Cardiac magnetic resonance imaging in coronary heart disease[1]

EXTRACT

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This report was prepared in collaboration with an external expert.

The responsibility for the contents of the report lies solely with IQWiG.

According to §139b (3) No. 2 of Social Code Book (SGB) V, Statutory Health Insurance, external experts who are involved in the Institute's research commissions must disclose "all connections to interest groups and contract organizations, particularly in the pharmaceutical and medical devices industries, including details on the type and amount of any remuneration received". The Institute received the completed Form for disclosure of potential conflicts of interest from each external expert. The information provided was reviewed by a Committee of the Institute specifically established to assess conflicts of interests. The information on conflicts of interest provided by the external experts and external reviewers is presented in Chapter A8 of the full report. No conflicts of interest were detected that could endanger professional independence with regard to the work on the present commission.

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IQWiG thanks the external expert for his collaboration in the project.

Patient and family involvement

Patients or family members were consulted during the preparation of the report.

One person participated in the discussion.

Its aim was to obtain information on the following topics: experiences, wishes and concerns regarding the diagnostic procedures, impact of the disease on life and everyday life, and coping with the disease.

IQWiG would like to thank the participant for taking part in the discussion. This person was not involved in the actual writing of the report.

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Key statement

Research question

The aim of this report is to

- assess the benefit of diagnostics using cardiac magnetic resonance imaging as part of a diagnostic strategy, compared with a diagnostic strategy without cardiac magnetic resonance imaging, in terms of patient-relevant outcomes. These diagnostics should be used as further diagnostics in patients who, following basic diagnostics, are suspected to have chronic coronary heart disease or progression of chronic coronary heart disease, in either case with moderate pretest probability (15% to 85%), and for whom a functional diagnostic technique is indicated.

Conclusion

In this assessment, as a first step, cardiac magnetic resonance imaging was investigated in comparison with other functional non-invasive diagnostic procedures (single photon emission computed tomography, stress echocardiography or exercise electrocardiography) on the basis of studies on the diagnostic-therapeutic treatment chain. One randomized controlled trial could be used for this purpose, namely on the comparison of cardiac magnetic resonance imaging with single photon emission computed tomography.

The study provided usable data for the outcomes all-cause mortality, cardiovascular mortality, unnecessary invasive diagnostics and health-related quality of life. For none of these patient-relevant outcomes was there an effect in favour or to the disadvantage of cardiac magnetic resonance imaging compared with single photon emission computed tomography, but the data situation was mostly insufficient due to the rarity of the events that occurred in these outcomes. Based on the randomized controlled trial, it was therefore not possible to derive a hint of (greater) benefit or harm of cardiac magnetic resonance imaging compared with single photon emission computed tomography.

Since no benefit conclusion could be derived for the diagnostic-therapeutic chain for the aforementioned comparison, in a 2nd step, cardiac magnetic resonance imaging was compared with single photon emission computed tomography on the basis of studies on diagnostic accuracy. For this comparison, 6 studies with usable results on diagnostic accuracy were used for the assessment. Studies on diagnostic accuracy comparing cardiac magnetic resonance imaging with stress echocardiography or exercise electrocardiography were not included because these 2 alternative functional diagnostic techniques were considered to be of less clinical importance.

An analysis of the results of test quality studies comparing cardiac magnetic resonance imaging with single photon emission computed tomography in terms of sensitivity and specificity resulted in at least comparable diagnostic accuracy. Cardiac magnetic resonance imaging also has the inherent advantage over single photon emission computed tomography that it is conducted without exposing patients to radiation. Overall, there is a hint of greater benefit of cardiac magnetic resonance imaging in comparison with single photon emission computed tomography.

Cardiac magnetic resonance imaging is therefore a suitable non-invasive diagnostic technique for patients with suspected coronary heart disease or suspected progression of known coronary heart disease for whom a functional diagnostic technique is indicated.

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List of abbreviations

Abbreviation	Meaning
ACS	acute coronary syndrome
AHRQ	Agency for Healthcare Research and Quality
BMI	body mass index
CABG	coronary artery bypass grafting
CCS	chronic coronary syndrome
CCTA	coronary computed tomography angiography
CHD	coronary heart disease
CI	confidence interval
CMRA	coronary magnetic resonance angiography
DGK	Deutsche Gesellschaft für Kardiologie (German Cardiac Society)
ECG	electrocardiogram
ESC	European Society of Cardiology
FFR	fractional flow reserve
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HTA	health technology assessment
ICA	invasive coronary angiography
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LGE	late gadolinium enhancement
MRI	magnetic resonance imaging
NICE	National Institute for Health and Care Excellence
NVL	Nationale VersorgungsLeitlinie (National Care Guideline)
PCI	percutaneous coronary intervention
PTP	pretest probability
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SPECT	single photon emission computed tomography
SR	systematic review

1 Background

Cardiac magnetic resonance imaging (MRI) is a multiparametric, non-invasive imaging technique that does not involve ionizing radiation [1]. It uses strong magnetic fields and electromagnetic impulses to generate cross-sectional images, which are primarily analysed both visually and with regard to pump function and volumes using appropriate post-processing software [2]. Cardiac MRI used to diagnose coronary heart disease (CHD) is based on 3 essential components, all of which are acquired during a single MRI examination: Firstly, there is myocardial *ischemia testing* (so-called stress MRI as a functional diagnostic technique), where primarily vasodilators are used to induce hyperaemia and coronary dilatation. Following the administration of a gadolinium-containing contrast agent, the acquisition of dynamic perfusion sequences enables the detection of perfusion defects in this stress state, which indicate stress-induced myocardial ischaemia or a narrowing of the coronary arteries in the context of CHD. An additional recording of perfusion at rest can help identify any artefacts in the perfusion test. The inotropic drug dobutamine can be used as an alternative drug, whereby myocardial wall motion abnormalities under stress indicate CHD [3-5]. Secondly, after administration of the gadolinium-containing contrast agent and using the late gadolinium enhancement (LGE) technique, cardiac MRI allows the tissue of the myocardium to be characterized and, in the context of CHD, its *vitality* to be assessed and a myocardial infarction to be detected. Thirdly, MRI, without the use of additional drugs or contrast agents, allows the assessment of cardiac *morphology* (e.g. volumes, myocardial mass, heart valves) and *function* (e.g. left and right ventricular ejection fraction) as well as the detection of *wall motion abnormalities* at rest using cine sequences. Depending on the medical indication, cardiac MRI therefore uses drugs to increase cardiac activity, or contrast agents [1,4,6,7].

CHD is a form of arteriosclerosis affecting the walls of the coronary arteries or coronary vessels. It involves atherosclerosis where various types of deposits build up in the vessel walls of the coronary arteries [8]. As the disease progresses, stenosis of the coronary arteries leads to an imbalance between oxygen demand and supply in the heart muscle. People with CHD have an increased risk of morbidity and mortality [3].

A distinction is made between a stable, chronic form of CHD, also known as chronic CHD or chronic coronary syndrome (CCS), and acute coronary syndrome (ACS). The spectrum of ACS encompasses unstable angina pectoris, non-ST-elevation myocardial infarction and ST-elevation myocardial infarction [9]. The subject of this assessment is CCS. CCS is the most frequently cited single cause of death in Germany [10,11].

Early-stage chronic CHD does not yet involve stenosis and is therefore asymptomatic. As the disease progresses, there is increasing stenosis of the coronary arteries, which initially leads to perfusion disorders or an increased reduction in blood flow (ischaemia) to the heart muscle.

This is where stress MRI (and also single photon emission computed tomography [SPECT], see below) comes in for the diagnosis of CHD. In the course of the so-called ischaemic cascade, wall motion abnormalities of the myocardium occur as the disease progresses. The typical leading symptom of stenotic CHD is angina pectoris, a painful feeling of tightness in the chest, during physical exertion. Angina pectoris is triggered by the increased oxygen demand of the heart muscle during exertion, which can no longer be adequately met due to the stenosis. In addition, patients often complain of dyspnoea, which is also a leading symptom of CCS [8]. The symptoms initially only occur during intense physical exertion, then during mild exertion such as normal walking or getting dressed, and finally – in severe cases – even during minor physical exertion or at rest [3]. According to the European Society of Cardiology (ESC) guideline [8], the angina pectoris symptoms of CCS typically occur during exertion, are of short duration and subside within a few minutes after interrupting the exertion triggering the symptoms and/or administration of nitroglycerin [8]. This allows CCS and ACS to be distinguished from one another [3,8].

Diagnostics

When a person presents with symptoms of angina pectoris, the suspected cause is CHD or progression of already known CHD. This is followed by basic diagnostics, including medical history, laboratory tests and physical examination. A resting electrocardiogram (ECG) and resting echocardiography are also conducted. If ACS and other differential diagnoses are ruled out on the basis of the basic diagnostics, stable stenotic CHD is the most likely tentative diagnosis. Depending on the pretest probability (PTP), which is determined based on age, sex and symptoms [12], various non-invasive and invasive imaging procedures are available for further diagnosis [3].

The choice of procedure depends on the PTP determined for stenotic CHD. Other factors that influence the decision on which procedure to use include the suitability of the patient for a particular procedure (e.g. non-eligibility due to existing intolerances to certain drugs), the risks (e.g. radiation exposure) and the equipment and expertise available on site [3].

If the PTP is < 15%, causes for the symptoms other than CHD should be sought; if the PTP is > 85%, stenotic CHD should be presumed to be the cause of the symptoms without further diagnostics, and planning of treatment should be started [3]. In case of moderate PTP of 15% to 85%, the following alternative non-invasive procedures are an option according to the German National Care Guideline (NVL) on chronic CHD:

- As functional procedures
  - Exercise ECG (only very limited recommendation for low-moderate PTP),
  - Stress echocardiography,

  - SPECT myocardial scintigraphy (hereinafter referred to as ‘cardiac SPECT’) and
  - Cardiac MRI and
- As a morphological procedure, coronary computed tomography angiography (CCTA).

The CCTA is particularly recommended for low-moderate PTP of 15% to 50%. With the exception of MRI, all alternative non-invasive diagnostic techniques mentioned here are covered by the German statutory health insurance [3,13].

According to the NVL, invasive coronary angiography (ICA) with or without measurement of fractional flow reserve (FFR) should only be used in certain cases with a high PTP [3,12]. As an invasive procedure, it carries risks of complications such as post-procedural bleeding or vascular injury, and patients are also exposed to a relevant radiation dose [12]. ICA is therefore only recommended under certain conditions. ICA is generally regarded as the reference standard for determining the diagnostic accuracy of the various non-invasive techniques [3].

Cardiac MRI is a non-invasive diagnostic technique. Furthermore, compared with SPECT, it has the inherent advantage of being conducted without any radiation exposure for patients. It is used to diagnose patients who, following basic diagnostics, are suspected to have chronic CHD or progression of chronic CHD, in either case with moderate PTP (15% to 85%), and for whom a functional diagnostic technique is indicated. Cardiac MRI is also becoming increasingly important in the clinical care context [14,15].

2 Research question

The aim of this report is to

- assess the benefit of diagnostics using cardiac magnetic resonance imaging as part of a diagnostic strategy, compared with a diagnostic strategy without cardiac magnetic resonance imaging, in terms of patient-relevant outcomes. These diagnostics should be used as further diagnostics in patients who, following basic diagnostics, are suspected to have chronic coronary heart disease or progression of chronic coronary heart disease, in either case with moderate pretest probability (15% to 85%), and for whom a functional diagnostic technique is indicated.

3 Methods

3.1 Study selection

The following hierarchical process was specified for the assessment:

As a first step, cardiac MRI was investigated in comparison with other functional non-invasive diagnostic procedures (SPECT, stress echocardiography or exercise ECG) on the basis of studies on the diagnostic-therapeutic treatment chain. If a conclusion on the benefit of cardiac MRI compared with other functional non-invasive procedures could already be drawn for this type of study (randomized controlled trials [RCTs]), the assessment ended there.

If no conclusion on benefit was possible on the basis of the studies on the diagnostic-therapeutic chain, in a 2nd step studies on diagnostic accuracy were used that compared cardiac MRI with other functional non-invasive diagnostic techniques.

3.2 Target population

The target population of the benefit assessment consisted of patients who, following basic diagnostics, are suspected to have chronic CHD or progression of chronic CHD, in either case with moderate PTP (15% to 85%), and for whom a functional diagnostic technique is indicated.

3.3 Information retrieval

In parallel to the preparation of the report protocol, a search for systematic reviews was conducted in the MEDLINE database (which includes the Cochrane Database of Systematic Reviews) and the HTA database as well as on the websites of the National Institute for Health and Care Excellence (NICE) and the Agency for Healthcare Research and Quality (AHRQ).

It was ascertained whether at least one high-quality, current systematic review existed whose information retrieval could be used as a suitable basis (hereinafter: basic SR).

If that was the case, a 2nd step followed, in which a supplementary search was conducted for studies for the time period not covered by the basic SR(s). Otherwise, the search for studies was carried out without time restriction.

The systematic literature search for studies on the diagnostic-therapeutic chain was conducted in the following databases: MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials.

The systematic literature search for studies on diagnostic accuracy was conducted in the MEDLINE and Embase databases.

In addition, the following information sources and search techniques were taken into account: trial registries, manufacturer queries, author queries, documents transmitted by the Federal Joint Committee (G-BA), and the screening of reference lists and documents made available from the hearing procedure.

For this report, 2 separate bibliographic searches were conducted in accordance with the hierarchical approach. As a first step, a bibliographic search for studies on the diagnostic-therapeutic chain was conducted and relevant studies were selected.

If necessary (as described in Section 3.1), a further bibliographical search for studies on diagnostic accuracy was then carried out.

3.4 Studies on the diagnostic-therapeutic chain

In studies on the diagnostic-therapeutic chain, the experimental intervention was a diagnostic strategy using cardiac MRI. The comparator intervention was a diagnostic strategy using other functional non-invasive diagnostic techniques (without the use of cardiac MRI).

The following patient-relevant outcomes were taken into account in the assessment:

- Mortality
- Morbidity (e.g. nonfatal myocardial infarction, angina pectoris, unstable angina pectoris or health status)
- Health-related quality of life
- Side effects

Radiation exposure was considered as a further outcome.

Subjective outcomes (e.g. health-related quality of life) were taken into account only if they had been recorded using valid measurement instruments (e.g. validated scales). Only RCTs were included.

There were no restrictions regarding the study duration.

Study selection and evaluation of results

The selection of relevant studies was performed by 2 people independently of each other. Any discrepancies were resolved by discussion between them. Data were extracted into standardized tables.

To assess the qualitative certainty of results, risk of bias criteria across outcomes and outcome-specific risk of bias criteria were assessed, and the risk of bias was rated as low or high in each case. The results of the individual studies were described, organized by outcomes.

For each outcome, a conclusion was drawn regarding the evidence base for (greater) benefit and (greater) harm, with 4 levels of certainty of conclusions: There was either proof (highest certainty of conclusions), indication (moderate certainty of conclusions), hint (lowest certainty of conclusions), or none of those 3 situations. The latter was the case if either no data were available or the available data did not allow any of the other 3 conclusions to be drawn. In this case, the conclusion "There is no hint of (greater) benefit or (greater) harm" was drawn.

Subsequently, an assessment of benefit and harm was carried out across outcomes.

3.5 Studies on diagnostic accuracy

In the event that no RCT on the diagnostic-therapeutic chain was identified or that no conclusion on benefit could be drawn from the RCTs identified, the benefit assessment was to be conducted on the basis of studies on diagnostic accuracy. In this case, it was sufficient if the cardiac MRI showed at least a comparable diagnostic accuracy compared with other functional non-invasive diagnostic techniques.

Included were studies on diagnostic accuracy in which an alternative, non-invasive functional diagnostic technique was conducted as a further index test in addition to cardiac MRI and the reference standard (ICA or ICA plus measurement of FFR). All studies in which only one index test was compared with the reference test were therefore excluded.

Only SPECT was investigated as an alternative, functional non-invasive technique, as the other diagnostic techniques – stress echocardiography and exercise ECG – are considered to be of secondary importance due to their low clinical significance:

- Stress echocardiography is widely applicable as an alternative functional diagnostic procedure in CHD diagnostics [16,17] and, like cardiac MRI, is radiation-free. In stress echocardiography, cardiac stress can be induced by either pharmacological or physical stressors (e.g. cycle ergometers). An additional contrast agent can be administered [18]. According to the algorithm provided in the NVL, stress echocardiography is also recommended at the same points in the diagnostic pathway as cardiac MRI [3]. It is based on the detection of wall motion abnormalities, which become apparent due to a narrowing of the coronary arteries under stress. However, stress echocardiography is decreasingly being used in everyday clinical practice [19-22]. One reason for the declining use of stress echocardiography is its limitations, e.g. the fact that adequate stress levels cannot be achieved or its limitations in obese patients. [8,23]. Maximum stress can be achieved with medication by administering dobutamine and, if necessary, atropine. However, this carries a higher potential for side effects than the vasodilators used in SPECT and cardiac MRI, with the corresponding risk [24,25]. Furthermore, stress echocardiography can detect larger myocardial infarction scars only indirectly based on wall motion abnormalities, whereas SPECT and MRI allow the simultaneous assessment

of cardiac perfusion, function and scar imaging in a single test, with MRI already considered the reference standard for the latter 2 aspects in some cases [26,27]. Thus, a diagnosis using stress echocardiography occurs later in the ischaemic cascade than cardiac MRI or SPECT. Furthermore, it is examiner-dependent, which makes its results difficult to reproduce [8]. Due to these limitations and disadvantages, stress echocardiography now plays a minor and declining role in everyday clinical care.

- According to the NVL, the exercise ECG as a non-invasive functional diagnostic technique has 'limited accuracy' and 'in particular limited sensitivity' and should therefore only 'potentially' be used in a subpopulation of the research question with a low-moderate PTP of 15% to 30% [3]. (This concurs with recommendations in the ESC guideline [8]). The exercise ECG therefore only plays a very subordinate role in clinical care.

Study selection and evaluation of results

The selection of relevant studies was performed by 2 people independently of each other. Any discrepancies were resolved by discussion between them.

Data were extracted into standardized tables. In addition to the assessment of the qualitative certainty of results based on the risk of bias (low or high risk of bias), an assessment was made of the transferability of the results (minor or major concerns).

The diagnostic accuracy of the studies was investigated on the basis of the criteria of sensitivity and specificity. The results of the primary studies were pooled meta-analytically in a bivariate model, with separate meta-analyses for each index test. These pooled results on the sensitivity and specificity of the various index tests were then compared with one another.

3.6 Summarizing assessment

To derive a conclusion on the benefit, an overview was conducted of the benefit conclusions on the outcomes and of the benefit-harm considerations across both study types.

4 Results

4.1 Results of the information retrieval

No systematic reviews were taken into account as basic SRs for the purpose of identifying primary studies.

With regard to studies on the diagnostic-therapeutic chain, the information retrieval yielded only one study (RCT) relevant to the research question, namely on the comparison of cardiac MRI with SPECT.

One further planned RCT – also comparing cardiac MRI with SPECT – was identified for this study type. No additional ongoing, discontinued or completed studies without reported results were identified.

The search strategies for bibliographic databases and trial registries can be found in the appendix. The last search was conducted on 5 November 2024.

With regard to studies on the diagnostic accuracy, the information retrieval yielded 6 studies relevant to the research question that had usable data on the comparison of cardiac MRI with SPECT.

No additional planed, ongoing, discontinued or completed studies without reported results on the comparison of cardiac MRI with SPECT were identified.

The search strategies for bibliographic databases and trial registries can be found in the appendix. The last search was conducted on 16 January 2025.

Table 1: Study pool of the benefit assessment

Study	**Available documents**		
	Full publication (in scientific journals)	**Registry entry / results report from trial registries**	**Other documents**
RCTs			
CE-MARC 2	Yes [28-32]	Yes [33] / yes	No
Studies on diagnostic accuracy			
Arai 2023	Yes [34,35]	Yes [36] / yes	No
Becker 2015	Yes [37]	Yes [38]/ no	No
CE-MARC	Yes [39-44]	Yes [45] / no	No
Dan-NICAD	Yes [46-48]	Yes [49] / no	No
Driessen 2022	Yes [50]	No/no	No
MR-IMPACT II	Yes [51,52]	Yes [53] / no	No
RCT: randomized controlled trial			

4.2 Results regarding randomized controlled trials on the diagnostic-therapeutic chain of cardiac MRI compared with other functional non-invasive diagnostic techniques

4.2.1 Characteristics of the randomized controlled trial on the diagnostic-therapeutic chain included in the assessment

One RCT was identified for the comparison of MRI-based diagnostics and SPECT-based diagnostics.

The CE-MARC 2 study [30] is a 3-arm multicentre RCT conducted in the United Kingdom between November 2012 and March 2015. The study included 1202 patients with suspected CHD and a PTP between 10 and 90%. In the study, 481 patients were randomized to MRI-directed and 481 patients to SPECT-directed care. The remaining 240 patients were randomized a diagnostic procedure based on a NICE guideline; this comparison was not relevant to this assessment and is not presented below.

Patients in the MRI study arm underwent both stress and rest perfusion imaging on a 3.0 Tesla scanner. Adenosine was used as a vasodilator. The MRI scans were evaluated by assessors with at least 5 years of experience in the field of cardiology or radiology. In the SPECT study arm, the images were acquired on either a dual headed gamma camera or cadmium zinc telluride camera, both under stress and at rest, using a 1- or 2-day protocol (no more than 5 days apart). The stressors used for stress perfusion imaging were physical exercise, regadenoson or adenosine. The SPECT scans were also evaluated by assessors with at least 5 years of experience and a qualification in the field of cardiology or radiology.

The study included patients over 30 years of age who had clinically stable symptoms of angina pectoris requiring further assessment, a score-based PTP for CHD between 10% and 90%, and who were suitable for revascularization if required. The PTP was recorded using the Pryor score and averaged 49.9% (MRI arm) and 48.6% (SPECT arm). Exclusion criteria included normal SPECT or CTCA results within the previous 2 years, previous revascularization, previous myocardial infarction, being clinically unstable, markedly reduced renal function, MRI contraindications or known allergy to a contrast agent. The primary outcome of the study was unnecessary ICA performed within 1 year due to a positive MRI or SPECT finding. ICA was considered unnecessary if the FFR was > 0.8 (measured in all visual stenoses between ≥ 40% and ≤ 90% in coronary arteries with a diameter ≥ 2.5 mm) or the coronaries did not have a high-grade stenosis (high-grade stenosis was defined as quantitative stenosis ≥ 70% in one orthogonal view or ≥ 50% in 2 views for vessels with a diameter ≥ 2.5 mm). Other outcomes were all-cause mortality, cardiovascular mortality, nonfatal myocardial infarction, health-related quality of life and others. The group allocation was not blinded to the patients or the treating physicians.

4.2.2 Overview of the patient-relevant outcomes of the randomized controlled trial on the diagnostic-therapeutic chain

Data on patient-relevant outcomes were extracted from the CE-MARC 2 study. Table 2 presents an overview of the data available on patient-relevant outcomes from the included study. Although the study recorded data on the outcome nonfatal myocardial infarction and on revascularization by means of percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), these data were not usable for the benefit assessment. The outcome MACE was not included as a patient-relevant outcome in the benefit assessment due to the varying clinical significance of its components (cardiovascular mortality, myocardial infarction, coronary revascularization, arrhythmia, cardiac failure, stroke or transient ischaemic attack).

Table 2: Matrix of patient-relevant outcomes

Study	Outcomes						
	Mortality		Morbidity			QoL	Side effects
	All-cause mortality	Cardiovascular mortality	Nonfatal myocardial infarction	Unnecessary invasive diagnostics	Revascularization	Health-related quality of life (SF-12)	(Serious) adverse events
CE-MARC 2	●	●	○[a]	●	○[a]	●	○[a]

●: Data were reported and usable.
○: Data were reported but unusable for the benefit assessment.
a. The reported data refer to the number of events and not to the number of patients with event.
QoL: health-related quality of life

4.2.3 Assessment of the risk of bias of the results of the randomized controlled trial on the diagnostic-therapeutic chain

The risk of bias across outcomes was rated as high for the CE-MARC 2 study. This was because the treating staff were allowed to determine further procedures or treatment deviating from the examination results, and these protocol violations occurred with varying frequency in the study arms: in the cardiac MRI group in approximately 14% of patients and in the SPECT group in approximately 24% of patients. In addition, neither the patients nor the treating staff were blinded to the diagnostic techniques, with the exception of the staff conducting the ICA.

Due to the high risk of bias already at study level, no further assessment was made at outcome level.

4.2.4 Results on the patient-relevant outcomes of the randomized controlled trial on the diagnostic-therapeutic chain

4.2.4.1 Results on all-cause mortality

The results for all-cause mortality showed no statistically significant difference for the comparison of cardiac MRI and SPECT (see Table 13 of the full benefit assessment). However, the data situation was insufficient. The effect estimation was imprecise, as the 95% confidence interval for the relative effect covered both 0.5 and 2 and thus neither a halving nor a doubling of the effect could be ruled out. There is therefore no hint of (greater) benefit or harm of cardiac MRI compared with SPECT for the outcome all-cause mortality.

4.2.4.2 Results on cardiovascular mortality

The results for cardiovascular mortality showed no statistically significant difference for the comparison of cardiac MRI and SPECT (see Table 14 of the full benefit assessment). However, the data situation was insufficient. The effect estimation was imprecise, as the 95% confidence interval for the relative effect covered both 0.5 and 2 and thus neither a halving nor a doubling of the effect could be ruled out. There is therefore no hint of (greater) benefit or harm of cardiac MRI compared with SPECT for the outcome cardiovascular mortality.

4.2.4.3 Results on unnecessary invasive diagnostics

Unnecessary invasive diagnostics at the analysis date after 1 year was the primary study outcome of CE-MARC 2. The results showed no statistically significant difference between the number of patients with unnecessary invasive diagnostics for cardiac MRI compared with SPECT (see Table 15 of the full benefit assessment). There is therefore no hint of (greater) benefit or harm of cardiac MRI compared with SPECT for the outcome unnecessary invasive diagnostics.

4.2.4.4 Results on health-related quality of life

Data on health-related quality of life was collected using the SF-12v2 instrument and presented at the analysis dates after 1 and 3 years (see Table 16 of the full benefit assessment). No p-values were reported for the results on health-related quality of life in the study and no conclusions on significance were drawn. However, as the confidence intervals for the mean differences covered 0 for all comparisons shown, it was assumed that there were no statistically significant differences for any of the comparisons. There is therefore no hint of (greater) benefit or harm of cardiac MRI compared with SPECT for the outcome health-related quality of life.

4.2.5 Overall assessment of the results of the randomized controlled trial on the diagnostic-therapeutic chain

Evidence map

Due to the clear evidence base, a table showing the evidence map in relation to patient-relevant outcomes is not provided. There was no hint of (greater) benefit or harm of cardiac MRI for the outcomes all-cause mortality, cardiovascular mortality and unnecessary invasive diagnostics. In addition, the effect estimations were imprecise, as neither a halving nor a doubling of the effect could be ruled out. For health-related quality of life, no hint of (greater) benefit or harm of cardiac MRI could be derived from the available data either. Although data on nonfatal myocardial infarction were reported, they were not usable for the benefit assessment, as the reported data related to the number of events and not the number of patients with event. No usable data was available on other patient-relevant outcomes, as the results were not analysed at patient level.

Assessment of the volume of unpublished data

A search of trial registries did not identify any ongoing RCTs on the diagnostic-therapeutic chain. Furthermore, no studies of unclear status, no discontinued studies, and no completed studies without reported results were identified for this study type.

The bibliographic literature search identified a 2022 design publication on the Japanese RCT AQUAMARINE-CKD [54], whose research question only concurred with the research question of this report to a very limited extent: In AQUAMARINE-CKD, cardiac MRI was used as a morphological procedure to visualize the coronary arteries and detect vulnerable plaques, and not for diagnosing ischaemia. According to the design publication, it was planned to include a total of 524 patients with chronic kidney disease and suspected CHD. Patients were to be randomized to 2 study arms: Participants in one study arm were to receive a T1-weighted sequence of the coronaries (detection of vulnerable plaques) and coronary magnetic resonance angiography (CMRA, visualization of the coronaries), each without a contrast agent, while participants in the other study arm were to receive an examination using SPECT. Since the planned follow-up period was 3 years, it can be assumed that even if recruitment has already been completed, the study cannot yet have been concluded. The lack of published data at the present time therefore does not suggest a publication bias.

Weighing up the benefits and harms

No effect in favour or to the disadvantage of cardiac MRI compared with SPECT was shown for any of the outcomes presented. Due to the rarity of the events that occurred in the binary outcomes (such as all-cause mortality), the estimations of the effects were very imprecise and did not allow any conclusions to be drawn about (greater) benefit or harm. Based on the

included study CE-MARC 2 on the diagnostic-therapeutic chain, no hint of a (greater) benefit or harm of cardiac MRI compared with SPECT can therefore be derived.

In the following, studies on diagnostic accuracy were therefore used.

4.3 Results regarding studies on the diagnostic accuracy of cardiac MRI compared with SPECT

4.3.1 Characteristics of the studies on diagnostic accuracy included in the assessment

Six studies with usable results on the diagnostic accuracy of cardiac MRI compared with SPECT as an additional index test, and with ICA or ICA with FFR measurement (ICA/FFR) as the reference standard were identified [34,37,40,46,50,52] that covered the research question addressed in this report. Two of the studies had an RCT design (CE-MARC [40], Dan-NICAD [46]); in the CE-MARC study, however, all patients still underwent all 3 tests and were only randomized in terms of the order in which the cardiac MRI and SPECT were conducted. The other 4 studies (Arai 2023 [35], Becker 2015 [37], Driessen 2022 [50], MR-IMPACT II [52]) were prospective cohort studies. Between 189 patients (Driessen 2022) and 752 patients (CE-MARC) were included in the studies. Four of the 6 studies were conducted exclusively in a European country (Becker 2015 in Germany, CE-MARC in England, Dan-NICAD in Denmark and Driessen 2022 in the Netherlands), and 2 studies were multicentre: MR-IMPACT II was conducted in Europe and the United States, and Arai 2023 in 24 locations, mainly in centres in the United States, but also in Canada, Australia and Singapore.

The studies Arai 2023, Becker 2015, CE-MARC and MR-IMPACT II used ICA as the reference standard; Dan-NICAD and Driessen 2022 used ICA with FFR measurement as the reference standard.

The reference standard (ICA or ICA/FFR) was used to determine whether or not a patient had clinically significant CHD. Based on this diagnosis, it was determined whether the test results of cardiac MRI or SPECT were correct (i.e. identical to that of the ICA or ICA/FFR). To determine the presence of clinically significant CHD using ICA or ICA/FFR, cut-off values for a positive assessment of the reference test were defined in advance in each study. For the ICA/FFR reference test in the Dan-NICAD and Driessen 2022 studies, for example, a value of FFR ≤ 0.8 was specified as the cut-off value for a test-positive result (see also Table 18 of the full benefit assessment for information on the cut-off values). A test-positive result meant that the patient had clinically significant CHD. In 2022, Driessen also investigated the diagnostic accuracy of cardiac MRI and SPECT for a cut-off value of FFR < 0.75 as a sensitivity analysis.

The studies also differed with regard to the cut-off values for the ICA: In Becker 2015 and MR-IMPACT II, the test result was considered positive for the ICA at a value of ≥ 50% for the degree of stenosis (degree of vascular narrowing). In the CE-MARC study, clinically significant CHD

was defined as ≥ 70% stenosis of ≥ 1 first-order coronary artery measuring ≥ 2 mm in diameter or left main stem stenosis ≥ 50%. In Dan-NICAD, in addition to the above-mentioned FFR threshold values, the test result was also considered positive if there was > 90% stenosis, or a quantitative stenosis of ≥ 50% if FFR measurement was not technically possible. In Driessen 2022, an ICA test result was considered positive if there was a ≥ 90% stenosis in the absence of an FFR measurement, and negative if the diameter of the stenosis was less than 30%. Arai 2023 used ICA and CCTA as possible reference tests, but clinically significant CHD could only be diagnosed by ICA, defined as ≥ 70% stenosis in the ICA. CCTA was only used to exclude CHD: If the CCTA was normal (no calcifications and stenoses < 25%) a clinically significant CHD was excluded and no further ICA was not necessary. However, in the case of abnormal findings in the CCTA, a subsequent ICA was necessary for the final diagnosis of clinically significant CHD.

4.3.2 Characteristics of the study populations in the studies on diagnostic accuracy

The 6 studies differed in terms of key inclusion criteria (see also Table 19 of the full benefit assessment) and therefore also showed a heterogeneous picture in terms of patient characteristics. There were also differences between the studies in terms of CHD prevalence (prevalence calculations conducted by the Institute based on the 2x2 table data: Arai 2023: 25%; Becker 2015: 37%; CE-MARC 39%; Dan-NICAD: 40%; Driessen 2022: 56%; MR-IMPACT II: 56%). It should be noted that this was (presumably) also due to the different cut-off values of the individual studies.

One of the 6 studies only included postmenopausal women (Becker 2015). Although both women and men were to be included in the other 5 studies, the proportion of men predominated in all of them. In Driessen 2022, the proportion of men was as high as 81% (see Table 20 of the full benefit assessment).

With regard to previous CHD, no known CHD was allowed in one study (Becker 2015). In 3 other studies, patients were excluded if they had previously undergone revascularization by means of PCI, CABG or percutaneous transluminal angioplasty (Dan-NICAD) or by means of CABG (CE-MARC, MR-IMPACT II). In 2 studies (Arai 2023, MR-IMPACT II), patients with a history of acute myocardial infarction were excluded. In contrast, one study (Driessen 2022) included only patients who with a history of myocardial infarction and/or PCI.

In one study, PTP was an inclusion criterion: Only patients with a low intermediate PTP were included in Dan-NICAD. In addition, a CCTA to exclude CHD was conducted in Dan-NICAD before randomization to MRI or SPECT. In this study, only patients who had tested positive in the CCTA (> 50% stenosis or a non-evaluable coronary artery segment) underwent a further non-invasive diagnostic procedure.

4.3.3 Overview of the outcomes investigated in the studies on diagnostic accuracy

Data from the 6 included studies on diagnostic accuracy [34,37,40,46,50,52] were used for the benefit assessment. Sensitivity and specificity were assessed as a measure of diagnostic accuracy.

4.3.4 Assessment of the risk of bias of the results from studies on diagnostic accuracy

In summary, a high risk of bias was determined for 5 of the 6 studies on diagnostic accuracy analysed (see Table 21 of the full dossier assessment). This was partly due to the patient selection, for example because some aspects of the selection were unclear or a CCTA was used as a pretest for patient selection. In addition, the high PTP was based on the domain of patient flow and timing: Here, a high risk of bias was derived for 4 studies and an unclear risk of bias for one study, which was mainly due to the high proportion of missing values or patients not taken into account.

4.3.5 Assessment of the transferability of the results from studies on diagnostic accuracy

With regard to the transferability of the results from the 6 studies on diagnostic accuracy, 3 studies were rated as ‘unclear’ in the domain patient selection either because they included only postmenopausal women (Becker 2015) or 81% men (Driessen 2022), or because of the uncertainty (in Dan-NICAD) due to the upstream CCTA as a pretest and the inclusion of only CCTA-positive patients in the study (see also Table 22 of the full benefit assessment). Across domains, however, there were overall only minor concerns regarding the transferability of the results for all 6 studies.

4.3.6 Results of the studies on diagnostic accuracy

A meta-analytical summary and analysis of the 4x4 table data (see also Table 23 of the full benefit assessment) from all 6 studies on diagnostic accuracy was performed in the manner described in Section 3.5.

4.3.6.1 Results for the sensitivity outcome

The bivariate meta-analyses of the main analysis were conducted across all 6 studies included in this assessment. The meta-analytical summary showed a sensitivity (%) [95% confidence interval (CI)] of 73.3 [56.3; 85.4] for cardiac MRI versus a sensitivity of 63.5 [48.4; 76.4] for SPECT. In 5 of the 6 studies, there was a higher point estimation value for the sensitivity of cardiac MRI in the direct comparison with SPECT (see also Figure 3 and Figure 4 of the full benefit assessment). One exception was the Driessen 2022 study, with only a small numerical disadvantage of cardiac MRI (point estimate 66.1%) compared with SPECT (point estimate 67.0%).

Overall, the results indicated that the sensitivity of cardiac MRI is at least comparable to that of SPECT.

4.3.6.2 Results for the specificity outcome

For specificity (%) [95% CI], there were values of 78.3 [65.0; 87.5] for cardiac MRI and 79.4 [67.7; 87.7] for SPECT, i.e. a small numerical disadvantage for cardiac MRI compared with SPECT. In 4 of the 6 studies, there was a higher point estimation value for the specificity of cardiac MRI in comparison with SPECT (see also Figure 3 and Figure 4 of the full benefit assessment). In the 2 remaining studies (Dan-NICAD and MR-IMPACT II), there was a notably lower specificity of cardiac MRI compared with SPECT.

Overall, the results indicated an almost comparable specificity of cardiac MRI and SPECT, with less precise results for cardiac MRI (see also Figure 7 of the full benefit assessment). Apparently, there was overall greater heterogeneity of the results between the studies in terms of specificity than in terms of sensitivity.

There was no recognizable correlation between prevalence and diagnostic accuracy (sensitivity and specificity).

4.3.6.3 Subgroups and sensitivity analyses

Sensitivity analyses

Only the Dan-NICAD study used a diagnostic preselection by means of an upstream CCTA in patients with low-moderate PTP, with only those who tested positive in the CCTA ultimately being included in the study. The results also deviated notably from the results of the other 5 studies, particularly with regard to sensitivity. The sensitivity (%) [95% CI] in Dan-NICAD was unusually low for both cardiac MRI and SPECT, at 40.7 [28.1; 54.3] and 36.2 [24.0; 49.9], respectively, and contributed notably to the heterogeneity of the results of the studies. For this reason, a sensitivity analysis was performed omitting the Dan-NICAD study.

The meta-analytical summary of the results from the 5 remaining studies showed a sensitivity (%) [95% CI] of 78.6 [68.2; 86.3] for cardiac MRI and a sensitivity (%) [95% CI] of 68.0 [57.3; 77.2] for SPECT (see Figure 5 and Figure 6 of the full benefit assessment).

Without the Dan-NICAD study, there were thus markedly higher values for sensitivity for the overall estimation in the meta-analytic summary of the results.

Without the Dan-NICAD study, the meta-analytical summary of the results showed a specificity (%) [95% CI] of 76.7 [59.2; 88.2] for cardiac MRI and 76.2 [67.7; 83.0] for SPECT (see Figure 5 and Figure 6 of the full benefit assessment), resulting in almost comparable test quality values in terms of point estimations for specificity. Numerically, the values were close

to each other, but the estimate of specificity for cardiac MRI in the meta-analytical summary was less precise than for SPECT.

Thus, in contrast to the main analysis, the sensitivity analysis without the Dan-NICAD study showed overall higher sensitivity for both cardiac MRI and SPECT, with a numerical advantage for cardiac MRI compared with SPECT. Unlike the main analysis, there was a numerical advantage of cardiac MRI versus SPECT also in terms of specificity, albeit only a small one.

The 2-dimensional representations of sensitivity and specificity using confidence and prediction regions for cardiac MRI and SPECT with regard to the analysis without the Dan-NICAD study (Figure 8 of the full benefit assessment) also showed clearer results regarding the advantage of cardiac MRI compared with SPECT for sensitivity, and similar but less precise results for cardiac MRI compared with SPECT for specificity than the corresponding 2-dimensional representation of the main analysis (Figure 7 of the full benefit assessment).

Subgroup analyses

The planned (subgroup) analyses regarding age, body mass index (BMI) and PTP were not possible as the reporting of results in the studies did not provide the necessary data. With regard to sex as a possible effect modifier, individual studies did provide separate results for women and men but the number of studies was insufficient to draw conclusions about possible interactions using the methods from the main analysis. The reason for the heterogeneity of the test quality results of the 6 studies could not be clarified.

4.3.7 Summary assessment of the risk of bias of the results from studies on diagnostic accuracy

Usable data from 6 studies on diagnostic accuracy were available. Since the results from Dan-NICAD deviated notably from those of the other studies, particularly with regard to sensitivity, the sensitivity analysis excluding the Dan-NICAD study was also taken into account in the assessment. For both analyses, the results from the bivariate meta-analytic summaries of the 6/5 studies on diagnostic accuracy showed a numerical advantage in favour of cardiac MRI compared with SPECT in terms of sensitivity. In terms of specificity, the point estimates for cardiac MRI and SPECT were (numerically) similar, with the specificity values for cardiac MRI showing greater dispersion.

Overall, the studies on diagnostic accuracy showed that the diagnostic accuracy of cardiac MRI is at least comparable to that of SPECT.

Assessment of the volume of unpublished data

It is not mandatory to register non-randomized studies in a trial registry at the start of the study. Therefore, the assessment of a publication bias can only be carried out to a very limited extent. The systematic search did not identify any registry entries for studies on diagnostic

accuracy without reported results on the comparison of cardiac MRI with SPECT and ICA or ICA/FFR as the reference standard.

Weighing up the benefits and harms

The results from the 5/6 studies on diagnostic accuracy showed that cardiac MRI has at least comparable diagnostic accuracy to SPECT in terms of sensitivity, with a numerical advantage in favour of cardiac MRI.

In this research question, sensitivity is given greater weight than specificity: It is more important for a new procedure to reduce the number of false negative findings than to reduce the number of false positive findings. In this way, fewer people with CHD are overlooked; if people with CHD are not identified as such, necessary treatment measures are not taken. If, on the other hand, a finding proves to be false positive, this results in unnecessary ICA with the associated risks. However, these risks are (notably) outweighed by the risk of not receiving treatment for CHD. If more people with CHD are identified by cardiac MRI (compared with other functional non-invasive procedures), it is assumed that these people additionally identified will benefit from treatment in the same way. Concerns about the transferability of the results from the studies on diagnostic accuracy were minor for all 6 studies. Even though, with the exception of the Dan-NICAD study, the studies did not specify the patients' PTP, transferability of the results in terms of diagnostic accuracy was assumed. According to the prevalence calculated by the Institute as an approximation of PTP, this ranged from 25% (Arai 2023) to 56% (Driessen 2022; MR-IMPACT II) in the 6 studies (see Section 4.3.2). It can therefore be assumed that the PTP of the study population was largely in the range of 15% to 85%.

In contrast to SPECT, cardiac MRI is conducted without exposing patients to radiation.

Overall, due to its at least comparable diagnostic accuracy and the inherent advantage of cardiac MRI of being a diagnostic procedure without any radiation exposure, a positive benefit conclusion can be drawn in favour of cardiac MRI.

4.4 Overall assessment of the results comparing cardiac MRI with SPECT from both study types

The assessment of the results from CE-MARC 2 as a study on the diagnostic-therapeutic chain did not result in any hints of a (greater) benefit or harm of cardiac MRI compared with SPECT, whereby the data situation was insufficient for the outcomes all-cause mortality and cardiovascular mortality due to the rare occurrence of these events. The assessment of the results of the studies on diagnostic accuracy showed that the diagnostic accuracy of cardiac MRI is at least comparable to that of SPECT. At the same time, cardiac MRI has the inherent advantage over SPECT that it can be conducted without exposing patients to radiation.

Overall, there is a hint of greater benefit of cardiac MRI in comparison with SPECT.

4.5 Cardiac MRI compared with other functional non-invasive diagnostic techniques

Other functional non-invasive diagnostic techniques include stress echocardiography and exercise ECG. No evidence was available regarding studies on the diagnostic-therapeutic chain comparing cardiac MRI with stress echocardiography or exercise ECG. Studies on the diagnostic accuracy of these techniques were available. However, as these 2 procedures were considered to be of less clinical importance, studies on diagnostic accuracy comparing cardiac MRI with these 2 procedures were not included in the assessment (for reasons, see Section 3.5).

5 Classification of the assessment result

Integration of cardiac MRI into upstream and downstream diagnostics

When considering the use of cardiac MRI in the included 7 studies (one RCT and 6 studies on diagnostic accuracy) in terms of its integration into the diagnostic algorithm, the following picture emerged: Cardiac MRI was used in the studies as a further diagnostic tool after taking a medical history and an initial diagnosis and, in some cases, after a positive CCTA result (Dan-NICAD). Its use in the studies concurred with the recommendations of the NVL, which recommends cardiac MRI as a functional procedure for PTP of 15% to 85%. For the range of low-moderate PTP of 15% to 50%, the NVL recommends CCTA as the preferred morphological procedure, as a negative finding can 'very reliably rule out' CHD (high negative predictive value). If the CCTA results are unclear, the guideline then recommends one of the functional tests as a further diagnostic procedure; these would be 'recommended for the entire spectrum of moderate PTP to diagnose stenotic CHD'. According to the position paper of the German Cardiac Society (DGK) [55], CCTA with detection of intermediate stenosis or stenosis with unclear functional significance or non-diagnostic CCTA (e.g. in the case of respiratory or motion artefacts) is followed by a functional diagnostic procedure. In contrast, the position paper does not recommend any further diagnostics in cases of unremarkable CCTA findings, CCTA findings of plaques without stenosing CHD, or negative findings using functional techniques [55]. However, if the CCTA results are positive in terms of high-grade stenosis or if the functional diagnostics results are positive in cases of higher intermediate PTP, an invasive catheter-guided diagnostic procedure (ICA) is indicated [55]. In the studies on diagnostic accuracy, cardiac MRI was regularly followed by ICA – even if the findings were unremarkable – but this was due to the study design in order to obtain a reference standard.

Assessment based on studies on diagnostic accuracy

Since no hint of (greater) benefit or harm could be derived from the results of the RCT-CE-MARC 2 on the diagnostic-therapeutic chain, the 2nd step was the assessment of cardiac MRI by means of studies on diagnostic accuracy. This was possible because cardiac MRI, as the diagnostic technique to be investigated, is intended to replace another, already established functional non-invasive diagnostic technique, and it is assumed that the new test will not, in principle, identify any additional patients in terms of expanding the population for therapy or exclude any patients in terms of restricting the population. SPECT was selected as the 2nd index test for comparison, as SPECT is an alternative functional diagnostic technique that is very common and widely used [56,57]. Furthermore, SPECT, like cardiac MRI, enables the simultaneous assessment of myocardial perfusion, function and scars, and is therefore used earlier in the ischaemic cascade for CHD diagnosis than stress echocardiography [5,58]. In addition, there was already evidence for this comparison at RCT level. Above all, however, the 2024 NVL algorithm recommends it for diagnosis in the same situations and with the same preference as cardiac MRI [3].

Diagnostic accuracy of cardiac MRI compared with stress echocardiography and exercise ECG

Stress echocardiography and exercise ECG were only considered cursorily due to their notably lower clinical significance, and studies using these procedures as a 2nd index test were not used to derive a benefit conclusion. Nevertheless, in order to provide a rough classification of the diagnostic accuracy of cardiac MRI in comparison with these 2 procedures, a supplementary overview of the available evidence from the preliminary literature search is provided here.

Diagnostic accuracy of cardiac MRI compared with stress echocardiography

The systematic review Haberkorn 2021 summarized 39 studies on cardiac MRI and 9 studies on stress echocardiography in a diagnostic meta-analysis [59]. With one exception [47] (which, however, only provided results at the vascular level), none of the primary studies used provided a direct comparison of cardiac MRI and stress echocardiography. The meta-analysis showed a higher sensitivity (%) [95% CI] of 88 [85; 90] for cardiac MRI versus 72 [61; 81] for stress echocardiography with similar specificity (%) [95% CI] of 84 [81; 87] versus 89 [83; 93], with ICA (with FFR if necessary) serving as the reference test. Similar results to those found in Haberkorn 2021 were also obtained in slightly older meta-analyses of test quality studies [60,61]. Here, too, the results were largely based on indirect comparisons.

In addition, 6 publications on 5 primary studies were identified that directly compared the diagnostic accuracy of cardiac MRI with that of stress echocardiography using the common reference test ICA (with FFR if necessary) [37,62-66]. In all 5 studies, the point estimates showed numerical advantages of varying degrees for cardiac MRI compared with stress echocardiography, both in terms of sensitivity and specificity; in Nagel 1999, these differences reached statistical significance with reference to the p-values ($p < 0.05$ in each case) [66]. In Arnold 2010, a numerical advantage (point estimate) of cardiac MRI in terms of sensitivity and specificity was also provided for a ≥ 50% degree of stenosis. However, at a stenosis degree of ≥ 70%, the results in the study deviated slightly from those in the other studies: The sensitivity of cardiac MRI and stress echocardiography was numerically identical (point estimate and CI), and for specificity, there was a small numerical disadvantage for cardiac MRI compared with stress echocardiography in the point estimate. Overall, the results indicated that the diagnostic accuracy of cardiac MRI is at least comparable to that of stress echocardiography.

Diagnostic accuracy of cardiac MRI compared with exercise echocardiography

For the comparison of cardiac MRI with exercise ECG, 2 primary studies on diagnostic accuracy were identified [67,68]. One study [67] showed both markedly higher sensitivity and markedly higher specificity of cardiac MRI compared with exercise ECG (point estimates). The other study [68] showed numerically identical sensitivity in the analysis of all patients (point estimate and CI) for the 2 diagnostic techniques – the analysis of patients with moderate PTP

alone produced a non-statistically significant difference to the disadvantage of cardiac MRI – and a statistically significant difference in favour of cardiac MRI in terms of specificity in both analyses.

A review of the results from the studies mentioned for comparisons with stress echocardiography and exercise ECG suggested that cardiac MRI has at least comparable diagnostic accuracy to these 2 procedures.

Radiation exposure from SPECT

The absence of radiation exposure as an inherent advantage of cardiac MRI was included in the assessment of cardiac MRI in comparison with SPECT so that overall, a hint of greater benefit of cardiac MRI compared with SPECT could be determined. This is because in a SPECT scan, the patient is injected with a radioactive substance, and a gamma camera then registers its distribution in the organ examined via the emitted gamma radiation. To detect ischaemia, 2 doses are necessary: one under stress and one at rest [58]. All included studies used 99mTc-tetrofosmin or 99mTc-sestamibi for this purpose. In the CE-MARC 2 study, the radiation dose was specified as a maximum of 1000 MBq per examination. This concurs with the diagnostic reference values for cardiac nuclear medicine investigations by the German Federal Office for Radiation Protection, which specifies 400 MBq per application for a 2-day protocol or 1000 MBq for both applications together for a 1-day protocol [69]. As the radiation exposure is higher with the 1-day protocol, the 2-day protocol is generally preferred [58]. To rule out CHD, it is recommended to start with a stress test, as further testing at rest is not necessary if the findings are unremarkable, and the radiation exposure can thus be kept to a minimum [58].

According to Section 83 (5), Radiation Protection Act [70], ‘an examination using ionizing radiation or radioactive substances shall be limited to the extent that this is compatible with the requirements of medical science’. The proof of benefit therefore does not require an assessment of whether the difference in radiation exposure between SPECT and cardiac MRI is sufficient in magnitude to actually prevent relevant health damage in terms of patient-relevant outcomes.

6 Conclusion

In this assessment, as a first step, cardiac magnetic resonance imaging was investigated in comparison with other functional non-invasive diagnostic procedures (single photon emission computed tomography, stress echocardiography or exercise electrocardiography) on the basis of studies on the diagnostic-therapeutic treatment chain. One randomized controlled trial could be used for this purpose, namely on the comparison of cardiac magnetic resonance imaging with single photon emission computed tomography.

The study provided usable data for the outcomes all-cause mortality, cardiovascular mortality, unnecessary invasive diagnostics and health-related quality of life. For none of these patient-relevant outcomes was there an effect in favour or to the disadvantage of cardiac magnetic resonance imaging compared with single photon emission computed tomography, but the data situation was mostly insufficient due to the rarity of the events that occurred in these outcomes. Based on the randomized controlled trial, it was therefore not possible to derive a hint of (greater) benefit or harm of cardiac magnetic resonance imaging compared with single photon emission computed tomography.

Since no benefit conclusion could be derived for the diagnostic-therapeutic chain for the aforementioned comparison, in a 2nd step, cardiac magnetic resonance imaging was compared with single photon emission computed tomography on the basis of studies on diagnostic accuracy. For this comparison, 6 studies with usable results on diagnostic accuracy were used for the assessment. Studies on diagnostic accuracy comparing cardiac magnetic resonance imaging with stress echocardiography or exercise electrocardiography were not included because these 2 alternative functional diagnostic techniques were considered to be of less clinical importance.

An analysis of the results of test quality studies comparing cardiac magnetic resonance imaging with single photon emission computed tomography in terms of sensitivity and specificity resulted in at least comparable diagnostic accuracy. Cardiac magnetic resonance imaging also has the inherent advantage over single photon emission computed tomography that it is conducted without exposing patients to radiation. Overall, there is a hint of greater benefit of cardiac magnetic resonance imaging in comparison with single photon emission computed tomography.

Cardiac magnetic resonance imaging is therefore a suitable non-invasive diagnostic technique for patients with suspected coronary heart disease or suspected progression of known coronary heart disease for whom a functional diagnostic technique is indicated.

References for English extract

Please see full final report for full reference list.

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The full report (German version) is published under https://www.iqwig.de/en/projects/d24-02.html.

Appendix A Search strategies

A.1 Searches in bibliographic databases

Search for systematic reviews

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) ALL 1946 to September 12, 2024

The following filter was adopted:

- Systematic review: Wong [71] – High specificity strategy (adapted)

#	Searches
1	exp Coronary Disease/
2	(coronary* adj1 (artery* or heart*) adj1 disease*).ti,ab.
3	(coronary* adj3 (stenos* or lesion*)).ti,ab.
4	or/1-3
5	exp magnetic resonance imaging/
6	((magnetic* adj1 resonance*) or mri).ti,ab.
7	or/5-6
8	and/4,7
9	cochrane database of systematic reviews.jn.
10	(search or MEDLINE or systematic review).tw.
11	(meta analysis or systematic review).pt.
12	or/9-11
13	12 not (exp animals/ not humans.sh.)
14	and/8,13
15	14 and (english or german or multilingual or undetermined).lg.
16	..l/ 15 yr=2015-Current

2. International HTA Database

Search interface: INAHTA

#	Searches
1	"Coronary Disease"[mhe]
2	(coronary* AND (artery* OR heart*) AND disease*)[Title] OR (coronary* AND (artery* OR heart*) AND disease*)[abs]
3	(coronary*AND (stenos* OR lesion*))[Title] OR (coronary*AND (stenos* OR lesion*))[abs]
4	#3 OR #2 OR #1
5	"Magnetic Resonance Imaging"[mhe]

#	Searches
6	((magnetic* AND resonance*) OR mri)[Title] OR ((magnetic* AND resonance*) OR mri)[abs]
7	#6 OR #5
8	#7 AND #4
9	(*) FROM 2015 TO 2024
10	#9 AND #8

Search for primary studies on the diagnostic-therapeutic treatment chain

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) ALL 1946 to November 04, 2024

The following filter was adopted:

- RCT: Lefebvre [72] – Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2023 revision)

#	Searches
1	exp Coronary Disease/
2	(coronary* adj1 (artery* or heart*) adj1 disease*).ti,ab.
3	(coronary* adj3 (stenos* or lesion*)).ti,ab.
4	or/1-3
5	exp magnetic resonance imaging/
6	((magnetic* adj1 resonance*) or mri).ti,ab.
7	or/5-6
8	and/4,7
9	exp randomized controlled trial/
10	controlled clinical trial.pt.
11	(randomized or placebo or randomly or trial or groups).ab.
12	drug therapy.fs.
13	or/9-12
14	13 not (exp animals/ not humans.sh.)
15	and/8,14
16	(animals/ not humans/) or comment/ or editorial/ or exp review/ or meta analysis/ or consensus/ or exp guideline/
17	hi.fs. or case report.mp.
18	or/16-17
19	15 not 18
20	19 and (english or german or multilingual or undetermined).lg.

#	Searches
21	remove duplicates from 20

2. Embase

Search interface: Ovid

- Embase 1974 to 2024 November 04

The following filter was adopted:

- RCT: Wong [71] – Strategy minimizing difference between sensitivity and specificity

#	Searches
1	coronary artery disease/
2	coronary artery obstruction.mp.
3	(coronary* adj1 (artery* or heart*) adj1 disease*).ti,ab.
4	(coronary* adj3 (stenos* or lesion*)).ti,ab.
5	or/1-4
6	cardiovascular magnetic resonance/
7	magnetic resonance angiography/
8	*nuclear magnetic resonance imaging/
9	((magnetic* adj1 resonance*) or mri).ti,ab.
10	or/6-9
11	and/5,10
12	(random* or double-blind*).tw.
13	placebo*.mp.
14	or/12-13
15	and/11,14
16	15 not medline.cr.
17	16 not (exp animal/ not exp human/)
18	17 not (Conference Abstract or Conference Review or Editorial).pt.
19	18 not ((afrikaans or albanian or arabic or armenian or azerbaijani or basque or belorussian or bosnian or bulgarian or catalan or chinese or croatian or czech or danish or dutch or english or esperanto or estonian or finnish or french or gallegan or georgian or german or greek or hebrew or hindi or hungarian or icelandic or indonesian or irish gaelic or italian or japanese or korean or latvian or lithuanian or macedonian or malay or norwegian or persian or polish or polyglot or portuguese or pushto or romanian or russian or scottish gaelic or serbian or slovak or slovene or spanish or swedish or thai or turkish or ukrainian or urdu or uzbek or vietnamese) not (english or german)).lg.
20	remove duplicates from 19

3. The Cochrane Library

Search interface: Wiley

- Cochrane Central Register of Controlled Trials: Issue 10 of 12, October 2024

#	Searches
1	[mh "Coronary Disease"]
2	(coronary*:ti,ab NEAR/1 (artery*:ti,ab OR heart*:ti,ab) NEAR/1 disease*:ti,ab)
3	(coronary*:ti,ab NEAR/3 (stenos*:ti,ab OR lesion*:ti,ab))
4	#1 OR #2 OR #3
5	[mh "magnetic resonance imaging"]
6	((magnetic*:ti,ab NEAR/1 resonance*:ti,ab) OR mri:ti,ab)
7	#5 OR #6
8	#4 AND #7
9	#8 not (*clinicaltrial*gov* or *trialsearch*who* or *clinicaltrialsregister*eu* or *anzctr*org*au* or *trialregister*nl* or *irct*ir* or *isrctn* or *controlled*trials*com* or *drks*de*):so
10	#9 not ((language next (afr or ara or aze or bos or bul or car or cat or chi or cze or dan or dut or es or est or fin or fre or gre or heb or hrv or hun or ice or ira or ita or jpn or ko or kor or lit or nor or peo or per or pol or por or pt or rom or rum or rus or slo or slv or spa or srp or swe or tha or tur or ukr or urd or uzb)) not (language near/2 (en or eng or english or ger or german or mul or unknown)))
11	#10 in Trials

Search for primary studies on diagnostic accuracy

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) ALL 1946 to January 15, 2025

#	Searches
1	exp Coronary Disease/
2	(coronary* adj1 (artery* or heart*) adj1 disease*).ti,ab.
3	(coronary* adj3 (stenos* or lesion*)).ti,ab.
4	or/1-3
5	exp magnetic resonance imaging/
6	((magnetic* adj1 resonance*) or mri or cmr).ti,ab.
7	or/5-6
8	exp Tomography, Emission-Computed, Single-Photon/
9	((single* adj1 photon* adj1 emission* adj3 tomograph*) or SPECT).ti,ab.
10	tomography, x-ray computed/
11	((computed* adj1 tomograph*) or (ct* adj3 angiography*)).ti,ab.
12	exp Echocardiography/ and (stress or exercise* or dipyridamol* or dobutamin*).mp.
13	Echocardiography, Stress/

#	Searches
14	((stress or exercise* or dipyridamol* or dobutamin*) and echocardiogra*).ti,ab.
15	Electrocardiography/ and (stress or exercise*).mp.
16	((stress or exercise*) adj1 (ecg or electrocardiogra*)).ti,ab.
17	or/8-16
18	and/4,7,17
19	(animals/ not humans/) or comment/ or editorial/ or exp review/ or meta analysis/ or consensus/ or exp guideline/
20	hi.fs. or case report.mp.
21	or/19-20
22	18 not 21
23	22 and (english or german or multilingual or undetermined).lg.
24	remove duplicates from 23

2. Embase

Search interface: Ovid

- Embase 1974 to 2025 January 15

The following filter was adopted:

- DTA: Wilczynski [73] – 97 % Sensitivity

#	Searches
1	(coronary* adj1 (artery* or heart*) adj1 disease*).ti,ab.
2	(coronary* adj3 (stenos* or lesion*)).ti,ab.
3	or/1-2
4	((magnetic* adj1 resonance*) or mri or cmr).ti,ab.
5	((single* adj1 photon* adj1 emission* adj3 tomograph*) or SPECT).ti,ab.
6	((computed* adj1 tomograph*) or (ct* adj3 angiography*)).ti,ab.
7	((stress or exercise* or dipyridamol* or dobutamin*) and echocardiogra*).ti,ab.
8	((stress or exercise*) adj1 (ecg or electrocardiogra*)).ti,ab.
9	(myocardial adj1 perfusion*).ti,ab.
10	or/5-9
11	and/3-4,10
12	(sensitiv: or detect: or accura: or specific: or reliab: or positive: or negative: or diagnos:).tw.
13	and/11-12
14	13 not medline.cr.
15	14 not (exp animal/ not exp human/)
16	15 not (Conference Abstract or Conference Review or Editorial).pt.

#	Searches
17	16 not ((afrikaans or albanian or arabic or armenian or azerbaijani or basque or belorussian or bosnian or bulgarian or catalan or chinese or croatian or czech or danish or dutch or english or esperanto or estonian or finnish or french or gallegan or georgian or german or greek or hebrew or hindi or hungarian or icelandic or indonesian or irish gaelic or italian or japanese or korean or latvian or lithuanian or macedonian or malay or norwegian or persian or polish or polyglot or portuguese or pushto or romanian or russian or scottish gaelic or serbian or slovak or slovene or spanish or swedish or thai or turkish or ukrainian or urdu or uzbek or vietnamese) not (english or german)).lg.
18	remove duplicates from 17

A.2 Searches in study registries

1. ClinicalTrials.gov

Provider: U.S. National Institutes of Health

- URL: http://www.clinicaltrials.gov
- Type of search: Basic Search

Search strategy
("coronary artery disease" OR coronary lesion) [Condition/disease] AND (magnetic resonance OR MRI) [Intervention/treatment]

2. International Clinical Trials Registry Platform Search Portal

Provider: World Health Organization

- URL: https://trialsearch.who.int
- Type of search: Standard Search

Search strategy
(coronary artery disease OR coronary heart disease OR ischemic heart disease OR coronary stenosis OR coronary lesion OR angina pectoris OR stable angina) AND (magnetic resonance OR MRI OR MR)