis, this should aid physicians' confidence in earlier discharge and appropriate timing of follow-up
		Also agree, but if good LV on ECHO and no clinical heart failure then discharge is safe. Unaware if that can be accelerated further by CMR
	Quality of supporting evidence	
		I don't think it has been proved that clinical outcomes are better with a CMR strategy
		Although this could be used in clinical practice, there are no studies that I am aware [of] that have assessed such a strategy

TABLE 34 Examples of respondents' comments for the three statements in consensus (3, 5 and 9) and the three statements not in consensus (1, 2 and 8)[4] (*continued*)

Statement 8	Importance of management change
	I'd accept perfusion scanning or DSE as adequate tests for ischaemia and would really only specifically request CMR if there were additional diagnostic questions
	Total revascularisation at one sitting with FFR guidance may render this unnecessary
	Stress CMR in my experience is better than SPECT or stress ECHO. This is because the improved prognostic and diagnostic accuracy helps physicians manage, with confidence, non-significant coronary disease medically rather than invasively. There are also additional benefits of CMR, for example definition of scar for CRT implant or for VT ablation. It can be helpful to 'archive' this information for latter use if the patient is going to receive a device such as an ICD that may preclude latter CMR scanning
	Quality of supporting evidence
	Evidence shows improved diagnostic accuracy compared to SPECT and DSE, but not in this specific cohort
	The evidence for ischaemia testing in the PPCI era does not really exist. There are no studies comparing MRI in this context with other modalities and definitely no RCT comparing CMR versus another modality

DSE, dobutamine stress echocardiography; IHD, ischaemic heart disease; MRI, magnetic resonance imaging; MSI, myocardial salvage index; VT, ventricular tachycardia.

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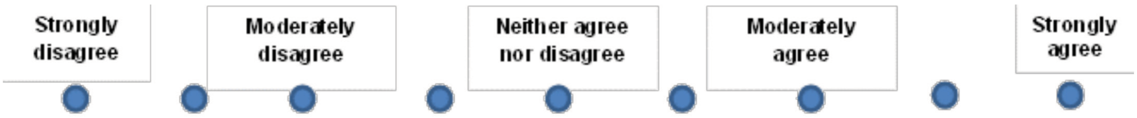
Appendix 8 Modified survey (statements, supporting paragraphs and references)

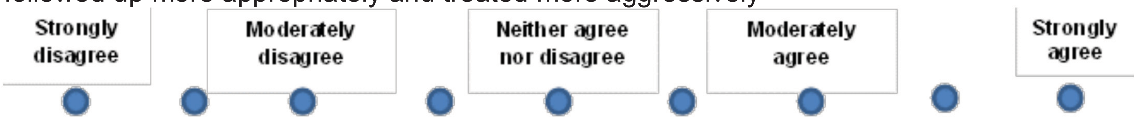
Modified survey (statements, supporting paragraphs and references)[4]

Accurate assessment of infarct characteristics is important for risk stratification after PPCI. CMR can quantify in a single scan all cardiac markers relevant to PPCI outcomes, with high reproducibility and accuracy. CMR has high spatial and temporal resolution and is superior to echocardiography for measuring left ventricular volumes and ejection fraction.[112] Additionally, CMR markers that cannot be measured by echocardiography, such as infarct size, microvascular obstruction and myocardial salvage have been shown to have long term prognostic value.[112–115] Late gadolinium enhancement CMR has added prognostic value over echocardiography.[116]

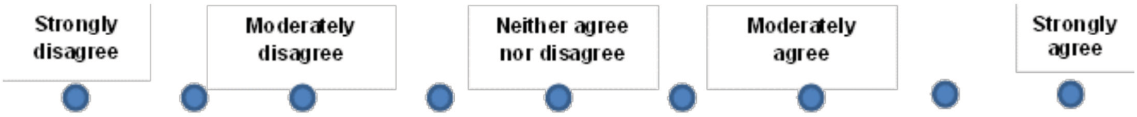
1. The following statements relate to the ability of CMR to identify patients who have a **poor** prognosis after PPCI.
    a. CMR markers (e.g. impaired left ventricular function, large infarct size, microvascular obstruction) better identify patients with a poor prognosis after PPCI than markers based on echocardiography.


Strongly disagree
Moderately disagree
Neither agree nor disagree
Moderately agree
Strongly agree

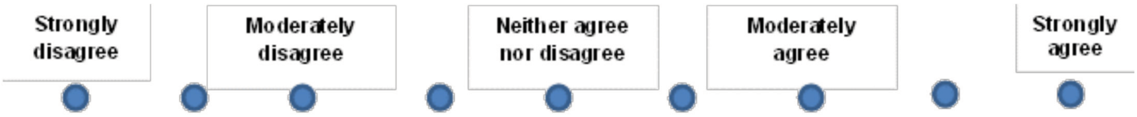
    b. Better identification of patients with a poor prognosis after PPCI allows these patients to be followed up more appropriately and treated more aggressively


Strongly disagree
Moderately disagree
Neither agree nor disagree
Moderately agree
Strongly agree

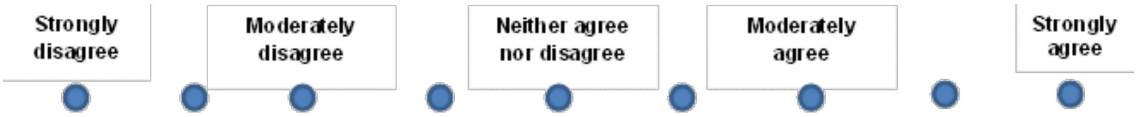
    c. More appropriate follow up and more aggressive treatment in these patients is expected to lead to a reduced risk of MACE in the long term.


Strongly disagree
Moderately disagree
Neither agree nor disagree
Moderately agree
Strongly agree

    d. More appropriate follow up and more aggressive treatment in these patients is expected to lead to less NHS resource use in the long term.


Strongly disagree
Moderately disagree
Neither agree nor disagree
Moderately agree
Strongly agree

    e. The anticipated benefit (reduced risk of MACE and/or less NHS resource use) is likely to be sufficiently large to make CMR cost effective among the patients in whom it would be indicated.


Strongly disagree
Moderately disagree
Neither agree nor disagree
Moderately agree
Strongly agree

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2. The following statements relate to the ability of CMR to identify patients who have a **good** prognosis after PPCI.

   a. CMR markers (e.g. normal left ventricular function, high myocardial salvage, no microvascular obstruction, no residual ischemia) better identify patients with a good prognosis after PPCI than markers based on echocardiography.

Strongly disagree		Moderately disagree		Neither agree nor disagree		Moderately agree		Strongly agree
○	○	○	○	○	○	○	○	○

   b. Better identification of patients with a good prognosis after PPCI allows these patients to be followed up less frequently.

Strongly disagree		Moderately disagree		Neither agree nor disagree		Moderately agree		Strongly agree
○	○	○	○	○	○	○	○	○

   c. Less frequent follow up in these patients is expected to lead to less NHS resource use in the long term.

Strongly disagree		Moderately disagree		Neither agree nor disagree		Moderately agree		Strongly agree
○	○	○	○	○	○	○	○	○

   d. The anticipated benefit (less NHS resource use) is likely to be sufficiently large to make CMR cost effective among the patients in whom it would be indicated.

Strongly disagree		Moderately disagree		Neither agree nor disagree		Moderately agree		Strongly agree
○	○	○	○	○	○	○	○	○

Out-of-hospital cardiac arrest (OHCA) affects about 60,000 people in the UK each year. Currently, hospital survival among patients alive on arrival is about 32%. Early identification of the cause of OHCA is essential to improve survival. Causes of OHCA include myocardial infarction (40%-90%) and inherited cardiomyopathies such as arrhythmogenic right ventricular cardiomyopathy (ARVC) and hypertrophic cardiomyopathy (HCM). Unlike echocardiography, CMR allows *in vivo* tissue characterisation, which differentiates scarring due to myocardial infarction from other causes of focal fibrosis (e.g. observed in non-ischaemic cardiomyopathies such as ARVC and HCM).[117] Late gadolinium enhancement on CMR can predict serious cardiac complications in patients with HCM (all-cause death, cardiac death and death from heart failure) [118] and identifies patients that may need more aggressive medical and device therapy (e.g. renin-aldosterone system inhibition for prevention of heart failure or implantable cardioverter defibrillator placement for primary prevention of sudden cardiac death.

3. The following statements relate to the ability of CMR to identify the causes of OHCA in patients who undergo an emergency angiogram.

   a. CMR better identifies the cause of OHCA (e.g. large myocardial infarction, ARVC, aberrant coronary arteries, HCM) than echocardiography.

Strongly disagree		Moderately disagree		Neither agree nor disagree		Moderately agree		Strongly agree
○	○	○	○	○	○	○	○	○

   b. Better identification of the cause of out-of-hospital cardiac arrest allows treatment to be optimised for these patients (e.g. defibrillator for primary arrhythmia or percutaneous coronary intervention) or their family members (e.g. genetic screening and counselling, primary prevention).

Strongly disagree		Moderately disagree		Neither agree nor disagree		Moderately agree		Strongly agree
○	○	○	○	○	○	○	○	○

   c. The ability to optimise treatment for these patients or family members is expected to lead to a reduced risk of MACE in the long term.

Strongly disagree		Moderately disagree		Neither agree nor disagree		Moderately agree		Strongly agree
○	○	○	○	○	○	○	○	○

   d. The ability to optimise treatment for these patients or family members is expected to lead to less NHS resource use in the long term.

Strongly disagree		Moderately disagree		Neither agree nor disagree		Moderately agree		Strongly agree
○	○	○	○	○	○	○	○	○

   e. The anticipated benefit (reduced risk of MACE and/or less NHS resource use) is likely to be sufficiently large to make CMR cost effective among the patients in whom it would be indicated.

Strongly disagree		Moderately disagree		Neither agree nor disagree		Moderately agree		Strongly agree
○	○	○	○	○	○	○	○	○

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Ventricular septal defect (VSD) and left ventricular free wall rupture are rare complications of myocardial infarction, occurring in less than 1% of PPCI patients, usually within one week of the infarct. Mortality ranges between 50% and 87%. Diagnosis usually requires multi-modality imaging (echocardiography, ventriculography, computed tomography, CMR) before surgical repair. Because of its high spatial resolution, CMR can be used to clarify the detailed structure of these lesions. CMR accurately identifies the location, size and tissue margins of VSD and is useful for detecting apical defects, which are not easily identified by echocardiography. CMR measurements may also be used to determine the size of ventricular patch required to close the VSD, which avoids the inflation of a sizing balloon in friable infarcted tissue.[119] These features, together with other CMR markers of damage (e.g. infarct size, microvascular obstruction, left ventricular dysfunction) are useful for guiding optimal management of patients with post-infarct VSD.

4. The following statements relate to the ability of CMR to identify patients with VSD after myocardial infarction.

   a. CMR identifies the location and characteristics of post-infarct VSD better than echocardiography.

Strongly disagree		Moderately disagree		Neither agree nor disagree		Moderately agree		Strongly agree
○	○	○	○	○	○	○	○	○

   b. Better identification of the location and characteristics of post-infarct VSD guides the optimal management of these patients.

Strongly disagree		Moderately disagree		Neither agree nor disagree		Moderately agree		Strongly agree
○	○	○	○	○	○	○	○	○

   c. Optimal management of patients with post-infarct VSD is expected to lead to a reduced risk of MACE in the long term.

Strongly disagree		Moderately disagree		Neither agree nor disagree		Moderately agree		Strongly agree
○	○	○	○	○	○	○	○	○

   d. Optimal management of patients with post-infarct VSD is expected to lead to less NHS resource use in the long term.

Strongly disagree		Moderately disagree		Neither agree nor disagree		Moderately agree		Strongly agree
○	○	○	○	○	○	○	○	○

   e. The anticipated benefit (reduced risk of MACE and/or less NHS resource use) is likely to be sufficiently large to make CMR cost effective among the patients in whom it would be indicated.

Strongly disagree		Moderately disagree		Neither agree nor disagree		Moderately agree		Strongly agree
○	○	○	○	○	○	○	○	○

Between 5% and 12% of patients who have an emergency angiogram are found to have unobstructed coronary arteries. In these patients, the lack of an accurate diagnosis may result in inappropriate or unnecessary treatment or follow-up and poorer prognosis.[19] CMR facilitates differential diagnosis in patients with unobstructed coronary arteries on angiography, providing a definitive diagnosis (e.g. myocardial infarction, myocarditis, Takotsubo cardiomyopathy) in 65-90% of these patients.[20,23] In patients with myocarditis, late gadolinium enhancement (LGE) on CMR may predict long term adverse outcomes.[26] In the context of myocardial infarction without an angiographic lesion, CMR can locate the culprit infarct-related artery in patients with spontaneous reperfusion or with distal embolization.

5. The following statements relate to the ability of CMR to differentiate myocaradial infarction from other diagnoses in patients found to have unobstructed coronary arteries on emergency angiography.
    a. Unlike echocardiography, CMR can provide a definitive ischaemic diagnosis (e.g. myocardial infarction with spontaneous reperfusion or distal embolization) or a non-ischaemic diagnosis (e.g. myocarditis, Takotsubo cardiomyopathy, aortic dissection) in patients with unobstructed coronary arteries on angiography.

Strongly disagree		Moderately disagree		Neither agree nor disagree		Moderately agree		Strongly agree
○	○	○	○	○	○	○	○	○

    b. A definitive diagnosis results in a patient treatment plan appropriate for that diagnosis.

Strongly disagree		Moderately disagree		Neither agree nor disagree		Moderately agree		Strongly agree
○	○	○	○	○	○	○	○	○

    c. A treatment plan appropriate for the diagnosis is expected to lead to a reduced risk of MACE in the long term.

Strongly disagree		Moderately disagree		Neither agree nor disagree		Moderately agree		Strongly agree
○	○	○	○	○	○	○	○	○

    d. A treatment plan appropriate for the definitive diagnosis is expected to lead to less NHS resource use in the long term.

Strongly disagree		Moderately disagree		Neither agree nor disagree		Moderately agree		Strongly agree
○	○	○	○	○	○	○	○	○

    e. The anticipated benefit (reduced risk of MACE and/or less NHS resource use) is likely to be sufficiently large to make CMR cost effective among the patients in whom it would be indicated.

Strongly disagree		Moderately disagree		Neither agree nor disagree		Moderately agree		Strongly agree
○	○	○	○	○	○	○	○	○

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About 6% of heart attack patients subsequently die suddenly from a presumed cardiac cause. Current guidelines recommend the use of an implantable cardioverter defibrillator (ICD) to prevent sudden cardiac death in patients who have a low left ventricular ejection fraction (EF) after a heart attack. EF is used in clinical practice to make decisions about ICD implantation, but it has a low predictive value and many patients with an ICD will never benefit from it.[120] EF is most commonly measured by echocardiography, but CMR is now considered the gold standard for EF measurement because it is more reproducible than echocardiography.[112] CMR has been shown to be better than echocardiography for selecting patients for ICD implantation when strict EF thresholds are used to guide implantation.[121] The extent of myocardial scar characterised by late gadolinium enhancement (LGE) CMR may also be used to predict whether ICD implantation is appropriate in this patient group.[122] Furthermore, LGE CMR can guide placement of the left ventricular lead away from scarred myocardium, which results in a better clinical outcome after cardiac resynchronisation therapy (CRT).[123]

6. The following statements relate to the ability of CMR to identify patients at high risk of sudden cardiac death after PPCI who would benefit most from an implantable cardiac device.
    a. CMR identifies PPCI patients who are at high risk of sudden cardiac death better than echocardiography.

Strongly disagree		Moderately disagree		Neither agree nor disagree		Moderately agree		Strongly agree
○	○	○	○	○	○	○	○	○

    b. Better identification of PPCI patients at high risk of sudden cardiac death allows optimal patient selection for an implantable cardiac device (ICD or CRT).

Strongly disagree		Moderately disagree		Neither agree nor disagree		Moderately agree		Strongly agree
○	○	○	○	○	○	○	○	○

    c. Optimal patient selection for an implantable cardiac device is expected to lead to a reduced risk of MACE in these patients in the long term.

Strongly disagree		Moderately disagree		Neither agree nor disagree		Moderately agree		Strongly agree
○	○	○	○	○	○	○	○	○

    d. Optimal patient selection for an implantable cardiac device is expected to lead to less NHS resource use in the long term.

Strongly disagree		Moderately disagree		Neither agree nor disagree		Moderately agree		Strongly agree
○	○	○	○	○	○	○	○	○

    e. The anticipated benefit (reduced risk of MACE and/or less NHS resource use) is likely to be sufficiently large to make CMR cost effective among the patients in whom it would be indicated.

Strongly disagree		Moderately disagree		Neither agree nor disagree		Moderately agree		Strongly agree
○	○	○	○	○	○	○	○	○

Cardiac resynchronisation therapy (CRT), or biventricular pacing, uses a specialised pacemaker to improve the contraction of the left ventricle and the overall efficiency of the heart. It is used in patients with systolic ventricular dysfunction and heart failure. However, about 30% of patients who meet the inclusion criteria for CRT do not respond to it.[124] CMR assessment of mechanical dyssynchrony and myocardial scar provides additional value over echocardiography for identifying non responsive patients.[125,126] Myocardial scar is an important feature of non-response to CRT[127,128] and late gadolinium enhancement (LGE) CMR accurately differentiates between transmural, mid-myocardial, epicardial, and subendocardial scar.

7. The following statements relate to the ability of CMR to identify patients who **would not** benefit from CRT after PPCI.

    a. CMR identifies patients who would not benefit from CRT better than echocardiography.

Strongly disagree		Moderately disagree		Neither agree nor disagree		Moderately agree		Strongly agree
○	○	○	○	○	○	○	○	○

    b. The ability to identify patients who would not benefit from CRT would reduce CRT use in patients who do not need it.

Strongly disagree		Moderately disagree		Neither agree nor disagree		Moderately agree		Strongly agree
○	○	○	○	○	○	○	○	○

    c. Reducing CRT use in patients who do not need it is expected to lead to reduced risk of MACE in these patients in the long term.

Strongly disagree		Moderately disagree		Neither agree nor disagree		Moderately agree		Strongly agree
○	○	○	○	○	○	○	○	○

    d. Reducing CRT use in patients who do not need it is expected to lead to less NHS resource use in the long term.

Strongly disagree		Moderately disagree		Neither agree nor disagree		Moderately agree		Strongly agree
○	○	○	○	○	○	○	○	○

    e. The anticipated benefit (reduced risk of MACE and/or less NHS resource use) is likely to be sufficiently large to make CMR cost effective among the patients in whom it would be indicated.

Strongly disagree		Moderately disagree		Neither agree nor disagree		Moderately agree		Strongly agree
○	○	○	○	○	○	○	○	○

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Between 40% and 65% of the patients who activate the PPCI pathway have multi-vessel disease. Adequate assessment of residual ischemia in non-culprit arteries post PPCI is important for effective management because this patient group has an adverse prognosis. Various techniques are currently used to assess the need for additional revascularisation, including stress echocardiography, single photon emission computed tomography (SPECT) and stress-perfusion CMR. Stress CMR has excellent prognostic value[129] and better diagnostic accuracy than SPECT[130,131] or stress echocardiography[132] for detecting coronary artery disease causing significant regional myocardial ischaemia.

8. The following statements relate to the ability of CMR to assess ischemia and viability in patients with multi-vessel disease.

   a. CMR assesses ischemia and viability of the myocardium better than echocardiography.

Strongly disagree		Moderately disagree		Neither agree nor disagree		Moderately agree		Strongly agree
●	●	●	●	●	●	●	●	●

   b. Better assessment of ischemia and viability of the myocardium optimises the revascularisation strategy for patients with multi-vessel disease and avoids additional diagnostic tests.

Strongly disagree		Moderately disagree		Neither agree nor disagree		Moderately agree		Strongly agree
●	●	●	●	●	●	●	●	●

   c. The ability to optimise the revascularisation strategy for patients with multi-vessel disease is expected to lead to a reduced risk of MACE in the long term.

Strongly disagree		Moderately disagree		Neither agree nor disagree		Moderately agree		Strongly agree
●	●	●	●	●	●	●	●	●

   f. The ability to optimise the revascularisation strategy and avoid additional diagnostic tests in patients with multi-vessel disease is expected to lead to less NHS resource use in the long term.

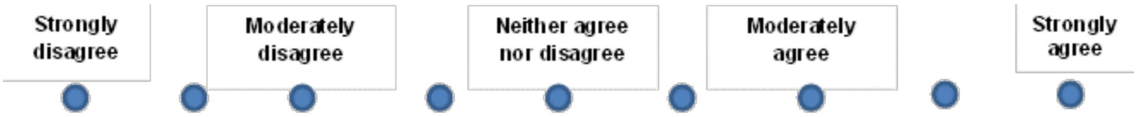
Strongly disagree		Moderately disagree		Neither agree nor disagree		Moderately agree		Strongly agree
●	●	●	●	●	●	●	●	●

   d. The anticipated benefit (reduced risk of MACE and/or less NHS resource use) is likely to be sufficiently large to make CMR cost effective among the patients in whom it would be indicated.

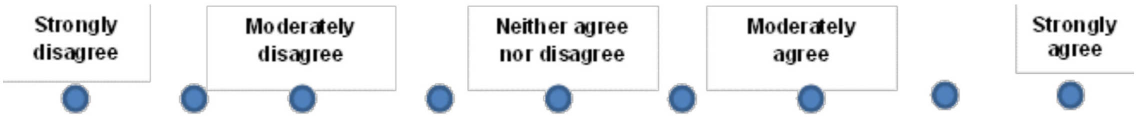
Strongly disagree		Moderately disagree		Neither agree nor disagree		Moderately agree		Strongly agree
●	●	●	●	●	●	●	●	●

Left ventricular (LV) thrombus is a serious complication of acute myocardial infarction. It increases risk of thromboembolic events, particularly stroke. LV thrombus develops in up to 10% of patients with anterior wall infarction after PPCI. Although echocardiography is most commonly used to detect LV thrombus and to assess its shape and size, between 10-46% of echocardiograms are inconclusive.[133] Late gadolinium enhancement (LGE) CMR is considered the gold standard for detecting LV thrombus, because it detects thrombus based on tissue characteristics rather than anatomic appearance. Fewer thrombi are detected by contrast-echocardiography than by LGE CMR.[134] CMR has a higher sensitivity (88%) than contrast (61%) and noncontrast (<33%) echocardiography.[134,135]

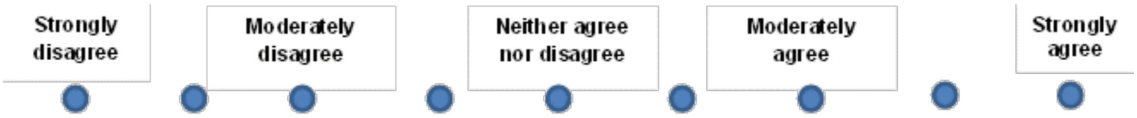
9. The following statements relate to the ability of CMR to identify patients with post-infarct LV thrombus.
    a. CMR identifies post-infarct LV thrombus better than echocardiography.


Strongly disagree
Moderately disagree
Neither agree nor disagree
Moderately agree
Strongly agree

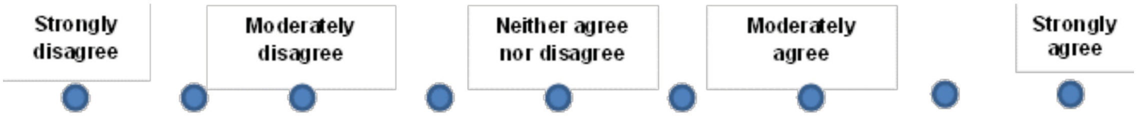
    b. Better detection of post-infarct LV thrombus in PPCI patients allows more affected patients to be treated with anticoagulation therapy.


Strongly disagree
Moderately disagree
Neither agree nor disagree
Moderately agree
Strongly agree

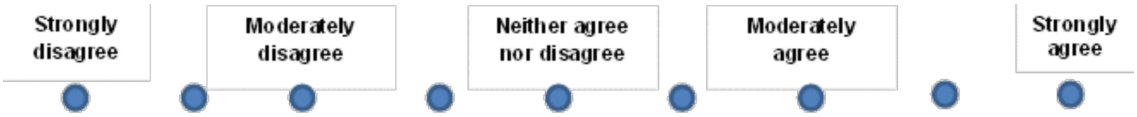
    c. Treatment with anticoagulation therapy in patients with post-infarct LV thrombus is expected to lead to a reduced risk of MACE in the long term.


Strongly disagree
Moderately disagree
Neither agree nor disagree
Moderately agree
Strongly agree

    d. Treatment with anticoagulation therapy in patients with post-infarct LV thrombus is expected to lead to less NHS resource use in the long term.


Strongly disagree
Moderately disagree
Neither agree nor disagree
Moderately agree
Strongly agree

    e. The anticipated benefit (reduced risk of MACE and/or less NHS resource use) is likely to be sufficiently large to make CMR cost effective among the patients in whom it would be indicated.


Strongly disagree
Moderately disagree
Neither agree nor disagree
Moderately agree
Strongly agree

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Compared with echocardiography, CMR provides versatile imaging planes, superior tissue contrast and advanced tissue characterisation, allowing a comprehensive assessment of cardiac anatomy, function and flow, and imaging of the great vessels (including venous return), the pericardium and suspected cardiac tumours.[138] As such, CMR can identify congenital coronary anomalies, cardiac masses, coronary artery aneurysms, valvular heart disease, thoracic aortic disease, etc. CMR can adequately differentiate benign from malignant tumours in the heart.[139] Unlike echocardiography, which provides limited imaging of mediastinal and extra-cardiac structures, CMR also images a substantial part of the thorax and abdomen in the field of view, which may potentially contain non-cardiac abnormalities. The prevalence of non-cardiac findings on CMR is up to 80% (with up to 30% of these representing potentially significant findings), depending on the characteristics of the population examined.[140–142]

10. The following statements relate to the ability of CMR to detect incidental cardiac and non-cardiac findings if offered routinely to patients who undergo an emergency angiogram.

    a. CMR identifies more incidental cardiac / non-cardiac findings than echocardiography.

Strongly disagree		Moderately disagree		Neither agree nor disagree		Moderately agree		Strongly agree
●	●	●	●	●	●	●	●	●

    b. Improved detection of potentially significant incidental findings allows affected patients to be investigated further and / or treated.

Strongly disagree		Moderately disagree		Neither agree nor disagree		Moderately agree		Strongly agree
●	●	●	●	●	●	●	●	●

    c. Further investigation and treatment is expected to reduce the risk of MACE / increase overall survival in affected patients in the long term.

Strongly disagree		Moderately disagree		Neither agree nor disagree		Moderately agree		Strongly agree
●	●	●	●	●	●	●	●	●

    d. Further investigation and treatment is expected to lead to less NHS resource use in the long term.

Strongly disagree		Moderately disagree		Neither agree nor disagree		Moderately agree		Strongly agree
●	●	●	●	●	●	●	●	●

    e. The anticipated benefit (reduced risk of MACE and/or less NHS resource use) is likely to be sufficiently large to make CMR cost effective among the patients who undergo an emergency angiogram.

Strongly disagree		Moderately disagree		Neither agree nor disagree		Moderately agree		Strongly agree
●	●	●	●	●	●	●	●	●

Appendix 9 Primary diagnoses in medical notes and Hospital Episode Statistics admissions data set for patients initially identified as having 'unobstructed coronary arteries' from hospital A

Summary from medical notes	Primary diagnoses (HES)	Frequency
Culprit lesion found, PCI	Pain in throat and chest	1
Culprit lesion found, no PCI	Acute MI	1
Culprit lesion found, no PCI	Acute MI and stroke, not specified as haemorrhage or infarction	1
Culprit lesion found, no PCI	Atrial fibrillation and flutter	1
Culprit lesion found, no PCI	Chronic ischaemic heart disease	2
Other/unknown problem	Cardiac arrest	1
Other/unknown problem	Pain in throat and chest	2
Unobstructed arteries	Other diseases of pericardium	1
Unobstructed arteries	Pain in throat and chest	1
Unobstructed arteries	Syncope and collapse	1
Unobstructed arteries *and* other cardiac cause	Acute MI	1
Unobstructed arteries *and* other cardiac cause	Acute MI *and* other diseases of pericardium	1
Unobstructed arteries *and* other cardiac cause	Acute pericarditis	1
Unobstructed arteries *and* other cardiac cause	Atrial fibrillation and flutter	3
Unobstructed arteries *and* other cardiac cause	Atrial fibrillation and flutter *and* other cardiac arrhythmias	1
Unobstructed arteries *and* other cardiac cause	Atrioventricular and left bundle-branch block	1
Unobstructed arteries *and* other cardiac cause	Chronic ischaemic heart disease	1
Unobstructed arteries *and* other cardiac cause	Non-rheumatic aortic valve disorders	1
Unobstructed arteries *and* other cardiac cause	Other diseases of pericardium	4
Unobstructed arteries *and* other cardiac cause	Other diseases of pericardium *and* atrial fibrillation and flutter	1
Unobstructed arteries *and* other cardiac cause	Pain in throat and chest	3
Unobstructed arteries *and* other cardiac cause	Paroxysmal tachycardia	1
Unobstructed arteries *and* other cardiac cause	Pneumonia, organism unspecified *and* acute renal failure	1
Unobstructed arteries *and* other cardiac cause	Pulmonary embolism	1
Unobstructed arteries *and* other/unknown problem	Acute MI	2
Unobstructed arteries *and* other/unknown problem	Chronic ischaemic heart disease	1
Unobstructed arteries *and* other/unknown problem	Other chronic obstructive pulmonary disease	1
Unobstructed arteries *and* other/unknown problem	Pain in throat and chest	5
Unobstructed arteries *and* other/unknown problem	Pain in throat and chest *and* acute MI	1
Unobstructed arteries *and* other/unknown problem	Pain in throat and chest *and* cerebral infarction	1
Unobstructed arteries *and* other/unknown problem	Pneumonia, organism unspecified	2
Unobstructed arteries *and* other/unknown problem	Syncope and collapse	1

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Appendix 10 Data sources and definitions used for identifying changes in management up to 12 months after the index admission

Important change in management resulting from CMR (identified in formal consensus)	Patient subgroup	Data source	ICD-10 diagnosis codes and OPCS procedure codes (up to 12 months after the index admission)
New diagnosis (non-ischaemic)	Unobstructed coronary arteries	HES/PEDW admission data	Any record of the following: • Takotsubo cardiomyopathy (I42.8 AND F43.8) • Myocarditis (I51.4) • Pericarditis (I30 OR I31.0 OR I31.1 OR I31.9 OR I32.0 OR I32.1 OR I32.8 OR I01.0 OR I02.0 OR I09.2) • Endocarditis (I33.9) • Coronary spasm (I20.1)
Changes in medication	All subgroups	Not available	Not available
Additional diagnostic tests	All subgroups	HES/PEDW admission data and outpatient data	Any record of the following: • PET scans (U10.4 OR U21.3 OR U36.2) • ECHO (K58.5 OR U20.1 OR U20.3 OR U20.4 OR U20.5) • IVUS (K51.2 OR L726) • Pressure wire [(K63.4 OR K63.5 OR K63.6) AND K51.8 AND Y44.2 AND Y53] • Radionuclide angiocardiography (U10.5) • CT angiography (U10.2) • SPECT (U21.4)
Implantation of devices	• PPCI • OHCA	HES/PEDW admission data	Any record of the following: • CRT (K60.7 OR K61.7 OR K59.6) • ICD (K59 OR K72)
Revascularisation (PCI or CABG) within 3 months	Multivessel disease	HES/PEDW admission data	Any record of the following (up to 3 months after the index admission): • PCI (K49 OR K50 OR K75) • CABG (K40 OR K41 OR K42 OR K43 OR K44 OR K45 Or K46)
Frequency of cardiology outpatient appointments	All subgroups	HES/PEDW outpatient data	Rate of outpatient visits attended (count of visits divided by follow-up time) where the treatment specialty in which the consultant responsible was working during the period of care was cardiology (code = 320)

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