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

Juerg Schwitter1*, Christian M. Wacker2, Norbert Wilke3, Nidal Al-Saadi4, Ekkehart Sauer5, Kalman Huettle6, Stefan O. Schönberg7, Andreas Luchner8, Oliver Strohm9, Hakan Ahlstrom10, Thorsten Dill11, Nadja Hoebel12, and Tamas Simor13, for the MR-IMPACT Investigators

1University Hospital Lausanne, Rue de Bugnon 46, CH-1011 Lausanne, Switzerland; 2University Hospital Wuerzburg, Wuerzburg, Germany; 3University of Florida Health Science Center, Gainesville/Jacksonville, FL, USA; 4Franz-Volhard Clinic-Humboldt University, Berlin, Germany; 5Landstuhl Hospital, Landstuhl, Germany; 6Semmelweis University Hospital, Budapest, Hungary; 7LMU Munich, Grosshadern, Germany; 8University Hospital Regensburg, Regensburg, Germany; 9St Gertrauden Hospital, Berlin, Germany; 10Uppsala University Hospital, Uppsala, Sweden; 11Kerckhoff Clinics, Bad Nauheim, Germany; 12GE Healthcare Buchler GmbH & Co. KG, Munich, Germany; and 13Medical University of Science, Pecs, Hungary

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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 multcentre, 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

* Corresponding author. Tel: ++41 21 314 4015, Fax: ++41 21 314 4013, Email: jurg.schwitter@chuv.ch

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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 and Europe. Approximately one-third of coronary attacks results in death in the USA 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, and ischaemia imaging takes a central position in guidelines for the work-up of patients with known or suspected CAD. Scintigraphy is widely used for ischaemia detection and it has been shown to be cost-effective. In recent years, several studies documented a high diagnostic performance of perfusion-cardiac magnetic resonance (CMR) vs. conventional X-ray coronary angiography (CXA) and showed its prognostic value. This evidence triggered an increasing utilization of perfusion-CMR in clinical practice and its impact on clinical patient management was recently demonstrated.

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 ≥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.

Table 1  Inclusion and exclusion criteria

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<td>Acute MI (&lt;2 weeks prior to study enrolment)</td>
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<td>CXA and SPECT must be performed within 4 weeks before or after CMR irrespective of findings in any of the 3 tests</td>
<td>History of coronary artery bypass grafting</td>
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<td>No interventions on the coronary arteries in the time period between the 3 tests</td>
<td>Unstable angina pectoris</td>
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<td>Decompensated heart failure</td>
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<td>Severe arrhythmias considered to compromise quality of CMR imaging</td>
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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.

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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, 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 ≥50% diameter stenosis (i.e. ≥75% area stenosis) measured in two orthogonal planes as was used in previous studies present in ≥1 coronary artery of ≥2 mm diameter using a core laboratory (Cleveland Clinic Foundation, Cleveland, OH, USA). Thus, a ≥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 fulfill 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 ≤75% in the actual CXA) and without a history of MI do not fulfill 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 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 myocardium being bright. Additional criteria indicative for perfusion (myocardium being light grey) was classified together with normal myocardium at the cumulated CM dose of 0.15 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 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.

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**Single-photon emission computed tomography examination**

Stress and rest SPECT examinations were performed according to generally accepted guidelines on machines of different vendors (two- or three-head cameras) with 99mTc- or 201Tl-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 99mTc-tracer was strongly recommended, but ungated acquisitions and/or 201Tl-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. 201Tl-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

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**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. 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 (SensSPECT and SpecSPECT) 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 at 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-IMPACT1). 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: $H_0: Sens_{CMR} - Sens_{SPECT} < -0.1$). 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: $H_0: Sens_{CMR} - Sens_{SPECT} < -0.1$). In the case of superiority, i.e. if the lower bounds of the CIs for sensitivity or specificity fall above 0, superiority is reported. 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 $\geq 75\%$ 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.
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 −0.17, 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 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).

### 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...
multicentre single-vendor perfusion-CMR study, \( ^8 \) which yielded a lower than that for SPECT. One may also speculate that this relatively low specificity of perfusion-CMR is related to the fact that sensitivity was associated with a specificity for CMR at a single threshold reading of the CMR and SPECT data, this high spatial resolution of perfusion-CMR and thereby allows 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, \( ^9 \) 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 \( \sim 70\% \). \( ^{20} \)

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 \( \sim 75\% \) 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 \( \sim 70\% \) on the ROC curve. \( ^{20} \) Nevertheless, one might have expected somewhat better results for either, SPECT and/or CMR for the detection of CAD. 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.

**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.

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**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**

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**Conflict of interest:** J.S. and N.A.-S. served as consultants for GE Healthcare (formerly Amersham Health) and received honoraria. A.L. received consultancy honorarium from GE Healthcare, and O.S. is a consultant of Circle (a software company not involved in data analysis for this trial). N.H. was an employee of GE Healthcare and was responsible for the statistical analyses (current employer: INC Research, Munich, Germany).

**References**