MR-IMPACT II: Magnetic Resonance Imaging for Myocardial Perfusion Assessment in Coronary artery disease Trial: perfusion-cardiac magnetic resonance vs. single-photon emission computed tomography for the detection of coronary artery disease: a comparative multicentre, multivendor trial

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Aims	Perfusion-cardiac magnetic resonance (CMR) has emerged as a potential alternative to single-photon emission computed tomography (SPECT) to assess myocardial ischaemia non-invasively. The goal was to compare the diagnostic performance of perfusion-CMR and SPECT for the detection of coronary artery disease (CAD) using conventional X-ray coronary angiography (CXA) as the reference standard.
Methods and results	In this multivendor trial, 533 patients, eligible for CXA or SPECT, were enrolled in 33 centres (USA and Europe) with 515 patients receiving MR contrast medium. Single-photon emission computed tomography and CXA were performed within 4 weeks before or after CMR in all patients. The prevalence of CAD in the sample was 49%. Drop-out rates for CMR and SPECT were 5.6 and 3.7%, respectively ($P = 0.21$). The primary endpoint was non-inferiority of CMR vs. SPECT for both sensitivity and specificity for the detection of CAD. Readers were blinded vs. clinical data, CXA, and imaging results. As a secondary endpoint, the safety profile of the CMR examination was evaluated. For CMR and SPECT, the sensitivity scores were 0.67 and 0.59, respectively, with the lower confidence level for the difference of +0.02, indicating superiority of CMR over SPECT. The specificity scores for CMR and SPECT were 0.61 and 0.72, respectively (lower confidence level for the difference: −0.17), indicating inferiority of CMR vs. SPECT. No severe adverse events occurred in the 515 patients.
Conclusion	In this large multicentre, multivendor study, the sensitivity of perfusion-CMR to detect CAD was superior to SPECT, while its specificity was inferior to SPECT. Cardiac magnetic resonance is a safe alternative to SPECT to detect perfusion deficits in CAD.
Keywords	Magnetic resonance imaging • Scintigraphy • Coronary disease • Perfusion • Ischaemia

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Introduction

Despite considerable progress in the treatment of acute and chronic coronary artery disease (CAD) during the past years, CAD still remains the largest single killing disease in the USA[1] and Europe.[2] Approximately one-third of coronary attacks results in death in the USA[1] and similar numbers apply to Europe. These numbers stress the need for early detection of disease. The presence of perfusion deficits has been shown to be one of the strongest predictors of cardiac death and non-fatal myocardial infarction (MI) in large studies,[3] and ischaemia imaging takes a central position in guidelines for the work-up of patients with known or suspected CAD.[4,5] Scintigraphy is widely used for ischaemia detection and it has been shown to be cost-effective.[6] In recent years, several studies documented a high diagnostic performance of perfusion-cardiac magnetic resonance (CMR) vs. conventional X-ray coronary angiography (CXA)[7–13] and showed its prognostic value.[14] This evidence triggered an increasing utilization of perfusion-CMR in clinical practice and its impact on clinical patient management was recently demonstrated.[15]

The current MR-IMPACT II trial was designed to compare the diagnostic performance of CMR vs. single-photon emission computed tomography (SPECT) for the detection of perfusion deficits in CAD (defined as $\geq$75% area reduction in coronary vessels in CXA) in a large international multicentre, multivendor design. We enrolled 533 patients in 33 study centres across Europe and the USA. Patients were characterized for the presence of CAD by CXA (reference standard), perfusion-CMR, and SPECT. Cardiac magnetic resonance and SPECT were each analysed by three blinded readers in core laboratories for the presence or absence of perfusion abnormalities.

Methods

Study design and patient population

This Phase III clinical trial was conducted at 33 centres in Europe and the USA (see Supplementary material online for a list of participating sites). Eligible patients were those scheduled for a conventional CXA and/or a SPECT examination for clinical reasons. Before study entry, all patients had to agree to undergo all three imaging studies. *Table 1* shows the inclusion/exclusion criteria. The study was conducted according to the Declaration of Helsinki, the principles of Good Clinical Practice, and was approved by the Health Authorities and the local Ethics Committee of each participating institution. All patients gave written informed consent before study participation.

Efficacy measures

Diagnostic performances of CMR and SPECT were assessed with two efficacy measures: it was tested for non-inferiority of both sensitivity and specificity for CMR vs. SPECT for the detection of CAD (=primary study endpoint). Thus, a binary approach was used, i.e. reading was assessed at one threshold. As secondary endpoints, sensitivity, specificity, and negative and positive predictive values for the CMR examination were calculated as well as the safety profile of CMR.

Table I Inclusion and exclusion criteria

Inclusion

Patients scheduled for routine CXA and/or SPECT for clinical reasons

CXA and SPECT must be performed within 4 weeks before or after CMR irrespective of findings in any of the 3 tests

No interventions on the coronary arteries in the time period between the 3 tests

Exclusion

Acute MI (<2 weeks prior to study enrolment)

History of coronary artery bypass grafting

Unstable angina pectoris

Decompensated heart failure

Any interventions on the coronary arteries in the time period between CXA, SPECT, and CMR

Contraindications for adenosine and contrast media

Severe arrhythmias considered to compromise quality of CMR imaging

CXA, invasive coronary angiography; SPECT, single-photon emission computed tomography; CMR, cardiac magnetic resonance; MI, myocardial infarction.

Definition of coronary artery disease: reference standard

The study was designed to determine the sensitivity and specificity of CMR and SPECT to detect perfusion deficits in patients with suspected or known CAD. It was not the aim to discriminate perfusion deficits into ischaemia vs. scar tissue, since CMR is known for its excellent power to differentiate viable from scar tissue,[16] which could have introduced a bias in favour of CMR. For the definition of CAD, i.e. to define patients with perfusion deficits, two criteria were used: first, the presence of a $\geq$50% diameter stenosis (i.e. $\geq$75% area stenosis) measured in two orthogonal planes as was used in previous studies[7–9,17] present in $\geq$1 coronary artery of $\geq$2 mm diameter using a core laboratory (Cleveland Clinic Foundation, Cleveland, OH, USA). Thus, a $\geq$50% diameter reduction had to be present in both orthogonal projections to define CAD. This criterion accounted for 94.6% of all patients in this study. Secondly, the history of a previous MI was considered. This way, patients after MI (and thus with perfusion deficits in scar tissue on resting perfusion images) do fulfil the criteria for the presence of perfusion deficits in CAD [e.g. patients with successful percutaneous coronary interventions (PCI)/stenting in the setting of acute MI and consequently non-stenosed coronary arteries]. This second criterion to define CAD (=history of previous MI without significant stenosis on CXA) was relevant for 5.4% of all patients included. Conversely, patients with a history of successful PCI/stenting (with a residual area stenosis $\leq$75% in the actual CXA) and without a history of MI do not fulfil the definition of CAD (and are assumed to yield normal perfusion studies at stress and at rest). Vessels of <2 mm diameter were not considered for definition of CAD, since such small vessels are rarely treated (e.g. no stents available for <2 mm vessels).

Cardiac magnetic resonance examination

In 1.5 T scanners of various vendors, a breath-hold MR first-pass perfusion examination was performed to follow a bolus of 0.075 mmol/kg Gd-DTPA-BMA (Omniscan, GE Healthcare, USA) injected into a peripheral vein with power injectors at 5 mL/s (followed by a 25 mL saline flush) after 3 min of adenosine infusion (0.14 mg/min/kg i.v.).

The patients had to refrain from coffee, tea, chocolate, or other caffeinated beverages and food for at least 24 h before the CMR exam. A contrast medium (CM) dose of 0.075 mmol/kg was chosen according to recommendations of the food and drug administration (FDA) to test the minimal effective dose (i.e. a dose slightly lower than the optimum dose in MR-IMPACT I[9] used). During bolus arrival, three short-axis slices were acquired every heart beat at one-fourth, half, and three-fourth of the left ventricular (LV) long axis (non-slice selective 90°-preparation, fast gradient-echo acquisition with an echo-planar component where available; spatial resolution: 2−3 mm × 2−3 mm, slice thickness 8−10 mm). An example is given in *Figure 1*. At the same locations, at 10 and 25 min after the stress imaging, a rest perfusion imaging at the same CM dose and a late enhancement study (with the inversion time nulling normal myocardium at the cumulated CM dose of 0.15 mmol/kg) were performed, respectively.

Cardiac magnetic resonance data were analysed visually by three blinded readers in an independent core laboratory (Independent Review Center, GE Healthcare, former Nycomed Amersham Imaging, Princeton, NJ, USA). The three readers were blinded with respect to any clinical information of the patients or results of the other examinations. For the single threshold analysis, a binary assessment of the CMR studies was performed as either showing a perfusion abnormality in any of the 16 segments of the heart at rest and/or at stress (abnormal study) or not (normal study). Perfusion abnormalities were defined as myocardium being black or dark grey at the peak bolus. Borderline normal perfusion (myocardium being light grey) was classified together with normal perfusion (myocardium being bright). Additional criteria indicative for true hypoperfusion vs. artefacts were subendocardial signal reduction persisting longer than the CM first-pass through the LV cavity, signal reduction in several slices, and neighbouring regions.[9] From this binary judgement, sensitivity and specificity scores were defined as the number of readers with correct diagnosis (true-positive and true-negative, respectively) divided by the number of all readers (=3) yielding values between 0 and 1 (e.g. all three readers correct for true-positive: sensitivity score $Sens_{MR} = 1$; e.g. one reader of three correct for true-negative: specificity score $Spec_{MR} = 0.33$). By using scores of sensitivity and specificity, the sensitivity and specificity results of the three readers were combined into one value/patient, which facilitated subsequent non-inferiority testing.

Single-photon emission computed tomography examination

Stress and rest SPECT examinations were performed according to generally accepted guidelines[18] on machines of different vendors (two- or three-head cameras) with ^{99m}Tc- or ^{201}Tl-tracer, adenosine dose as for perfusion-CMR, or physical stress, and 1 or 2 days protocols. The patients had to refrain from coffee, tea, chocolate, or other caffeinated beverages and food for at least 24 h before the SPECT exam. Gated-SPECT using ^{99m}Tc-tracer was strongly recommended, but ungated acquisitions and/or ^{201}Tl-tracers were accepted if part of the performing institution's clinical routine. In the efficacy population, i.e. all three methods completed, gated-SPECT was performed in 253 patients. ^{201}Tl-tracer was used in 32 patients (rest and stress) and in 8 additional patients for rest studies only (6.9 and 1.7%, respectively). Algorithms for attenuation correction or resolution recovery were not applied as these were not available or not identical over all sites.

Single-photon emission computed tomography data were analysed visually by three blinded readers using a core laboratory (Beacon Bioscience, Inc., Doylestown, PA, USA). The three readers were blinded with respect to any clinical information of the patients or results of the other examinations. Each reader was presented with 10−12 short-axis as well as 6−9 vertical and horizontal long-axis
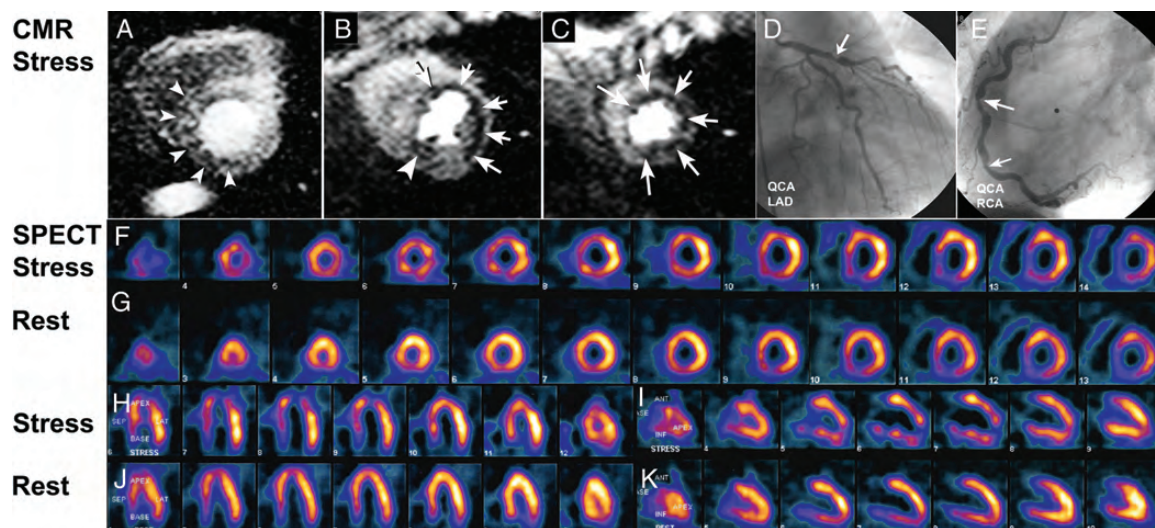
Figure 1 An example of a 67-year-old patient is shown with angina CCS II. The perfusion-cardiac magnetic resonance study during hyperaemia (at 0.075 mmol/kg Gd-DTPA-BMA) demonstrates a perfusion deficit in the subendocardium of the anterolateral wall (B and C; arrows). In the apical slice, almost the entire subendocardium is hypoperfused during hyperaemia (C, arrows). Another minor perfusion deficit is detected in the inferior wall of the basal and mid-ventricular slices (A and B, arrowheads). In the basal slice in (A), the inferior wall of the right ventricle also shows hypoperfusion in comparison with the right ventricular free wall. Single-photon emission computed tomography in this patient was positive with a predominant perfusion abnormality in the anteroseptal wall (F−K). Quantitative X-ray coronary angiography (QCA) demonstrated a severe stenosis in the left anterior descending coronary artery of 82% (LAD; D, arrow). The right coronary artery (RCA) shows two mild stenoses of 64 and 59% diameter reduction (E, arrows).

images for both stress and rest conditions. Gated-SPECT data were also presented to the readers, if they had been acquired. For the primary endpoint, a binary assessment of the SPECT studies was performed as either being normal or not according to generally accepted guidelines.[18] Specifically, SPECT studies were categorized as either showing a perfusion abnormality in any segment of a 17-segment model at rest and/or at stress (=abnormal study) or not (=normal study). Also, patients with a transient ischaemic LV dilation were categorized as abnormal. From this binary judgement, sensitivity and specificity scores ($Sens_{SPECT}$ and $Spec_{SPECT}$) were calculated as described for the CMR data.

Safety parameters

In all patients dosed with the CM, the following was recorded: adverse events, findings of physical examinations (1–24 h before CM administration and 24 h thereafter), vital signs (systolic/diastolic blood pressure, heart rate, and respiratory rate at 10 and 6 min before CM administration, during adenosine infusion, and at the end of the CMR study, as well as 15, 60–90 min, and 24 h thereafter), laboratory parameters (serum biochemistry, hematology, and coagulation parameters within 36 h before and 24 h after first CM administration), and 12-lead electrocardiographic (ECG) tracings (immediately before the CMR study, and 60–90 min and 24 h thereafter). Core laboratories for blood sample analyses and 12-lead ECG analyses were CRL-Medinet Europe, Breda, The Netherlands, and Biomedical Systems (BMS) Europe, Brussels, Belgium, respectively.

Statistical analysis

Sample size calculation for non-inferiority for sensitivity and specificity

To meet the efficacy measure for non-inferiority of sensitivity, this criterion had to be met in each of two parallel substudies. Accordingly, for the primary endpoint of sensitivity, 139 subjects were calculated to yield a 90% power to show non-inferiority of CMR vs. SPECT at an equivalence limit difference of −0.1 with a target significance level of 0.025 (nQuery Advisor 5.0) using an SD of the difference of 0.36 for CMR (derived from the Phase II clinical study: MR-IMPACT[1]). Hence, non-inferiority is inferred if the lower bound of the confidence interval (CI) falls within the equivalence margin of −0.10 (=10% non-inferiority margin: H_0: $Sens_{MR} - Sens_{SPECT} < -0.1$). The criterion of non-inferiority of specificity had to be met in the entire study (=substudies 1 and 2). Accordingly, for the primary endpoint assessment of specificity, the two identical Phase III substudies combined had to achieve a 90% power to show non-inferiority of CMR vs. SPECT at an equivalence limit difference of −0.1 with a target significance level of 0.025 (nQuery 5.0) expecting 30–40% of negative subjects from each of the two Phase III substudies. The substudies 1 and 2 included 238 and 227 patients, respectively (efficacy population = dosed patients with complete data sets).

For the primary endpoint of non-inferiority of CMR vs. SPECT, non-inferiority was inferred, if the lower bounds of the CIs for the sensitivity and specificity scores fall within the equivalence margin of −0.10 (=10% non-inferiority margin: H_0: $Sens_{MR} - Sens_{SPECT} < -0.1$). In the case of superiority, i.e. if the lower bounds of the CIs for sensitivity or specificity fall above 0, superiority is reported.[19] All tests were two-sided and a P-value of <0.05 was considered statistically significant. Statistical analyses were performed using SAS® software (Version 8.2).

Results

Patient characteristics

From the 533 patients enrolled, 515 entered the safety analysis (=patients received MR CM; Figure 2). Of the 465 patients with data of all three modalities complete (=efficacy population; Table 2), 227 (48.8%) had coronary artery stenoses with ≥75% area reduction, 73 had occlusions (15.7%), 129 (27.7%) had infarctions, and 25 patients (5.4%) of those with infarctions showed no significant stenoses (<75% area reduction) on CXA. The prevalence of CAD in the population without a history of infarction was 29%. No patients of the previous MR-IMPACT I were included in the analyses of MR-IMPACT II.

Non-inferiority analysis: binary sensitivity and specificity score: primary endpoint

For this evaluation, 26 (5.6% of 465) CMR and 17 (3.7% of 465, $P = 0.21$ vs. CMR) SPECT studies were deemed non-evaluable by the MR and SPECT readers, respectively. The prevalence of CAD on CXA was similar in the studies excluded and included in the efficacy analysis (21 of 40 vs. 206 of 425, respectively,
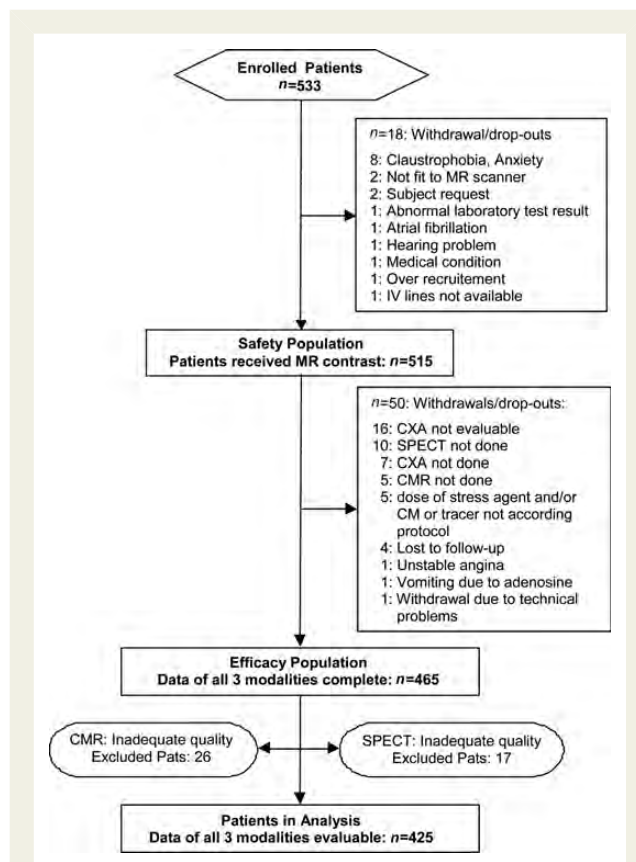
Figure 2 Flow chart demonstrating the number of eligible patients and drop-outs. CMR, cardiac magnetic resonance; CM, contrast medium (Gd-DTPA-BMA); CXA, coronary X-ray angiography; Pats, patients; SPECT, single-photon emission computed tomography.

Table 2 Demographics of study population

Characteristics	n (%)
All patients enrolled:	515
Age, years (mean ± SD)	60 ± 10.3
Range	26−85
Body mass index, kg/m^2 (mean ± SD)	28.2 ± 4.3
Range	16.0−50.0
Male sex	377 (73.2)
Race: Caucasian	488 (94.8)
Angina pectoris	414 (80.4)
CCS I	87 (16.9)
CCS II	227 (44.1)
CCS III	46 (8.9)
CCS IV	21 (4.1)
Risk factors	
Hypertension	358 (69.5)
Hypercholesterolaemia	354 (68.8)
Diabetes	92 (17.8)
Myocardial infarctions	139 (27.0)
PCI	170 (33.0)
History of heart failure	106 (20.6)
Efficacy population (patients with all 3 test data sets complete): n	465
Coronary artery disease	227 (48.8)
Left main	14 (3.0)
LAD	134 (28.8)
LCX	104 (22.4)
RCA	112 (24.1)
Multivessel disease	113 (24.3)
Myocardial infarction	129 (27.7)
Medication	
Any drugs	496 (96.4)
β-Blockers	367 (71.3)
Lipid lowering	354 (68.8)
Angiotensin-converting enzyme inhibitors	306 (59.4)
Diuretics	131 (25.5)
Calcium channel blockers	99 (19.2)
Antithrombotic	425 (82.6)
MR—not evaluable	26 (5.6)
SPECT—not evaluable	17 (3.7)

CCS, Canadian Cardiovascular Society; PCI, percutaneous coronary intervention; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary artery

Table 3 Safety profile of the cardiac magnetic resonance examination

Safety population (patients received MR contrast medium)	515
Serious adverse events[a]	6 (1.2)
Angina pectoris	1 (0.2)
Prolonged hospital stays	5 (1.0)
Death	0 (0)
Adverse events (in 74 patients)	114 (22.1)
Requiring treatment	12 (2.3)
Angina pectoris	4 (0.8)
Headache	4 (0.8)
Chest pain	3 (0.6)
Injection site bruising	1 (0.2)
Mild	91 (17.7)
Moderate	23 (4.5)
Severe	0 (0)
Subject withdrawal due to adverse events	0 (0)

[a]Safety: all six serious adverse events were classified by the treating physician as not drug-related. Prolonged hospital stays were due to treatment by PCI/CABG of severe CAD during the same hospitalization.

for the difference of −0.17, indicating inferiority of CMR vs. SPECT for specificity. For CMR and SPECT, sensitivities (mean ± SD of all readers) were 75 ± 7 and 59 ± 10%, respectively ($P = 0.03$) and specificities were 59 ± 8 and 72 ± 14%, respectively ($P = 0.03$). Positive and negative predictive values and accuracies (mean ± SD of all readers) for CMR were 70 ± 5, 65 ± 5, and 68 ± 5%, respectively, and for SPECT 73 ± 8, 60 ± 3, and 65 ± 3%, respectively (no significant differences).

Safety profile of the cardiac magnetic resonance examinations

In all 515 patients, who received the MR CM, no severe adverse events and no deaths occurred. *Table 3* shows the moderate and mild adverse events. There were no trends for clinically significant changes in vital signs or ECG changes following MR CM administration.

Discussion

The main results of the trial can be summarized as follows: (i) the primary endpoint of non-inferiority of CMR vs. SPECT for the detection of CAD was met for sensitivity, but not for specificity. (ii) No severe adverse effects occurred in the 515 patients who received the MR CM during pharmacological stress CMR.

Perfusion-cardiac magnetic resonance and single-photon emission computed tomography comparison

This large multicentre perfusion trial demonstrates a higher sensitivity of perfusion-CMR to detect perfusion deficits in CAD than

$P = 0.74$). When applying a single, i.e. binary threshold, to the CMR and SPECT images, the sensitivity scores were 0.67 and 0.59, respectively ($P = 0.024$, paired *t*-test), with the lower confidence level for the difference of +0.02, indicating superiority of CMR over SPECT for sensitivity (efficacy population: $n = 465$). The specificity score for CMR and SPECT was 0.61 and 0.72, respectively ($P = 0.038$, paired *t*-test) with a lower confidence level

SPECT. Thus, this trial confirms trends and results of earlier multi-centre[9] and single-centre studies,[11] respectively, and objectivates an important feature of CMR, i.e. to correct for both cardiac motion and respiratory motion during the few seconds of CM first-pass during hyperaemia. This approach preserves the nominally high spatial resolution of perfusion-CMR and thereby allows detecting small even subendocardial perfusion deficits. However, at a single threshold reading of the CMR and SPECT data, this level of sensitivity was associated with a specificity for CMR lower than that for SPECT. One may also speculate that this relatively low specificity of perfusion-CMR is related to the fact that perfusion was compared with the macroscopic coronary artery anatomy, which does not assess, for example, collateral flow on the microvascular level.

The MR-IMPACT II results are in accord with a previous smaller multicentre single-vendor perfusion-CMR study,[8] which yielded a sensitivity and specificity of 93% (95% CI of 77−99%) and 75% (95% CI of 48−92%), respectively, vs. MR-IMPACT II with 75% (69−80%) and 59% (52−65%), respectively. The 95% CIs for sensitivity are overlapping between the current MR-IMPACT II and the previous MR-IMPACT I (69−80 vs. 69−93%, respectively); however, there is a trend towards slightly lower sensitivity in the MR-IMPACT II vs. MR-IMPACT I with 85 vs. 75%, respectively. Also specificity showed a trend towards better performance in MR-IMPACT I with 67% vs. MR-IMPACT II with 59%, while the 95% CIs are overlapping (35−89 vs. 52−65%, respectively). This might be related to the larger number of participating sites in MR-IMPACT II, by which less experienced centres could have contributed to the database. Also, in MR-IMPACT II, a slightly lower CM dose was used than the most effective dose in MR-IMPACT I. The current MR-IMPACT II results are also in agreement with the large CE-MARC single-centre CMR study performed in 628 patients and published recently.[20] In this CE-MARC trial, a sensitivity of 80% on the receiver-operator characteristic (ROC) curve corresponds to a specificity of ∼70%.[20]

The SPECT results of the MR-IMPACT II with a sensitivity and specificity of 59 and 72%, respectively, are also in close match which those of MR-IMPACT I. In MR-IMPACT I, a sensitivity of 60% corresponded to a specificity of ∼75% on the ROC curve, which is also in line with the single-centre CE-MARC trial, where a SPECT sensitivity of 60% corresponded to a specificity of ∼70% on the ROC curve.[20] Nevertheless, one might have expected somewhat better results for either, SPECT and/or CMR for the detection of CAD in the MR-IMPACT II. The aim of this large MR-IMPACT II was to assess test performances in a realistic clinical environment across a substantial number of countries and not to repeat the results of a few leading high-performance centres. To this end, it was crucial to accept in the protocol a certain range of imaging parameters as long as they were in agreement with key features of the technique (such as spatial and temporal resolution for CMR and concordance with established guidelines for SPECT). Of note, gated SPECT was performed in 54% of the patients and attenuation correction algorithms were not applied (due to a lack of standardized criteria). These circumstances should be taken into account when considering the overall SPECT performance.

In addition, when assessing the current performances of both CMR and SPECT, it should be kept in mind that these results were obtained in a fully blinded fashion and, thus, are expected to potentially underestimate test performance in the clinical setting where imaging information is generally interpreted in the context of additional patient information.

Safety of perfusion-cardiac magnetic resonance examinations

The results of this MR-IMPACT II confirm the high safety profile reported in earlier CMR perfusion trials[8−10,12] as no severe adverse events occurred among the 515 patients in MR-IMPACT II. This finding is in good agreement with the safety profile observed in the European CMR registry with mild adverse reactions reported in 0.1% of 7285 stress CMR studies and where no severe reactions occurred.[21] Unlike SPECT, CMR does not expose patients to ionizing radiation.[22]

Limitations of the study

The area stenosis on CXA was used as the reference standard for the definition of CAD. Coronary artery disease was also present by definition in a small portion of 5.4% of the study patients with a history of infarction where the infarct-related artery was successfully treated by PCI, and thus, the treated vessel was no longer stenosed. Accordingly, this definition of CAD is primarily dependent on coronary anatomy and it is well known that the presence of perfusion deficits is not only dependent on stenoses of epicardial coronary arteries, but also on collateral flow and microcirculatory alterations. Nevertheless, this definition was deemed best as it is relatively easy to measure, is frequently used in such comparative studies, and often sets the basis for patient management in clinical routine. For future comparative studies, however, invasive perfusion assessment by fractional flow reserve measurements would be desirable. Importantly, an optimal patient management should always consider the patient prognosis. Perfusion techniques are very powerful prognostic tools, and in this regard, evidence is particularly well established for SPECT. The current study results apply for pharmacological stress testing only.

In this trial, patients with decompensated heart failure, after bypass surgery, and with relevant arrhythmias were excluded, and thus, the findings of this study cannot be applied to these patient groups. The frequency of CAD in this study was 48.8%, and therefore, the study results are applicable to patient populations with an intermediate CAD prevalence, but the trial results cannot be extrapolated to other populations with lower disease prevalence, e.g. to asymptomatic screening populations.

For this evaluation, 26 (5.6% of 465) CMR and 17 (3.7% of 465, $P = 0.21$ vs. CMR) SPECT studies were deemed non-evaluable by the MR and SPECT readers, respectively, which limit the applicability of the results to patients with evaluable studies.

Conclusions

This large international, multicentre, multivendor, prospective trial performed at 33 centres demonstrates a high performance of

perfusion-CMR to detect CAD. Sensitivity of perfusion-CMR was superior to perfusion SPECT, while specificity of perfusion-CMR was inferior in comparison to SPECT. In selected patients (no severe arrhythmias), CMR is a safe approach and an alternative to SPECT to detect perfusion abnormalities in CAD.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Funding

References

1. Heart disease and stroke statistics: update 2009. *Circulation* 2009;**119**:e21–e181.
2. Allender S, Scarborough P, Peto V, Rayner M, Leal J, Luengo-Fernandez R, Gray A. European Cardiovascular Disease Statistics—2008 Edition. *European Heart Network*, www.ehnheart.org/cdv-statistics.html: 1–112.
3. Iskander S, Iskandrian AE. Risk assessment using single-photon emission computed tomographic technetium-99m sestamibi imaging. *J Am Coll Cardiol* 1998; **32**:57–62.
4. Smith SJ, Feldman T, Hirshfeld JJ, Jacobs A, Kern M, King S III, Morrison D, O'Neill W, Schaff H, Whitlow P, Williams D. ACC/AHA/SCAI 2005 guidelines update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update 2001 Guidelines for Percutaneous Coronary Intervention). *Circulation* 2006;**113**:e166–e286.
5. Silber S, Albertsson P, Aviles F, Camici P, Colombo A, Hamm C, Jorgensen E, Marco J, Nordrehaug J-E, Ruzyllo W, Urban P, Stone G, Wijns W. Guidelines for percutaneous coronary interventions. *Eur Heart J* 2005;**26**:804–847.
6. Shaw LJ, Hachamovitch R, Berman D, Marwick T, Lauer M, Heller G, Iskandrian A, Kesler K, Travin M, Lewin H, Hendel R, Borges-Neto S, Miller D. The economic consequence of available diagnostic and prognostic strategies for the evaluation of stable angina patients: an observational assessment of the value of precatheterization ischemia. *J Am Coll Cardiol* 1999;**33**:661–669.
7. Schwitter J, Nanz D, Kneifel S, Bertschinger K, Buchi M, Knusel PR, Marincek B, Luscher TF, von Schulthess GK. Assessment of myocardial perfusion in coronary artery disease by magnetic resonance: a comparison with positron emission tomography and coronary angiography. *Circulation* 2001;**103**:2230–2235.
8. Giang T, Nanz D, Coulden R, Friedrich M, Graves M, Al-Saadi N, Lüscher T, von Schulthess G, Schwitter J. Detection of coronary artery disease by magnetic resonance myocardial perfusion imaging with various contrast medium doses: first European multicenter experience. *Eur Heart J* 2004;**25**:1657–1665.
9. Schwitter J, Wacker C, van Rossum A, Lombardi M, Al-Saadi N, Ahlstrom H, Dill T, Larsson HB, Flamm S, Marquardt M, Johansson L. MR-IMPACT: comparison of perfusion-cardiac magnetic resonance with single-photon emission computed tomography for the detection of coronary artery disease in a multicentre, multivendor, randomized trial. *Eur Heart J* 2008;**29**:480–489.
10. Plein S, Kozerke S, Suerder D, Luescher TF, Greenwood JP, Boesiger P, Schwitter J. High spatial resolution myocardial perfusion cardiac magnetic resonance for the detection of coronary artery disease. *Eur Heart J* 2008;**29**: 2148–2155.
11. Ishida N, Sakuma H, Motoyasu M, Okinaka T, Isaka N, Nakano T, Takeda K. Non-infarcted myocardium: correlation between dynamic first-pass contrast-enhanced myocardial MR imaging and quantitative coronary angiography. *Radiology* 2003; **229**:209–216.
12. Nagel E, Klein C, Paetsch I, Hettwer S, Schnackenburg B, Wegscheider K, Fleck E. Magnetic resonance perfusion measurements for the noninvasive detection of coronary artery disease. *Circulation* 2003;**108**:432–437.
13. Al-Saadi N, Nagel E, Gross M, Bornstedt A, Schnackenburg B, Klein C, Klimek W, Oswald H, Fleck E. Noninvasive detection of myocardial ischemia from perfusion reserve based on cardiovascular magnetic resonance. *Circulation* 2000;**101**: 1379–1383.
14. Jahnke C, Nagel E, Gebker R, Kokocinski T, Kelle S, Manka R, Fleck E, Paetsch I. Prognostic value of cardiac magnetic resonance stress tests: adenosine stress perfusion and dobutamine stress wall motion imaging. *Circulation* 2007;**115**: 1769–1776.
15. Bruder O, Schneider S, Nothnagel D, Dill T, Hombach V, Schulz-Menger J, Nagel E, Lombardi M, van Rossum A, Wagner A, Schwitter J, Senges J, Sabin G, Sechtem U, Mahrholdt H. EuroCMR (European Cardiovascular Magnetic Resonance) Registry. *J Am Coll Cardiol* 2009;**54**:1457–1466.
16. Wagner A, Mahrholdt H, Holly T, Kim RJ. Contrast-enhanced MRI and routine single photon emission computed tomography (SPECT) perfusion imaging for detection of subendocardial infarcts: an imaging study. *Lancet* 2003;**361**:374–379.
17. Hendel RC, Berman DS, Cullom SJ, Follansbee W, Heller GV, Kiat H, Groch MW, Mahmarian JJ. Multicenter clinical trial to evaluate the efficacy of correction for photon attenuation and scatter in SPECT myocardial perfusion imaging. *Circulation* 1999;**99**:2742–2749.
18. Imaging guidelines for nuclear cardiology procedures, part 1: American Society of Nuclear Cardiology. *J Nucl Cardiol* 1996;**3**:G1–G46.
19. Piaggio G, Elbourne D, Altman D, Pocock S, Evans S, for the CONSORT Group. Reporting of noninferiority and equivalence randomized trials. *J Am Med Assoc* 2006;**295**:1152–1160.
20. Greenwood J, Maredia N, Radjenovic A, Brown J, Nixon J, Farrin A, Dickinson C, Younger J, Ridgway J, Sculpher M, Ball S, Plein S. Clinical evaluation of magnetic resonance imaging in coronary heart disease: the CE MARC study. *Lancet* 2011; doi:10.1016/S0140–6736(11)61335–4.
21. Bruder O, Schneider S, Nothnagel D, Pilz G, Lombardi M, Sinha A, Wagner A, Dill T, Frank H, van Rossum A, Schwitter J, Nagel E, Senges J, Sabin G, Sechtem U, Mahrholdt H. Acute adverse reactions to gadolinium based contrast agents in cardiovascular MR. Multicenter experience with 17767 patients from the EuroCMR registry. *J Am Coll Cardiol Cardiovascular Imaging* 2011 (in press).
22. Gerber T, Carr J, Arai A, Dixon R, Ferrari V, Gomes A, Heller G, McCollough C, McNitt-Gray M, Mettler F, Mieres J, Morin R, Yester M. Ionizing radiation in cardiac imaging. *Circulation* 2009;**119**:1056–1065.