Washington State Health Care Authority

Use of Cardiac Magnetic Resonance Angiography in Adults and Children

Final Evidence Report

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Health Technology Assessment Program (HTA)

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This health technology assessment report is based on research conducted by the Center for Evidence-based Policy (Center) under contract to the Washington State Health Care Authority (HCA). This report is an independent assessment of the technology question(s) described based on accepted methodological principles. The findings and conclusions contained herein are those of the authors, who are responsible for the content. These findings and conclusions do not necessarily represent the views of the Washington HCA and thus, no statement in this report shall be construed as an official position or policy of the HCA.

The information in this assessment is intended to assist health care decision makers, clinicians, patients, and policy makers in making evidence-based decisions that may improve the quality and cost-effectiveness of health care services. Information in this report is not a substitute for sound clinical judgment. Those making decisions regarding the provision of health care services should consider this report in a manner similar to any other medical reference, integrating the information with all other pertinent information to make decisions within the context of individual patient circumstances and resource availability.

About the Center for Evidence-based Policy

The Center is recognized as a national leader in evidence-based decision making and policy design. The Center understands the needs of policymakers and supports public organizations by providing reliable information to guide decisions, maximize existing resources, improve health outcomes, and reduce unnecessary costs. The Center specializes in ensuring that diverse and relevant perspectives are considered and appropriate resources are leveraged to strategically address complex policy issues with high-quality evidence and collaboration. The Center is based at Oregon Health & Science University in Portland, Oregon.

Conflict of Interest Disclosures: No authors have conflicts of interest to disclose. All authors have completed and submitted the Oregon Health & Science University form for Disclosure of Potential Conflicts of Interest, and none were reported.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

ACHD	adult congenital heart disease
aHR	adjusted hazard ratio
AHRQ	Agency for Healthcare Research and Quality
AOCA	anomalous origin of the coronary artery
aOR	adjusted odds ratio
AUROC	area under the HSROC curve
BMI	body mass index
CAA	coronary artery anomalies
CABG	coronary artery bypass graft
CAD	coronary artery disease
CCTA	coronary computed tomography angiography
CCTGA	congenitally corrected transposition of the great arteries (commonly referred to as Levo-transposition of the great arteries, or L-TGA)
CHD	coronary heart disease
CI	confidence interval
CMRA	cardiac magnetic resonance angiography
CMRI	cardiac magnetic resonance imaging
CMS	Centers for Medicare & Medicaid Services
CoE	certainty of evidence
CRT	cardiac resynchronization therapy
CV	cardiovascular
DTA	diagnostic test accuracy
d-TGA	d-transposition of the great arteries
ECG	electrocardiography
ETT	exercise treadmill test
FDA	US Food and Drug Administration
FFR	fractional flow reserve
FPR	false positive rate
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
HR	hazard ratio
HSROC	hierarchical summary receiver operating curve

HTA	health technology assessment
ICA	invasive coronary angiography
ICER	incremental cost-effectiveness ratio
IQR	interquartile range
KQ	key question
LGE	late gadolinium enhancement
MACE	major adverse cardiovascular events
MAUDE	Manufacturer and User Facility Device Experience (FDA database)
MI	myocardial infarction
MPS	myocardial perfusion scintigraphy
MRI	magnetic resonance imaging
NCT	US National Clinical Trial
NICE	National Institute for Health and Care Excellence
NLR	negative likelihood ratio
NPV	negative predictive value
NR	not reported
NRS	nonrandomized study
PA	pulmonary artery
PCI	percutaneous coronary intervention
PLR	positive likelihood ratio
PPV	positive predictive value
QALY	quality-adjusted life year
RCT	randomized controlled trial
RD	risk difference
RV	right ventricle
SPECT	single photon emission computed tomography
SSFP	steady-state free precession
T	Tesla (unit of magnetic field intensity)
TPR	true positive rate
UN	United Nations
VA	US Department of Veterans Affairs

Executive Summary

Structured Abstract

Purpose

This report reviews the effectiveness and cost-effectiveness of cardiac magnetic resonance angiography (CMRA) in adults and children, when compared with invasive coronary angiography (ICA) or coronary computed tomography angiography (CCTA).

Methods

Data Sources

We searched Ovid MEDLINE, Ovid MEDLINE In-Process & Other Non-Indexed Citations, and Ovid MEDLINE Epub Ahead of Print from January 1, 2000 to May 3, 2021; the Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials from January 1, 2000 to May 3, 2021; the National Library of Medicine clinical trials registry to June 2021; relevant professional society and organization clinical practice guidelines; and public and private payer coverage policies.

Study and Guideline Selection

Using a priori criteria, we conducted dual independent title and abstract screening and full-text article review for English language randomized controlled trials (RCTs), observational studies, and economic evaluations of CMRA in adults and children. A third reviewer settled discrepancies, as needed. We also selected relevant clinical practice guidelines, using a similar process to select and assess them.

Data Extraction and Risk of Bias Assessment

One researcher from the Center for Evidence-based Policy (Center) used standardized procedures to extract data from the included studies and a second checked all data entry for accuracy. We performed dual independent risk-of-bias assessment on the included studies and guidelines. A third reviewer settled discrepancies.

Data Synthesis and Analysis

We applied the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) Working Group system to rate the overall certainty of evidence on selected measures of outcomes.

Results

A. Adults With Suspected Coronary Artery Disease (e.g., symptomatic patients)

- CMRA has a sensitivity of 88% (95% confidence interval [CI], 84% to 91%) and a specificity of 72% (95% CI, 64% to 78%), based on pooled data from 23 studies (high certainty of evidence [CoE], based on 23 nonrandomized studies [NRSs]).
    - In a population of 1,000 adults with a 53% prevalence of coronary artery disease (CAD; the median prevalence of the included studies), CMRA testing would result in:
        - 466 patients being diagnosed correctly as having CAD
        - 64 patients incorrectly classified as not having CAD
        - 338-patients being diagnosed correctly as not having CAD
        - 132 patients incorrectly classified as having CAD

- CMRA has high levels of observer agreement, both within reviewers (intraobserver) and between observers (interobserver; moderate CoE, based on 1 NRS).

B. Adults With Suspected Coronary Vessel Anomalies

- CMRA is highly concordant with surgical and ICA findings, and may identify vessel anomalies not identified using other tests, including ICA (low CoE, based on 3 NRSs).
- When compared with ICA, CMRA had a sensitivity of 88% (95% CI, 62% to 98%) and a specificity of 100% (95% CI, 66% to 100%) (low CoE, based on 1 NRS).
- CMRA may add information on the origin and course of the anomalies and can provide the information needed for clinical management, thus avoiding the need for conventional angiography (very low CoE, based on 1 NRS).

C. Adults Who Have Undergone Coronary Artery Bypass Graft Surgery

- No eligible studies were identified.

D. Adults Being Assessed For Cardiac Device Lead Placement

- CMRA may be useful to visualize the appropriate vein for cardiac device lead placement (low CoE, based on 2 NRSs).

E. Children With Suspected or Confirmed Congenital Heart Disease

- CMRA was highly concordant with surgical, ICA, and CCTA findings, and may identify vessel anomalies not identified using other tests, including ICA (low CoE, based on 6 NRSs).
- There was high interobserver agreement for CMRA in the visualization of coronary artery anomalies (very low CoE, based on 1 NRS.)
- CMRA can be diagnostic in most cases, with no additional imaging needed. CMRA also identifies new findings or new diagnoses in the majority of cases where they are present (very low CoE, based on 6 NRSs).

Safety

- In adults, CMRA appears to be a safe procedure, with few adverse events related to the procedure or to the pharmacological agents (low CoE, based on 8 NRSs).
- In children, CMRA appears to be a safe procedure, with few adverse events related to the procedure or to general anesthesia (low CoE, based on 4 NRSs).

FDA-Reported Harms

We did not identify any harms associated specifically with CMRA; however, patients and providers have reported burns, hearing loss or tinnitus, and issues with metal implants associated with magnetic resonance imaging for any indication.

Economic Outcomes

We did not identify any economic studies assessing the cost-effectiveness of CMRA for any of the populations of interest.

Clinical Practice Guidelines and Payer Policies

Recommendations from good-quality and moderate-quality methodological guidelines support the use of CMRA in adults with congenital heart disease, including coronary vessel anomalies, but there is no clear consensus on the use of CMRA for adults with suspected CAD.

The private payer policies we reviewed cover the use of CMRA for congenital heart disease or vessel anomalies, but do not consider the use of CMRA for other indications to be medically necessary.

Conclusions

In summary, CMRA performs well as a test to visualize the cardiac vessels, and can therefore be a useful test when clinicians need to understand the vascular anatomy of the heart. CMRA also appears to be a safe alternative for most patients. However, there is a lack of data on the impact on patient outcomes and clinical decision-making of CMRA, and on the cost-effectiveness of CMRA in the populations of interest. Overall, there is a lot of uncertainty around the clinical impact of the findings, given the paucity of outcome studies.

Background

Cardiac magnetic resonance imaging (CMRI) is an imaging modality that provides a mechanism to assess cardiac or vascular anatomy, function, perfusion, and tissue characteristics in a highly reproducible manner, during a single examination.[1] Images can be acquired without an invasive procedure or exposure to either ionizing radiation or iodinated intravenous contrast medium.[1] However, there are safety concerns around the use of CMRI in some populations, as in people with implantable devices (e.g., implantable ferromagnetic cardioverter defibrillators).[1] Other risks associated with contrast agents include nephrogenic systemic fibrosis and allergic reactions, including anaphylaxis.[1] There are also some people for whom CMRI is contraindicated (e.g., people with ventricular assist devices).[1]

Technology of Interest

Cardiac magnetic resonance angiography (CMRA) is a specific CMR imaging (CMRI) technique for assessing the coronary vessels and major cardiac vessels such as the ascending aorta.[1] CMRA can be used alone, or in combination with other CMRI techniques, such as stress perfusion or late gadolinium enhancement (LGE).

Policy Context

There have been a number of CMRA technological advances in the past decade; however, its accuracy and clinical utility for diagnosis in routine clinical practice are unclear. This topic was selected because of medium-level concerns about the safety and efficacy of CMRA and high-level concern about costs.

This evidence review will help inform Washington's independent Health Technology Clinical Committee as they determine coverage regarding CMRA in adults and children.

Methods

This evidence review is based on the final key questions (KQs) published on March 15, 2021.[2] The draft KQs were available for public comment from March 16 to March 30, 2021, and

appropriate revisions were made to the KQs based on the comments and responses.[3] All public comments received and a table of responses can be found on the Washington Health Technology Assessment website. This draft report was available for public comment from September 7 through October 6, 2021, and appropriate revisions based on comments were made, with the final report being posted to the program's website. This draft report was also peer-reviewed by subject matter experts, with appropriate revisions reflected in the final report.

Key Questions

1. What is the evidence for the diagnostic validity (i.e., accuracy) and clinical utility (i.e., effectiveness) of CMRA (with or without contrast) in adults with suspected or confirmed coronary artery disease (CAD) and children with suspected or confirmed congenital heart disease? The use of CMRA will be assessed in the following populations:
    a. Adults with suspected CAD (e.g., symptomatic patients)
    b. Adults with suspected coronary vessel anomalies
    c. Adults who have undergone coronary artery bypass graft (CABG) surgery
    d. Adults being assessed for cardiac device lead placement
    e. Children with suspected or confirmed congenital heart disease
2. What direct harms are associated with CMRA in adults with suspected or confirmed CAD and children with suspected or confirmed congenital heart disease? The harms of CMRA will be assessed in the following populations:
    a. Adults with suspected CAD (e.g., symptomatic patients)
    b. Adults with suspected coronary vessel anomalies
    c. Adults who have undergone CABG surgery
    d. Adults being assessed for cardiac device lead placement
    e. Children with suspected or confirmed congenital heart disease
3. Do important diagnostic validity (i.e., accuracy) outcomes, clinical utility (i.e., effectiveness) outcomes, or direct harms of CMRA in adults with suspected or confirmed CAD and children with suspected or confirmed congenital heart disease vary by the following populations or circumstances?
    a. Sex (i.e., men, women)
    b. Adults with atypical symptoms of CAD
    c. Age, specifically in older adults
    d. Adults and children with comorbidities
    e. Setting (e.g., high-volume setting vs. low-volume setting)
4. What are the cost-effectiveness and other economic outcomes of CMRA in adults with suspected or confirmed CAD and children with suspected or confirmed congenital heart disease? The economic outcomes of CMRA will be assessed in the following populations:
    a. Adults with suspected CAD (e.g., symptomatic patients)
    b. Adults with suspected coronary vessel anomalies
    c. Adults who have undergone CABG surgery
    d. Adults being assessed for cardiac device lead placement
    e. Children with suspected or confirmed congenital heart disease

Data Sources and Searches

We searched Ovid MEDLINE, Ovid MEDLINE In-Process & Other Non-Indexed Citations, and Ovid MEDLINE Epub Ahead of Print from January 1, 2000 to May 3, 2021; the Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials from January 1, 2000 to May 3, 2021; the National Library of Medicine clinical trials registry to June 2021; relevant professional society and organization clinical practice guidelines; and public and private payer coverage policies.

Study and Guideline Selection

Using a priori criteria, we conducted dual independent title and abstract screening and full-text article review for English language randomized controlled trials (RCTs), observational studies, and economic evaluations of CMRA in adults and children. A third reviewer settled discrepancies, as needed. We also selected relevant clinical practice guidelines, using a similar process.

Data Abstraction and Quality Assessment

One Center researcher used standardized procedures to extract data from the included studies and a second checked all data entry for accuracy. We performed dual independent risk-of-bias assessment on the included studies and guidelines. A third reviewer settled discrepancies, as needed.

Data Analysis and Synthesis

When study authors did not report measures of test performance, or when the studies included reporting discrepancies, we calculated relevant test performance statistics with 95% confidence intervals (CIs), based on the reported or calculated 2 × 2 tables.

To assess the diagnostic accuracy of CMRA using meta-analysis, we used the bivariate and hierarchical summary receiver operating curve (HSROC) models to directly model sensitivity and specificity while accounting for the correlation across the 2 measures. In the primary analysis, we included all diagnostic test accuracy studies evaluating CMRA against our predefined reference standards (i.e., invasive coronary angiography [ICA] and coronary computed tomography angiography [CCTA]). We pooled data across studies where more than 3 studies reported the same reference standard. If more than 3 studies reported similar thresholds using the same reference standard, we conducted analyses according to threshold.

We assigned selected outcomes a summary judgment for the overall certainty of evidence (Appendix E) using the system developed by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) Working Group.[4,5] The outcomes varied by population and the aim of testing, but focused on diagnostic performance and clinical utility, in-line with the KQs.

Results

After duplicate studies were removed, we screened 2,493 remaining records. Of these, 915 required full-text review to determine eligibility. In total, 37 studies of diagnostic test accuracy (in 40 publications) and 9 nonrandomized studies (NRSs; in 9 publications) met the inclusion criteria for KQ1, KQ2, and KQ3.[6-54]

KQ1 and KQ2

A. Adults With Suspected CAD

- CMRA has a sensitivity of 88% (95% CI, 84% to 91%) and a specificity of 72% (95% CI, 64% to 78%), based on pooled data from 23 studies (high certainty of evidence [CoE], based on 23 NRSs).
    - In a population of 1,000 adults with a 53% prevalence of CAD (the median prevalence of the included studies), CMRA testing would result in:
        - 466 patients being diagnosed correctly as having CAD
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- CMRA has high levels of observer agreement, both within reviewers (intraobserver) and between observers (interobserver; moderate CoE, based on 1 NRS).

B. Adults With Suspected Coronary Vessel Anomalies

- CMRA is highly concordant with surgical and ICA findings, and may identify vessel anomalies not identified using other tests, including ICA (low CoE, based on 3 NRSs).
- When compared with ICA, CMRA had a sensitivity of 88% (95% CI, 62% to 98%) and a specificity of 100% (95% CI, 66% to 100%) (low CoE, based on 1 NRS).
- CMRA may add information on the origin and course of the anomalies and can provide the information needed for clinical management, thus avoiding the need for conventional angiography (very low CoE, based on 1 NRS).

C. Adults Who Have Undergone CABG Surgery

- No eligible studies were identified.

D. Adults Being Assessed For Cardiac Device Lead Placement

- CMRA may be useful to visualize the appropriate vein for cardiac device lead placement (low CoE, based on 2 NRSs).

E. Children With Suspected or Confirmed Congenital Heart Disease

- CMRA was highly concordant with surgical, ICA, and CCTA findings, and may identify vessel anomalies not identified using other tests, including ICA (low CoE, based on 6 NRSs).
- There was high interobserver agreement for CMRA in the visualization of coronary artery anomalies (very low CoE, based on 1 NRS.)
- CMRA can be diagnostic in most cases, with no additional imaging needed. CMRA also identifies new findings or new diagnoses in the majority of cases where they are present (very low CoE, based on 6 NRSs).

Safety

- In adults, CMRA appears to be a safe procedure, with few adverse events related to the procedure or to the pharmacological agents (low CoE, based on 8 NRSs).
- In children, CMRA appears to be a safe procedure, with few adverse events related to the procedure or to general anesthesia (low CoE, based on 4 NRSs).

FDA-Reported Harms

We did not identify any harms associated specifically with CMRA; however, patients and providers have reported burns, hearing loss or tinnitus, and issues with metal implants associated with magnetic resonance imaging (MRI) for any indication.

We found 253 entries in the US Food and Drug Administration's (FDA's) Manufacturer and User Facility Device Experience (MAUDE) database, including voluntary, user facility, distributor, and manufacturer reports of adverse events relating to MRI scanner use in the last 5 years. We were not able to analyze the reports by condition and many of the entries were not specific to the use of CMRA alone. The types of adverse events were very different to those reported in our eligible studies for CMRA across the selected populations of interest. Common adverse events included burns, hearing loss or tinnitus, and adverse consequences due to unknown metal implants in patients.

We also found 2 entries in the Medical Device Recall database related to other devices or components of devices used for MRI, neither of which were specific to the use of CMRA.

KQ3

The diagnostic performance of CMRA in adults with suspected CAD did not appear to differ by patient characteristic. We did not identify any evidence in the other populations of interest.

KQ4

We did not identify any economic studies assessing the cost-effectiveness of CMRA for any of the populations of interest.

Summary

When compared with ICA, CMRA is a good test for adults with suspected CAD, with an overall estimated accuracy of 89%. Pooled estimates of sensitivity and specificity are 88% and 72% respectively. However, there is no direct evidence on the effectiveness of CMRA in changing clinical practice or in improved outcomes for patients with CAD.

In other populations, where anatomical imaging of the vessels is clinically important, CMRA does appear to be a useful test. CMRA often performs as well as ICA, and may be able to identify anomalies that are not identified using ICA. CMRA also appears to be a useful tool for informing and changing clinical pathways and actions in adults and children whose vascular anatomy needs to be visualized, which would be expected to lead to improved surgical and other outcomes. However, no evidence on patient outcomes was identified.

There is also a lack of evidence on the cost-effectiveness of CMRA in any of the populations of interest; overall, there is a lot of uncertainty around the findings given the paucity of clinical outcome studies.

Clinical Practice Guidelines

We identified 1 clinical practice guideline and 2 appropriateness criteria documents developed by the American College of Radiology (ACR) on the use of CMRA in adults with suspected CAD. We also identified 2 guidelines for the use of CMRA in adults with congenital heart disease, which we have included as being relevant to adults with suspected coronary vessel

anomalies.[55,56] We assessed 2 of the guidelines as being of good methodological quality and 3 as being of moderate methodological quality.

In summary, recommendations from good-quality and moderate-quality methodological guidelines support the use of CMRA in adults with congenital heart disease, including coronary vessel anomalies. The use of CMRA for adults with suspected CAD is less clear, with only conditional recommendations from the ACR[57,58] and a 'do not do' recommendation from NICE.[59]

Selected Payer Coverage Determinations

We did not identify any current Medicare national coverage determinations, or any local coverage determinations relevant to Washington, on the use of CMRA in a population of interest.

Each of the 3 private payers that we reviewed (Aetna, Cigna, and Regence) had coverage policies for CMRA.[60-62]

In summary, the private payer policies cover the use of CMRA for congenital heart disease or vessel anomalies, but do not consider the use of CMRA for other indications to be medically necessary.

Ongoing Studies

We did not identify any ongoing studies of CMRA in a population of interest.

Conclusions

Findings

When compared with ICA, CMRA is a good test for adults with suspected CAD, with an overall estimated accuracy of 89%. Pooled estimates of sensitivity and specificity are 88% and 72% respectively. However, there is no direct evidence on the effectiveness of CMRA in changing clinical practice or in improved outcomes for patients with CAD.

In other populations, where anatomical imaging of the vessels is clinically important, CMRA does appear to be a useful test. CMRA often performs as well as ICA, and may be able to identify anomalies not identified using ICA. CMRA also appears to be a useful tool in informing and changing clinical pathways and actions in adults and children whose vascular anatomy needs to be visualized, which would be expected to lead to improved surgical and other outcomes. However, we identified no evidence on patient outcomes. We also did not identify any evidence on the cost-effectiveness of CMRA in any of the populations of interest. Overall, there is a lot of uncertainty around the clinical impact of these findings given the paucity of clinical outcome studies.

FDA-Reported Harms

Adverse events appear to be minimal in both adults and children. However, patients may be exposed to harm through the use of MRI (e.g., burns, loss of hearing, tinnitus) and other procedures associated with MRI (e.g., general anesthesia in young children, gadolinium contrast agents in people with diminished renal function). MRI may also not be suitable for people who are unable to tolerate MRI (e.g., people with severe claustrophobia).

Clinical Practice Guidelines and Coverage Policies

Clinical practice guidelines and payer policies are also in agreement on the use of CMRA, supporting the use for CMRA in adults with congenital heart disease, including coronary vessel anomalies, with only limited support for the use of CMRA for adults with suspected CAD.

Summary

When compared with ICA, CMRA is a good test for adults with suspected CAD, with an overall estimated accuracy of 89%. Pooled estimates of sensitivity and specificity are 88% and 72%. However, there is no direct evidence on the effectiveness of CMRA in changing clinical practice or in improving outcomes for patients with CAD. The economic impact of CMRA in patients with suspected CAD is also unknown when compared to standard care.

In other populations, where anatomical imaging of the vessels is clinically important, CMRA does appear to be a useful test. CMRA often performs as well as ICA, and may be able to identify anomalies that are not identified using ICA. However, it should be noted that ICA is not usually considered to be the reference standard for the diagnosis of coronary anomalies. CMRA also appears to be a useful tool for informing and changing clinical pathways and actions in adults and children whose vascular anatomy needs to be visualized, which could lead to improved surgical and other outcomes. However, no evidence on patient outcomes was identified. Overall, there is a lot of uncertainty around these findings given the paucity of clinical outcome studies.

Adverse events appear to be minimal in both adults and children. However, patients may be exposed to harm (e.g., burns, loss of hearing, tinnitus) through the use of MRI and other procedures associated with MRI (e.g., general anesthesia or sedation in young children, gadolinium contrast agents in people with diminished renal function). MRI also may not be suitable for people who are unable to tolerate the MRI procedure (e.g., people with severe claustrophobia). In general, the use of MRI is considered a safe procedure; patients are not exposed to the harmful effects of ionizing radiation present in other imaging modalities (e.g., computed tomography). When CMRA is used as an alternative, patients may also avoid the risks associated with surgery or with invasive testing, including radiation exposure and test-related complications.

Clinical practice guidelines and payer policies also agree on the use of CMRA in adults with congenital heart disease, including coronary vessel anomalies; however, there is no clear consensus on the use of CMRA for adults with suspected CAD.

In summary, CMRA performs well as a test to visualize the cardiac vessels, and can therefore be a useful tool when clinicians need to understand the vascular anatomy of the heart. CMRA also appears to be a safe alternative for most patients. However, there is a lack of data on the impact on patient outcomes and clinical decision-making of using CMRA, and on the cost-effectiveness of CMRA in the populations of interest. Overall, there is a lot of uncertainty around the findings given the paucity of clinical outcome studies.

Technical Report

Background

Technology of Interest

Cardiac magnetic resonance imaging (CMRI) is an imaging modality that provides a mechanism to assess cardiac or vascular anatomy, function, perfusion, and tissue characteristics in a highly reproducible manner, during a single examination.[1] Images can be acquired without an invasive procedure or exposure to either ionizing radiation or iodinated intravenous contrast medium.[1] However, there are safety concerns around the use of CMRI in some populations, as in people with implantable devices (e.g., implantable ferromagnetic cardioverter defibrillators).[1] Other risks associated with contrast agents include nephrogenic systemic fibrosis and allergic reactions, including anaphylaxis.[1] There are also some people for whom CMRI is contraindicated (e.g., people with ventricular assist devices).[1] Other risks include claustrophobia, hearing damage if adequate protection is not used, and heating of the body.[63]

Cardiac magnetic resonance angiography (CMRA) is a specific CMRI technique for assessing the proximal aorta and other coronary vessels.[1] CMRA can be used alone, or in combination with other CMRI techniques, such as stress perfusion or late gadolinium enhancement (LGE).

Clinical Need and Target Populations

CMRI, including CMRA, may be useful for identifying coronary artery anomalies and aneurysms, and may be used to assess cardiac structure, blood flow, and cardiac and extracardiac conduits in children and adults with simple and complex congenital heart disease.[1]

CMRA can also be used to determine coronary artery patency in adults with coronary artery disease (CAD), and as a diagnostic modality for patients with suspected anomalous coronary anatomy.[1]

CMRA can be used all along the care pathway from initial evaluation and diagnosis through to longer-term monitoring, which for some patients may continue for their lifetime.

CMRA is generally considered safe, but there are important safety concerns related to the administration of the gadolinium contrast agents.[1] Harms range from mild and moderate reactions to the contrast agent to severe anaphylaxis; others may experience the rare complication of nephrogenic systemic fibrosis, particularly older people, individuals with a history of renal disease or dysfunction, or patients with a prior renal transplant.[1] The use of CMRI must also be weighed against the potential risk of implantable device failure, or potential for injury to a patient with metal fragments in their body (e.g., welders, veterans).[1,64]

Policy Context

There have been a number of CMRA technological advances in the past decade; however, its accuracy and clinical utility for diagnosis in routine clinical practice are still unclear. This topic was selected because of medium-level concerns about the safety and efficacy of CMRA and high-level concern about costs.

The objective of the health technology assessment (HTA) is to evaluate the diagnostic validity (i.e., accuracy), clinical utility (i.e., effectiveness), safety, and cost-effectiveness of CMRA in adults

with suspected or confirmed CAD, and in children with congenital heart disease. This evidence review will help inform Washington's independent Health Technology Clinical Committee as they determine coverage regarding the use of CMRA in adults with CAD and children with congenital heart disease.

Washington State Utilization and Cost Data

The following Washington State Utilization and Cost Data section was prepared by staff at the Washington State Health Care Authority, and has been edited for formatting only.

Disclaimer: Fee schedules, relative value units, conversion factors and/or related components aren't assigned by the AMA, aren't part of CPT, and the AMA isn't recommending their use. The AMA doesn't directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein.

Populations

Administrative claims and encounter data for CMRA from the following Washington State health programs were assessed: the Public Employees Benefit Board Uniform Medical Plan (PEBB/UMP), Medicaid managed care (MCO) and fee-for-service (FFS), and the Department of Labor and Industries (L&I) Workers' Compensation Plan.

The assessment includes final paid and adjudicated claims and encounters. Denied claims or rejected encounters are excluded. Individuals that were dually eligible for both Medicare and Medicaid are excluded from the Medicaid program analysis. The PEBB/UMP experience includes claims for non-Medicare services.

Methods

The assessment includes only procedures and services specific to CMRA with a date of service between January 1, 2017, and December 31, 2020. Analysis does not include additional services associated with imaging procedures.

Claims and encounters with qualifying procedures or services according to current procedural terminology (CPT) code or Level II Healthcare Common Procedure Coding System (HCPCS) during the period were extracted for analysis.

Findings

Table I. Utilization of CMRA, by State Health Program (2017-2020)

	2017	2018	2019	2020	Total (Unique)
Medicaid					
Fee For Service (FFS)					
Individuals with at least one CMRA-related procedure	39	29	36	29	129
Female, count	17	NR	NR	16	51
Male, count	22	19	27	13	78

	2017	2018	2019	2020	Total (Unique)
Amount paid (estimated), CMRA	$7,372	$5,949	$9,296	$6,452	$29,068
Individuals	39	29	36	29	129
Average payments per individual	$205	$212	$282	$239	$242
Managed Care (MC)					
Individuals with at least one CMRA	342	354	403	427	1,490
Female, count	161	169	193	199	703
Male, count	181	185	210	228	787
Amount paid (estimated), CMRA	$90,645	$96,850	$104,140	$114,166	$405,802
Individuals	328	344	394	411	1,443
Average payments per individual	$240	$221	$239	$232	$239
Public Employees Benefit Board Uniform Medical Plan (PEBB/UMP)					
Individuals with at least one CMRA-related procedure/service	166	202	225	231	787
Female, count	65	93	95	110	349
Male, count	101	109	130	121	438
Amount paid, CMRA	$133,697	$130,541	$158,878	$161,865	$584,980
Individuals	166	202	225	231	787
Average payments per individual	$820	$676	$716	$716	$760
Washington State Department of Labor and Industries (L&I)					
Individuals with at least one CMRA-related procedure/service	NR	NR	NR	NR	NR
Female, count	NR	NR	NR	NR	NR
Male, count	NR	NR	NR	NR	NR
Amount paid, CMRA	$561	NR	$1,862	$1,696	$4,120
Individuals	NR	NR	NR	NR	NR
Average payments per individual	NR	NR	NR	NR	NR
Washington State: Combined Medicaid, PEBB/UMP, L&I					
Individuals with at least one CMRA-related procedure/service	548	585	667	689	2,412
Female, count	243	272	298	326	1,105
Male, count	305	313	369	363	1,307
Amount paid, CMRA	$232,275	$233,340	$274,176	$284,179	$1,023,970

Notes. Annual members for Medicaid excludes members that are dually eligible for Medicaid and Medicare. NR = not reported; small numbers suppressed to protect patient privacy. Managed care amount paid reflects an estimate of the amount paid for the procedure. UMP data does not reflect patient cost share. Individuals who had a procedure in more than 1 year are only counted once in the "Total" summary. Amounts paid of $0 were excluded from amount paid table value calculations.

Table II. Demographics of Medicaid Beneficiaries With at Least 1 CMRA procedure, SFY 2017-2020

Age	Total (Count)
20 years and below	106
21–44 years	695
45 years and above	818
Total	**1,618**

Table III. Codes and Cost by HCPCS/CPT Code (Maximum Allowable), by State Health Program and Setting

Code	Description	Medicaid FFS		L&I	
		Nonfacility	Facility	Nonfacility	Facility
75557	Cardiac magnetic resonance imaging for morphology and function without contrast material	$187.81	EAPG pricing	$607.91	$607.91
75559	Cardiac magnetic resonance imaging for morphology and function without contrast material; with stress imaging	$261.41	EAPG pricing	$846.15	$846.15
75561	Cardiac magnetic resonance imaging for morphology and function without contrast material(s), followed by contrast material(s) and further sequences	$247.01	EAPG pricing	$799.54	$799.54
75563	Cardiac magnetic resonance imaging for morphology and function without contrast material(s), followed by contrast material(s) and further sequences; with stress imaging	$292.81	EAPG pricing	$947.79	$947.79
75565	Cardiac magnetic resonance imaging for velocity flow mapping (List separately in addition to code for primary procedure)	$31.00	EAPG pricing	$100.35	$100.35

Sources. Medicaid FFS from 10-1-2020 Physician-Related Services Fee Schedule and OPPS Fee Schedule (accessed October 1, 2021; webpage). L&I from 2020 provider fee schedule (accessed October 1, 2021). PEBB/UMP fees are confidential and not publicly available (proprietary). CPT only copyright 2020 American Medical Association; all rights reserved.

Methods

This evidence review is based on the final key questions (KQs) published on March 15, 2021.[2] The draft KQs were available for public comment from March 16 to March 30, 2021, and appropriate revisions were made to the KQs based on the comments and responses.[3] All public comments received and a table of responses can be found on the Washington Health Technology Assessment website.[3] The draft report was available for public comment from September 7 through October 6, 2021, and appropriate revisions were made based on comments received, with the final report being posted to the program's website. This draft report was also peer-reviewed by subject matter experts, with appropriate revisions reflected in the final report. The PICO (population, intervention, comparator, outcome) statement, along with

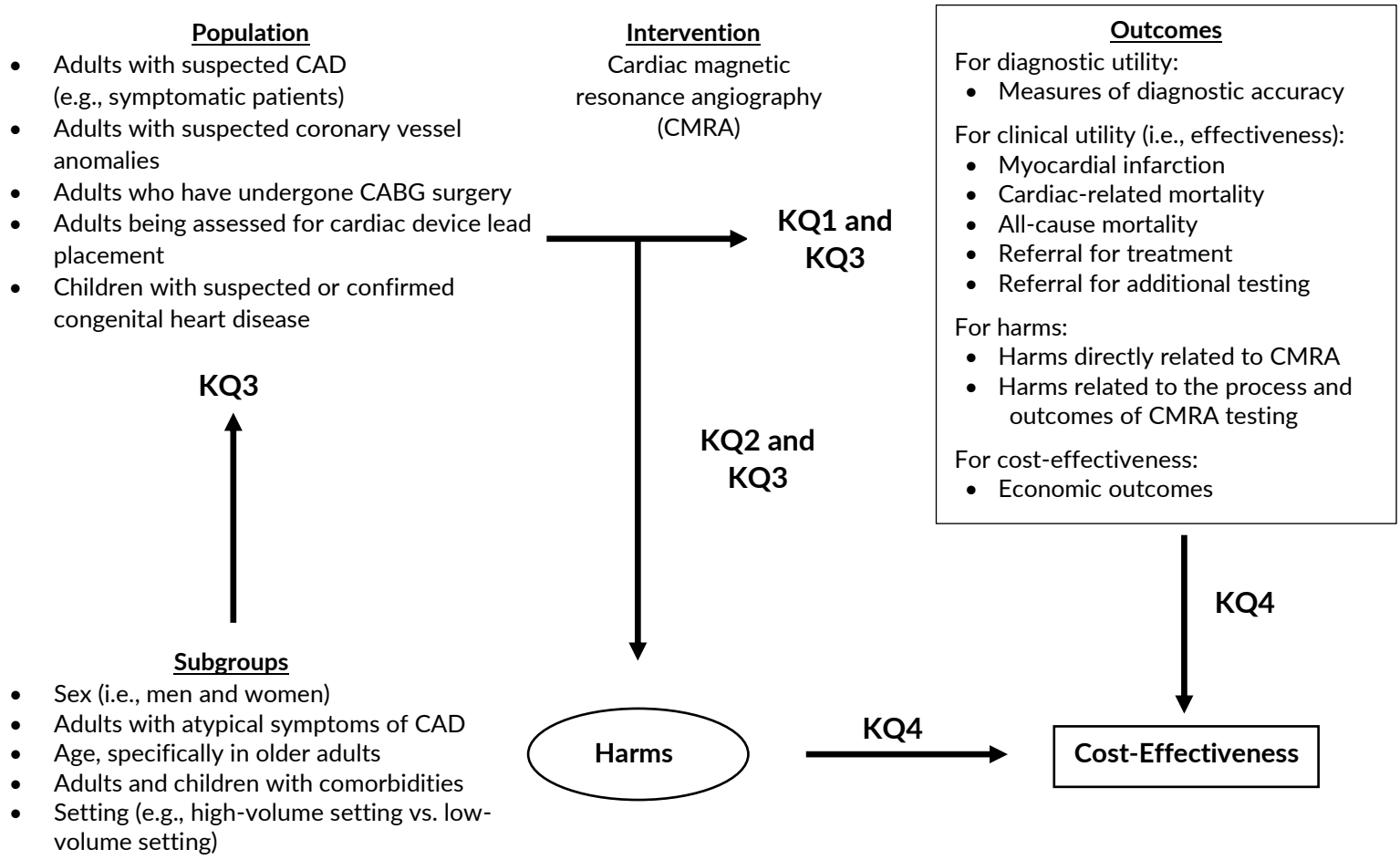
the setting, study design, and publication factors that guided development of the KQs and study selection are presented in Table 1 and Figure 1 below.

Key Questions

1. What is the evidence for the diagnostic validity (i.e., accuracy) and clinical utility (i.e., effectiveness) of CMRA (with or without contrast) in adults with suspected or confirmed CAD and children with suspected or confirmed congenital heart disease? The use of CMRA will be assessed in the following populations:
    a. Adults with suspected CAD (e.g., symptomatic patients)
    b. Adults with suspected coronary vessel anomalies
    c. Adults who have undergone coronary artery bypass graft (CABG) surgery
    d. Adults being assessed for cardiac device lead placement
    e. Children with suspected or confirmed congenital heart disease
2. What direct harms are associated with CMRA in adults with suspected or confirmed CAD and children with suspected or confirmed congenital heart disease? The harms of CMRA will be assessed in the following populations:
    a. Adults with suspected CAD (e.g., symptomatic patients)
    b. Adults with suspected coronary vessel anomalies
    c. Adults who have undergone CABG surgery
    d. Adults being assessed for cardiac device lead placement
    e. Children with suspected or confirmed congenital heart disease
3. Do important diagnostic validity (i.e., accuracy) outcomes, clinical utility (i.e., effectiveness) outcomes, or direct harms of CMRA in adults with suspected or confirmed CAD and children with suspected or confirmed congenital heart disease vary by the following populations or circumstances?
    a. Sex (i.e., men, women)
    b. Adults with atypical symptoms of CAD
    c. Age, specifically in older adults
    d. Adults and children with comorbidities
    e. Setting (e.g., high-volume setting vs. low-volume setting)
4. What are the cost-effectiveness and other economic outcomes of CMRA in adults with suspected or confirmed CAD and children with suspected or confirmed congenital heart disease? The economic outcomes of CMRA will be assessed in the following populations:
    a. Adults with suspected CAD (e.g., symptomatic patients)
    b. Adults with suspected coronary vessel anomalies
    c. Adults who have undergone CABG surgery
    d. Adults being assessed for cardiac device lead placement
    e. Children with suspected or confirmed congenital heart disease

Analytic Framework

Figure 1. Analytic Framework



Abbreviations. CABG: coronary artery bypass graft; CAD: coronary artery disease; CMRA: cardiac magnetic resonance angiography; KQ: key question.

Eligible Studies

Table 1 summarizes the study inclusion and exclusion criteria. During the development of this report, we also decided to limit studies of diagnostic test accuracy to those reporting results at the patient level to maximize the clinical utility of the findings, therefore excluding studies reporting results at the vessel level alone.

Table 1. Key Study Inclusion and Exclusion Criteria for CMRA in Adults and Children

Study Component	Inclusion	Exclusion
Populations	• Adult patients (≥ 18 years of age) with symptoms of suspected (previously undiagnosed) CAD who present with: ○ Stable (nonemergent) typical or atypical symptoms suspicious for CAD (e.g., chest pain, chest tightness, chest burning, shoulder pain, palpitations, jaw pain, or non-chest pain symptoms, such as dyspnea or worsening effort tolerance) • Adults with suspected coronary vessel anomalies • Adults who have undergone CABG surgery • Adults being assessed for cardiac device lead placement • Infants and children with suspected or confirmed congenital heart disease	• Studies including adults asymptomatic for CAD or adults presenting with an acute cardiac emergency • Studies in pregnant women • Studies in people with atrial fibrillation or heart failure • Studies assessing the use of CMRA in populations other than those specified (e.g., heart transplant patients, assessment of fetal cardiac abnormalities) • Studies assessing the use of MRA for vessels other than coronary vessels
Interventions	• CMRA (with or without contrast)	• Other cardiac imaging techniques, including stress perfusion CMRI, without angiographic evaluation • Novel uses of CMRA • Outdated CMRA equipment or methods of CMRA • Use of CMRA for screening or for monitoring purposes • Use of CMRA for preoperative assessment
Comparators	For diagnostic validity (i.e., accuracy): • Invasive coronary angiography (ICA) • Coronary computed tomography angiography (CCTA) For clinical utility (i.e., effectiveness), safety, and cost-effectiveness: • ICA • Other noninvasive testing • Usual care • No testing	• Comparisons of CMRA techniques, algorithms, analytic methods or protocols • Studies without a comparator intervention (except for harms) • Studies with indirect comparisons • Studies with an outdated comparator or a comparator intervention not available in the US • Studies evaluating CMRA for risk prediction or prognostic assessment • Studies published prior to 2000

Study Component	Inclusion	Exclusion

Outcomes	For diagnostic validity (i.e., accuracy):
	• Sensitivity and specificity
	• Positive and negative predictive values
	• Intra- and inter-rater reliability
	
	For clinical utility (i.e., effectiveness):
	• Primary outcomes
	  ○ Myocardial infarction
	  ○ Cardiac-related mortality
	  ○ All-cause mortality
	• Secondary outcomes
	  ○ Referral for treatment
	  ○ Referral for additional testing
	
	For harms:
	• Harms directly related to CMRA (e.g., severe reaction to the contrast dye, radiation exposure)
	• Harms related to the process and outcomes of CMRA testing (e.g., anxiety requiring sedation during testing, psychological consequences of testing, work days lost)
	
	For cost-effectiveness:
	• Cost-effectiveness outcomes (e.g., cost per improved outcome) or cost-utility outcomes (e.g., cost per QALY, ICER)
		• Other outcomes not listed
		• Outcomes not reported at the patient level (e.g., only vessel level results reported)
		• Economic outcomes from studies performed in non-US countries
		• Economic outcomes from studies performed in the US that were published more than 5 years ago

Timing	• Any point in the diagnostic workup, including in the emergency setting • After CABG surgery • Prior to cardiac lead placement	• Timing other than those stated
Setting	• Any outpatient or inpatient clinical setting in countries categorized as very high on the UN Human Development Index[65]	• Emergency settings • Nonclinical settings (e.g., studies in healthy volunteers, animal models of disease) • Countries categorized other than very high on the UN Human Development Index[65]
Study Design	For KQ1–KQ4: • Randomized controlled trials • Nonrandomized, comparative studies with 10 or more participants in each group Additional studies/data for KQ2 and KQ3 (harms): • Governmental or other large, multisite registries with 100 or more participants • Databases of procedure-related harms or device recalls (e.g., FDA MAUDE database, FDA Medical Device Recall database)	• Abstracts, conference proceedings, posters, editorials, letters • Nonrandomized, comparative studies with fewer than 10 participants in each group • Studies without a comparator (except for harms) • Proof-of-principle studies (e.g., technology development or technique modification) • Registries with fewer than 100 participants

Study Component	Inclusion	Exclusion
	Additional studies/data for KQ4: • Cost-effectiveness studies and other formal comparative economic evaluations For effectiveness, we will search for RCTs and only include observational studies in the absence of RCTs. Studies published in publicly available FDA reports will also be included, if they meet the additional criteria reported above.	
Publication	• Studies in peer-reviewed journals, technology assessments, or publicly available FDA or other US government reports • Published in English • Published since January 2000	• Studies with abstracts that do not allow study characteristics to be determined • Studies that cannot be located • Duplicate publications of the same study that do not report different outcomes or follow-up times, or single site reports from published multicenter studies • Studies in languages other than English

Abbreviations. CABG: coronary artery bypass graft; CAD: coronary artery disease; CMRA: cardiac magnetic resonance angiography; FDA: US Food and Drug Administration; ICA: invasive coronary angiography; ICER: incremental cost-effectiveness ratio; KQ: key question; MAUDE: Manufacturer and User Facility Device Experience; MRI: magnetic resonance imaging; QALY: quality-adjusted life year; RCT: randomized controlled trial; UN: United Nations.

Data Sources and Searches

We conducted searches of the peer-reviewed published literature using multiple electronic databases. The time periods for searches were:

- Ovid MEDLINE and Epub Ahead of Print, In-Process & Other NonIndexed Citations and Daily: from January 1, 2000 to May 3, 2021
- Cochrane Library databases (Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials): from January 1, 2000 to May 3, 2021

Randomized controlled trials (RCTs) and systematic reviews (with and without meta-analyses) and health technology assessments that included RCTs were considered for KQ1 to KQ4. Nonrandomized comparative studies and nonrandomized studies (NRS) without a comparator from large, multicenter, national and international registries were considered for KQ1 and KQ3 and for the harm-related aspects of KQ2 and KQ3 if evidence for the intervention was included in KQ1. For KQ4, we also considered cost-effectiveness studies and other comparative economic evaluations, as well as systematic reviews (with and without meta-analyses) reporting economic outcomes.

The Ovid MEDLINE search strategy is shown in Appendix A. We also screened reference lists of relevant studies and used lateral search functions, such as *related articles* and *cited by*. We searched the following additional sources:

- Agency for Healthcare Research and Quality (AHRQ)
- National Institute for Health and Care Excellence (NICE) – Evidence
- Veterans Administration Evidence-based Synthesis Program

We searched these sources for systematic reviews and clinical practice guidelines using the same search terms outlined for the evidence search. In addition, we conducted a search of GuidelineCentral[66]and the Guidelines International Network guidelines library[67] in July and August 2021, as well as the websites of professional organizations for relevant guidelines. In these searches we used terms related to CMRA, and considered guidelines published in the past 5 years (January 2016 to July 2021) for inclusion. We included studies on CMRA published since 2000.

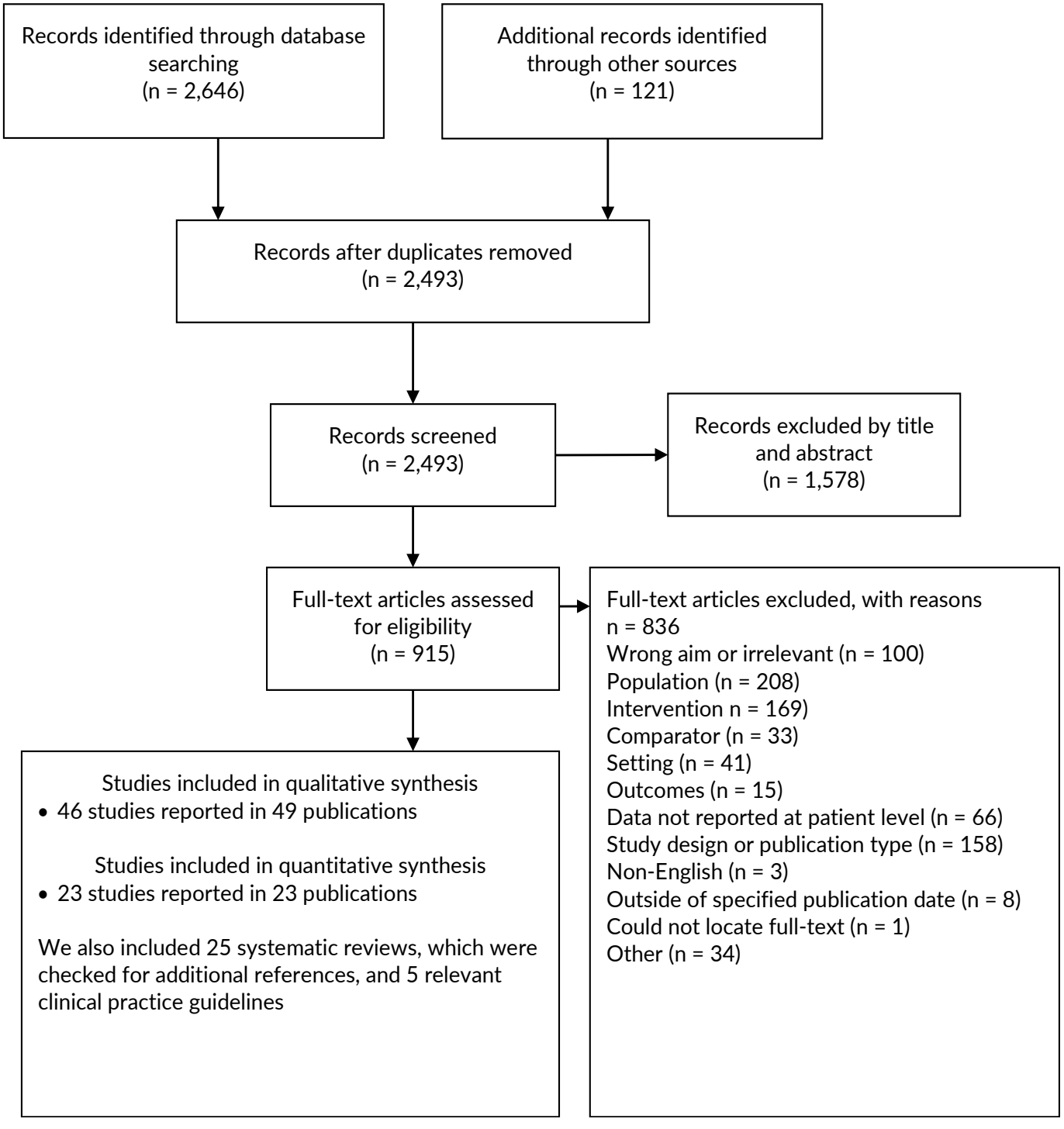
Using Google, we conducted a general internet search for appropriate published studies and relevant gray literature. Because of the limited reporting of harms in published studies, we also conducted a search of the US Food and Drug Administration (FDA) Manufacturer and User Facility Device Experience database (MAUDE) for CMRA. We searched for reports posted through July 2021, and the searchable database contains reports from the past 5 years. We also conducted a search of the FDA database of Medical Device Recalls, from its inception in 2002 through July 2021. Findings from these searches are described in the relevant sections, and a detailed table of reports from both of these databases can be found in Appendix F. We searched for National Coverage Determinations and Local Coverage Determinations relevant to the state of Washington in the Medicare Coverage Database located on the Centers for Medicare & Medicaid Services (CMS) website. We also searched the Aetna, Cigna, and Regence websites for private payer coverage policies.

To identify relevant ongoing clinical trials, in June 2021 we searched the online database of ClinicalTrials.gov maintained by the National Library of Medicine at the National Institutes of Health for terms related to CMRA. The information in this database was provided by the sponsor or principal investigator of each study. Studies are generally registered in the database when they begin and information is updated as the study progresses. We also considered studies submitted during the public comment process for possible inclusion.

Screening

We (VK, MR, and BS) independently screened titles and abstracts and reached agreement on the exclusion of studies or guidelines through discussions. We performed dual full-text review for any study not excluded by review of title and abstract (Appendix G lists the excluded studies at full-text review, with reasons). For studies or guidelines on which we did not agree after initial full-text review, we discussed each study and came to consensus. Any remaining disagreements were settled by a third independent researcher (CH) from the Center for Evidence-based Policy (Center).

Figure 2. PRISMA Study Flow Diagram



Data Abstraction and Quality Assessment

We used standardized procedures to extract relevant data from each of the included trials and fully cross-checked all entered data for accuracy.

We (VK and BS) evaluated each eligible study for methodological risk of bias (see Appendix D) and held discussions to reach agreement on these assessments. Any remaining disagreement was settled by a third independent researcher (CH). Each trial was assessed using Center instruments adapted from national and international standards and assessments for risk of bias.[68-72] A rating of high, moderate, or low risk of bias was assigned to each study based on adherence to recommended methods and the potential for internal and external biases. The risk-of-bias criteria for the study types are shown in Appendix B.

We (MR and BS) evaluated the methodological quality of eligible clinical practice guidelines. Any remaining disagreement among these assessments was settled by a third independent researcher (VK). The methodological quality of clinical practice guidelines was rated as good, fair, or poor; the assessment criteria for the methodological quality of the clinical practice guidelines are shown in Appendix D, Table D3.

Data Analysis and Synthesis

When study authors did not report measures of test performance or the studies included reporting discrepancies, we calculated relevant test performance statistics with 95% confidence intervals (CIs), based on the reported or calculated 2 × 2 tables.

While traditional meta-analysis involves the quantitative synthesis of data across studies for a single outcome, meta-analysis of diagnostic test accuracy (DTA) studies requires a method that simultaneously synthesizes a pair of outcomes: sensitivity and specificity. Sensitivity can be defined as a test's ability to classify an individual with a disease as having that disease. The specificity of a test quantifies its ability to classify an individual without a disease as not having that disease. Given the interdependent relationship between the 2 measures, they tend to be inversely correlated. To assess the diagnostic accuracy of CMRA, we used the bivariate and hierarchical summary receiver operating curve (HSROC) models to directly model sensitivity and specificity while accounting for the correlation across the 2 measures.

In the primary analysis, we included all diagnostic test accuracy studies evaluating CMRA against our predefined reference standards (i.e., invasive coronary angiography [ICA] and coronary computed tomography angiography [CCTA]). We pooled data across studies where more than 3 studies reported the same reference standard. If more than 3 studies reported similar thresholds using the same reference standard, we conducted analyses according to threshold.

We assigned selected outcomes a summary judgment for the overall certainty of evidence (CoE; Appendix E) using the system developed by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) Working Group.[4,5] The outcomes varied by population and the aim of testing, but focused on diagnostic performance and clinical utility, in line with the KQs.

The GRADE system[5] defines the overall certainty of a body of evidence for an outcome in the following manner:

- **High**: Raters are very confident that the estimate of the effect of the intervention on the outcome lies close to the true effect. Typical sets of studies are RCTs with few or no limitations, and the effect estimate is likely stable.
- **Moderate**: Raters are moderately confident in the estimate of the effect of the intervention on the outcome. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is different. Typical sets of studies include RCTs with some limitations or well-performed NRSs with additional strengths that guard against potential bias and have large estimates of effects.
- **Low**: Raters have little confidence in the estimate of the effect of the intervention on the outcome. The true effect may be substantially different from the estimate of the effect. Typical sets of studies include RCTs with serious limitations or nonrandomized studies without special strengths.
- **Very low**: Raters have no confidence in the estimate of the effect of the intervention on the outcome. The true effect is likely to be substantially different from the estimate of the effect. Typical sets of studies include NRSs with serious limitations or inconsistent results across studies.
- **Not applicable**: Researchers did not identify any eligible articles.

Key Concepts and Definitions

A summary of key concepts and definitions for diagnostic performance can be seen in Table 2.

Table 2. Key Concepts and Definitions for Diagnostic Performance

Term	Definition
Area Under the HSROC Curve (AUROC)	The probability that the test will correctly rank a randomly chosen diseased individual above a randomly chosen non-diseased individual. Higher values indicated higher probability that the test will correctly discriminate between diseased and non-diseased individuals. An AUROC of 1 represents a perfect test, while an AUROC of 0.5 represents an uninformative test.
False Positive Rate (FPR)	The proportion of individuals with a target disease that are identified as not having the target disease (1 – specificity)
Negative Likelihood Ratio (NLR)	The probability of a patient testing negative who has a disease divided by the probability of an individual testing negative who does not have a disease (i.e., the FPR divided by the specificity). In other words, the NLR indicates how much less likely the negative test result is to occur in an individual with a disease than in a healthy individual. The lower the NLR, the stronger the evidence of absence of the disease.
Positive Likelihood Ratio (PLR)	The probability that a positive test would be expected in individuals with a disease relative to the probability that a positive test would be expected in individuals without a disease (i.e., the TPR divided by the FPR). In other words, the PLR indicates how many times more likely a positive test result will occur in individuals with the disease than those without the disease. The higher the PLR, the more likely an individual with a disease will be identified as having the disease.
Sensitivity	The proportion of individuals with a target disease that are identified as having the disease by the diagnostic test

Term	Definition
Specificity	The proportion of individuals that do not have a target disease that are identified as not having the disease by the diagnostic test
True Positive Rate (TPR)	Otherwise known as sensitivity

Abbreviation. HSROC: hierarchical summary receiver operating curve.

Evidence Summary

Our database searches returned a total of 2,646 records, published since 2000. We also checked the reference lists of relevant systematic reviews.

We found 121 additional studies beyond those identified in electronic databases, through reference list checking, Google, gray literature searches, or suggested by peer reviewers and public commenters. After duplicate studies were removed, 2,493 records remained (Figure 2). Of these, 915 required full-text review to determine eligibility. In total, 37 diagnostic test accuracy studies (in 40 publications) and 9 NRSs (in 9 publications) met the inclusion criteria for KQ1, KQ2, and KQ3.

KQ1 and KQ2

A. Adults With Suspected CAD

We found 26 studies, reported in 29 publications, evaluating the diagnostic validity (i.e., accuracy) of CMRA (with or without contrast) in adults with suspected CAD. (Table 3 and Appendix C, Table C1).[8,9,11,14,16-23,25-27,29-32,34-37,40-42,52-54] We rated the risk of bias in these studies as follows, with the categories ordered by the order of KQs:

- 6 DTA studies had a low risk of bias, with no significant concerns identified.[8,16,21,27,32,42]
- 14 DTA studies had a moderate risk of bias due to uncertainty about patient selection or blinding of results, and funding sources or conflicts of interest not being reported.[9,11,14,17-20,22,23,25,29,34,35,37,41]
- 6 DTA studies had a high risk of bias due to concerns including the lack of blinding, uncertainty around patient selection, and small sample sizes.[26,29-31,36,40]

We did not find any RCTs or comparative NRSs evaluating the clinical utility (i.e., effectiveness) of CMRA in this population.

Study Characteristics

Across the 26 included diagnostic test accuracy studies[8,9,11,14,16-23,25-27,29-32,34-37,40-42]:

- Publication dates ranged from 2000 to 2020.
- Sample sizes ranged from 10 to 628 (median 53, interquartile range [IQR] 31 to 75), and included over 1,113 total participants.
- The majority of participants were male (median, 70%; range from 60% to 87%), with no studies recruiting women only.
- The mean age ranged from 58 to 69 across studies.

The 26 studies evaluated CMRA, using a range of protocols and comparators (Table 3).

We assessed the majority of studies as being at low to moderate risk of bias, with 5 studies being at high risk of bias because of patient selection concerns and conflicts of interest.[8,9,11,14,16-23,25-27,29-32,34-37,40-42,52-54]

Table 3. Characteristics of Eligible Studies Evaluating the Performance of CMRA in Adults With Suspected CAD

Study Risk of Bias	Setting	Population	CMRA Protocol	Magnet Strength	Comparator(s) and Threshold(s)
Bettencourt et al., 2013[8] Low risk of bias	Cardiology outpatient clinic in a non-academic hospital, Portugal	43 adults with suspected CAD and at least 2 CV risk factors or an inconclusive treadmill test	Whole-heart CMRA, alone or with cine imaging, rest/stress perfusion, and LGE	1.5 T	Combined ICA, at a threshold of 90% or more, and ICA-FFR, at a threshold of 80% or more
Bogaert et al., 2003[9] Moderate risk of bias	2 clinics, 1 each in the US and in Belgium	19 adults referred for ICA (e.g., stable angina pectoris, positive stress test results, recurrent chest pain after previous CABG surgery)	CMRA alone No gadolinium-based contrast used	1.5 T	ICA, at a threshold of 50% or more
Dewey et al., 2006[11] Moderate risk of bias	Single tertiary referral center in Germany	108 adults scheduled to undergo ICA within 14 days for clinically suspected CAD, based on symptoms or results of diagnostic tests (e.g., treadmill exercise test, myocardial scintigraphy, or ECG), at least 40 years of age, and who were in sinus rhythm	CMRA alone No gadolinium-based contrast used	1.5 T	ICA, at a threshold of 50% or more
Greenwood et al., 2012[14] Moderate risk of bias	Multisite study in 2 hospitals (1 university hospital) in the UK	628 adults with suspected angina pectoris, at least 1 major CV risk factor and a cardiologist judged them to have stable angina needing investigation	3-D CMRA, with cine imaging, rest/stress perfusion, and LGE Gadopentetate used as the contrast agent	1.5 T	ICA, at a threshold of 50% or more
Hamdan et al., 2011[16] Low risk of bias	2 hospitals, 1 each in Germany and in Israel	110 adults aged 50 and older, referred for ICA for suspected or known CAD	3-D CMRA, with cine imaging No gadolinium-based contrast used	3.0 T	ICA, at a threshold of 50% or more
Heer et al., 2013[17]	University hospital in Germany	144 adults with known or suspected CAD	Whole-heart CMRA alone or with	1.5 T	ICA, at a threshold of 50% or more

Study Risk of Bias	Setting	Population	CMRA Protocol	Magnet Strength	Comparator(s) and Threshold(s)
Moderate risk of bias			rest/stress perfusion, and LGE Gadodiamide used as the contrast agent, as appropriate		
Ikonen et al., 2003[18] Moderate risk of bias	Clinic at in a university hospital in Finland	69 adults referred to for ICA because of suspected or previously diagnosed CAD stable angina pectoris	CMRA No gadolinium-based contrast used	1.5 T	ICA, at a threshold of greater than 50%
Kato et al., 2010[19] Moderate risk of bias	Multisite study conducted at 7 hospitals in Japan	127 adults with suspected CAD who presented with chest pain that suggested newly developed or recurrent coronary artery stenosis and were scheduled for ICA	Whole-heart CMRA, with cine imaging No gadolinium-based contrast used	1.5 T	ICA, at a threshold of 50% or more
Kefer et al., 2005[20] Moderate risk of bias	Clinic at a university hospital in Belgium	52 adults referred for ICA, in sinus rhythm and no prior revascularization (no stents or bypass operation)	CMRA No gadolinium-based contrast used	1.5 T	ICA, at a threshold of greater than 50%
Kim et al., 2001[21] Low risk of bias	Multisite study across 7 institutions in Denmark, Germany, Netherlands, Switzerland, UK, and US	103 adults, in sinus rhythm and with a body mass of 100 kg or less, scheduled to undergo ICA for suspected CAD within 14 days	CMRA No gadolinium-based contrast used	1.5 T	ICA, at a threshold of 50% or more
Klein et al., 2008[22] Moderate risk of bias	Specialist clinic in Germany	54 adults with suspected CAD who were referred for ICA	Whole-heart CMRA, with cine imaging, rest/stress perfusion, and LGE Gadolinium-BOPTA used as the contrast agent	1.5 T	ICA, at a threshold of 50% or more
Kunimasa et al., 2009[23] Moderate risk of bias	Clinic at a university hospital in Japan	43 adults with suspected CAD, scheduled for ICA	Whole-heart CMRA, with cine imaging No gadolinium-based contrast used	1.5 T	ICA, at a threshold of 50% or more

Study Risk of Bias	Setting	Population	CMRA Protocol	Magnet Strength	Comparator(s) and Threshold(s)
Langer et al., 2009[25] Moderate risk of bias	Clinic at a university hospital in Germany	68 adults referred for ICA	CMRA alone No gadolinium-based contrast used	1.5 T	ICA, at a threshold of 50% or more
Maintz et al., 2007[26] High risk of bias	Clinic at a university hospital in Germany	25 adults who had previously undergone ICA and coronary computed tomography angiography	Whole-heart CMRA, with cine imaging No gadolinium-based contrast used	1.5 T	ICA, at a threshold of 50% or more
Nagata et al., 2011[27] Low risk of bias	Radiology and cardiology departments at a university hospital in Japan	67 adults suspected of having CAD and presented with chest pain suggestive of newly developed or recurrent coronary artery stenosis and who were scheduled for ICA	Whole-heart CMRA, with cine imaging No gadolinium-based contrast used	1.5 T	ICA, at a threshold of 50% or more
Ogawa et al., 2020[29] High risk of bias	Single hospital in Japan	28 adults scheduled for CMRA (no further details)	Whole-heart CMRA, with cine imaging, rest/stress perfusion, and LGE Gadobutrol used as the contrast agent	3.0 T	ICA, at a threshold of 50% or more
Piccini et al., 2014[30] High risk of bias	University hospital in Switzerland	29 adults referred for a range of indications, including CAD and other reasons (e.g., cardiomyopathy)	Whole-heart CMRA, with cine imaging, rest/stress perfusion, and LGE Gadobutrol used as the contrast agent	1.5 T	ICA, at a threshold of greater than 50%
Plein et al., 2002[31] High risk of bias	Clinic at a university hospital in the UK	10 adults who attended the cardiology outpatient clinic and had recently undergone or were waiting to undergo ICA	3D CMRA, with cine imaging, rest/stress perfusion, and LGE Gadopentetate dimeglumine used as the contrast agent	1.5 T	ICA, at a threshold of greater than 70%
Pouleur et al., 2008[32] Low risk of bias	Cardiac clinic at a university hospital in Belgium	77 adults referred for ICA, who were in sinus rhythm and who had no prior revascularization (no stent or bypass operation)	Whole-heart CMRA, with cine imaging No gadolinium-based contrast used	1.5 T	ICA, at a threshold of greater than 50%

Study Risk of Bias	Setting	Population	CMRA Protocol	Magnet Strength	Comparator(s) and Threshold(s)
Regenfus et al, 2000[34] Moderate risk of bias	Clinic at a university hospital in Germany	50 adults admitted for diagnostic ICA due to clinically suspected CAD	CMRA alone Gadopentetate dimeglumine used as the contrast agent	1.5 T	ICA, at a threshold of greater than 50%
Sakuma et al., 2005[36] High risk of bias	Clinic at a university hospital in Japan	20 adults with suspected CAD	Whole-heart CMRA, with cine imaging No gadolinium-based contrast used	1.5 T	ICA, at a threshold of 50% or more
Sakuma et al., 2006[35] Moderate risk of bias	Clinic at a university hospital in Japan	113 adults with suspected CAD, scheduled for ICA	Whole-heart CMRA, with cine imaging No gadolinium-based contrast used	1.5 T	ICA, at a threshold of 50% or more
Sardanelli et al., 2000[37] Moderate risk of bias	Clinic at a university hospital in Italy	39 adults with angina and ECG signs of ischemic heart disease	3D CMRA alone No gadolinium-based contrast used	1.5 T	ICA, at a threshold of 50% or more
Wagner et al., 2011[40] Moderate risk of bias	Clinic at a university hospital in Germany	27 adults with suspected CAD on computed tomography and indication for ICA	Whole-heart CMRA, with cine imaging, with or without contrast Gadofosveset trisodium used as the contrast agent	1.5 T	ICA, at a threshold of 50% or more
Yang et al., 2003[41] Moderate risk of bias	VA hospitals in the US	40 adults with suspected CAD	CMRA alone No gadolinium-based contrast used	1.5 T	ICA, at a threshold of greater than 50%
Yonezawa et al., 2014[42] Low risk of bias	Radiology and cardiology departments at a university hospital in Japan	62 adults with suspected CAD who presented with chest pain suggestive of newly developed or recurrent coronary artery stenosis	Whole-heart CMRA, with cine imaging No gadolinium-based contrast used	1.5 T	ICA, at a threshold of greater than 50%

Abbreviations. CABG: coronary artery bypass graft; CAD: coronary artery disease; CMRA: cardiac magnetic resonance angiography; CV: cardiovascular; ECG: electrocardiogram; FFR: fractional flow reserve; ICA: invasive coronary angiography; LGE: late gadolinium enhancement; T; Tesla; VA: US Department of Veterans Affairs.

Further details of the included studies can be seen in Appendix C, Table C1. Of these, only 1 study did not provide enough data to construct 2 × 2 tables.[14] We also found 1 study reporting results for 2 readers, without presenting a consensus finding, and we therefore excluded this study from the meta-analysis.[9]

Study Findings

Meta-Analysis of Diagnostic Accuracy

We combined 23 unique studies evaluating the diagnostic performance of CMRA to diagnose CAD in adults with known or suspected CAD.[11,16-23,25-27,29-32,34-37,40-42] In the primary analysis, we included studies evaluating CMRA against ICA, where data allowed. We did not identify any studies directly comparing CMRA against CCTA that could be combined in adults with suspected CAD. We pooled data across studies where more than 3 studies reported the same reference standard. Summary estimates for sensitivity, specificity, the diagnostic odds ratio, positive and negative likelihood ratios, and the area under the receiver operator characteristic curve were calculated (Table 4; Figures 3 to 6).

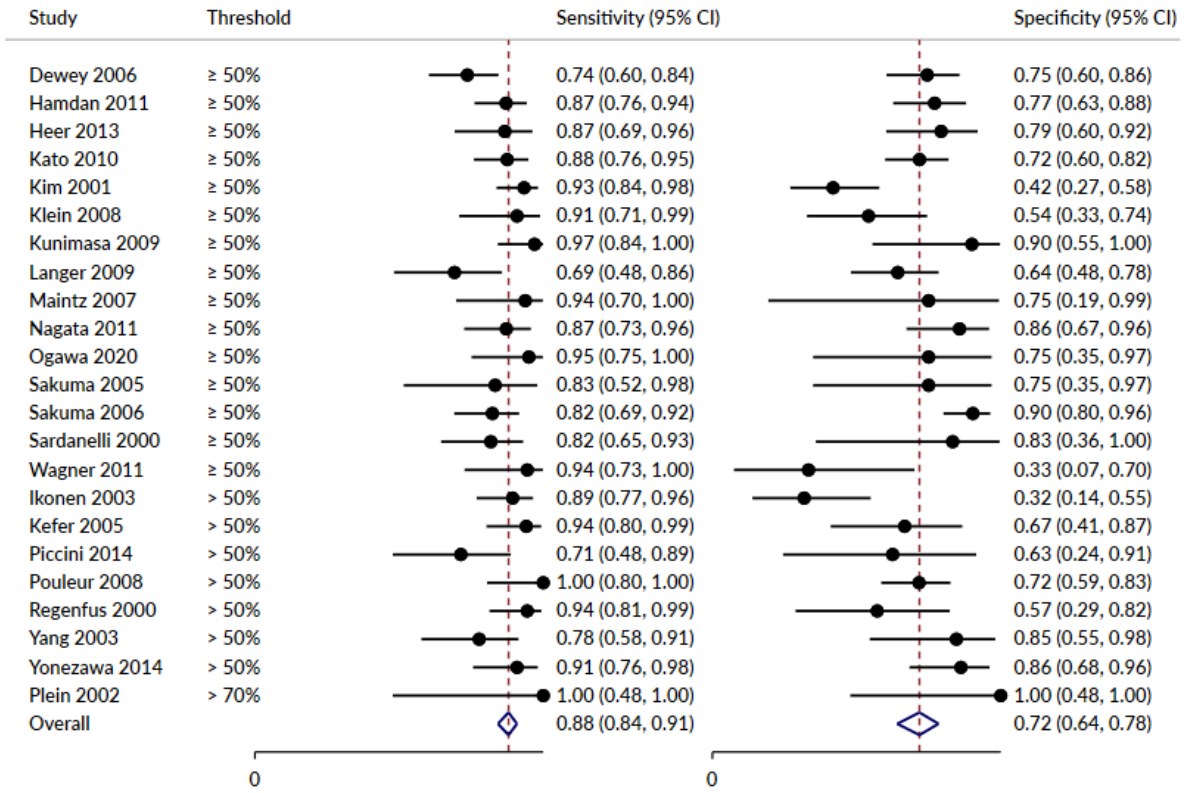
Across the 22 individual studies comparing CMRA to ICA with a 50% threshold for CAD, sensitivity ranged from 69% to 100% and specificity from 32% to 90%. In the single study comparing CMRA against ICA with a 70% threshold for CAD, sensitivity and specificity were both 100%. When pooled, the summary sensitivity was 88% (95% CI, 84% to 91%) and the summary specificity was 72% (64% to 78%; Table 4). The results did not change substantially if the analysis excluded the single study with a 70% ICA threshold.

Table 4. Summary of Pooled Results Comparing CMRA to ICA in Adults with Suspected CAD

Reference Threshold	Studies	Corr.	Pooled Sensitivity (95% CI)	Pooled Specificity (95% CI)	PLR (95% CI)	NLR (95% CI)	AUROC (95% CI)
≥ 50%, > 50%, or > 70%	N = 23	−0.42	0.88 (0.84 to 0.91)	0.72 (0.64 to 0.78)	3.1 (2.4 to 4.0)	0.17 (0.13 to 0.22)	0.89 (0.86 to 0.92)
≥ 50% or > 50%	N = 22	−0.45	0.88 (0.84 to 0.91)	0.71 (0.63 to 0.78)	3.0 (2.4 to 3.9)	0.17 (0.13 to 0.22)	0.89 (0.86 to 0.91)

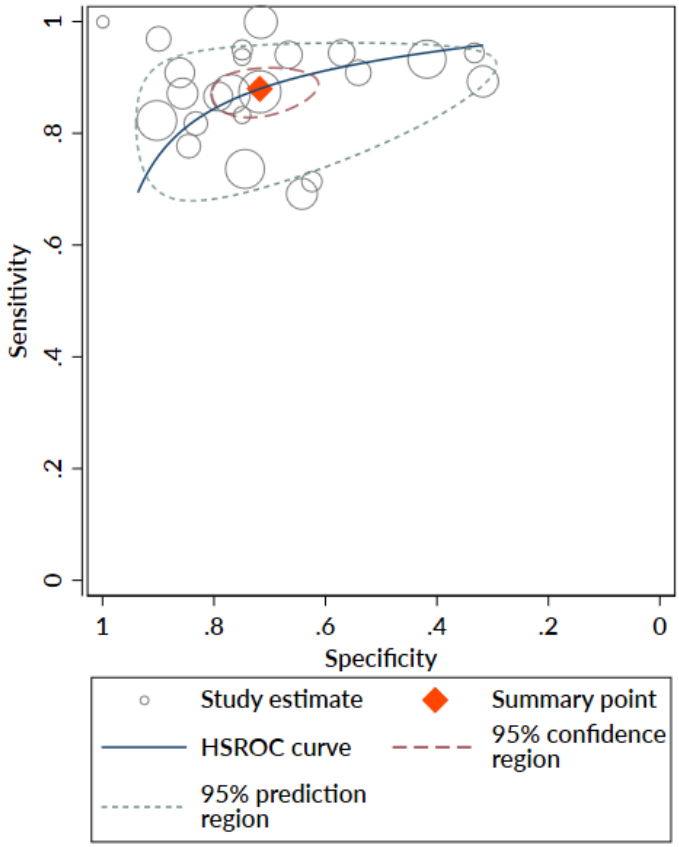
Abbreviations. AUROC: area under the receiver operator characteristic curve; CAD: coronary artery disease; CI: confidence interval; CMRA: cardiac magnetic resonance angiography; Corr.: Spearman's rank correlation; ICA; Invasive Coronary Angiography; NLR: negative likelihood ratio; PLR: positive likelihood ratio.

Figure 3. Diagnostic Accuracy Results: CMRA vs. ICA (All Thresholds)



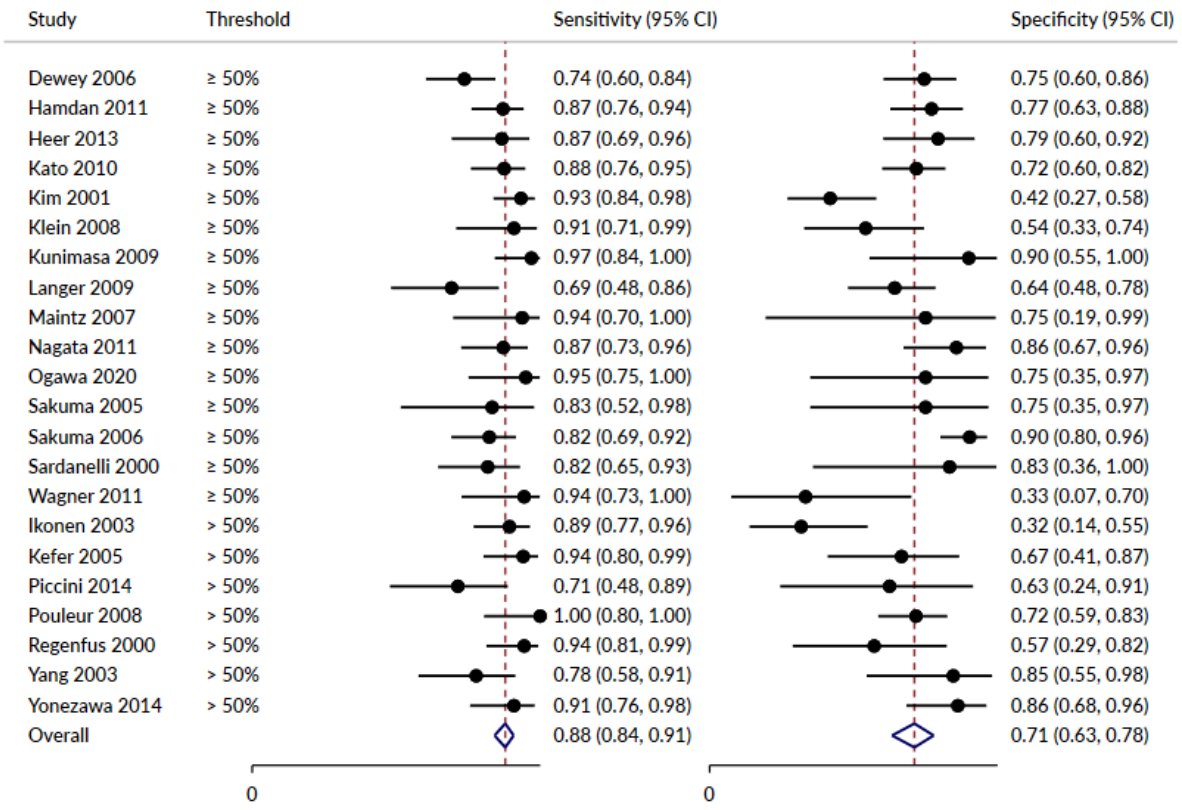
Abbreviations. CI: confidence interval; CMRA: cardiac magnetic resonance angiography; ICA: invasive coronary angiography.

Figure 4. HSROC Analysis for CMRA vs. ICA (All Thresholds)



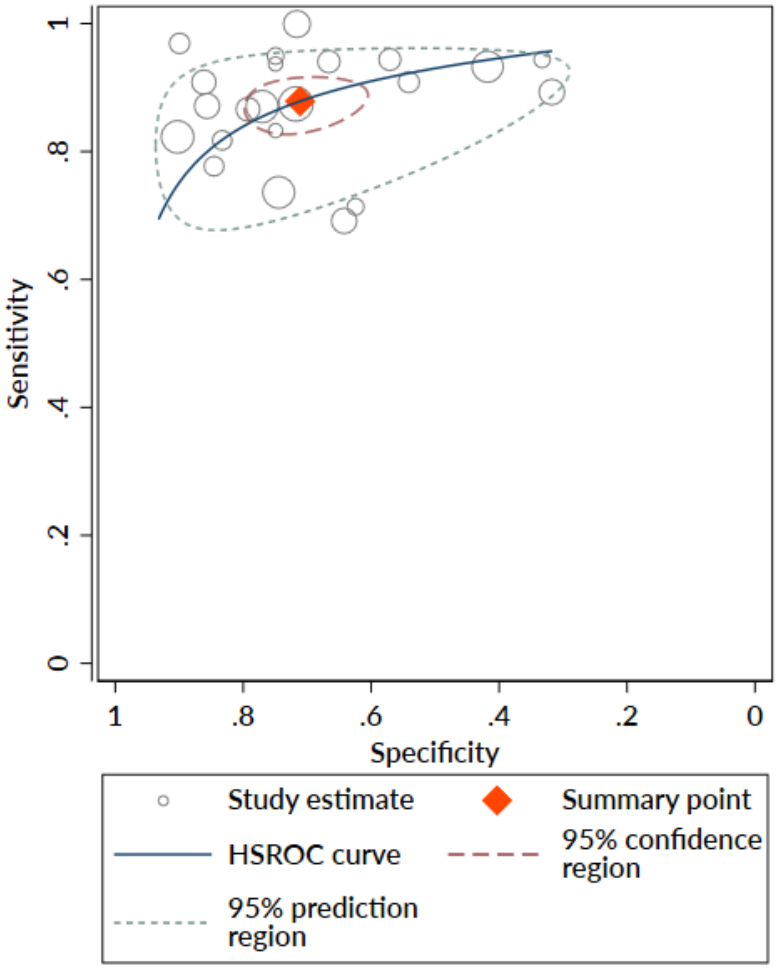
Note. The HSROC curve illustrates the tradeoff between sensitivity and specificity across the study estimates; the 95% confidence region provides a visual estimate of the amount of variation around the pooled estimate that is due to sampling error (i.e., chance); the 95% prediction region provides a visual estimate of the between-study variability that cannot be attributed to chance, and is the region where any future study is predicted to lie.
Abbreviations. CMRA: cardiac magnetic resonance angiography; HSROC: hierarchical summary receiver operating curve; ICA: invasive coronary angiography.

Figure 5. Diagnostic Accuracy Results: CMRA vs. ICA (≥ 50% or > 50% Thresholds)



Abbreviations. CI: confidence interval; CMRA: cardiac magnetic resonance angiography; ICA: invasive coronary angiography.

Figure 6. HSROC Analysis for CMRA vs. ICA (≥ 50% and > 50% Thresholds)



Note. The HSROC curve illustrates the tradeoff between sensitivity and specificity across the study estimates; the 95% confidence region provides a visual estimate of the amount of variation around the pooled estimate that is due to sampling error (i.e., chance); the 95% prediction region provides a visual estimate of the between-study variability that cannot be attributed to chance, and is the region where any future study is predicted to lie.
Abbreviations. CMRA: cardiac magnetic resonance angiography; HSROC: hierarchical summary receiver operating curve; ICA: invasive coronary angiography.

Additional Data on Diagnostic Performance From Studies Included in the Meta-Analysis

In this section, we report additional data from several studies included in the meta-analysis.

Dewey and colleagues[11] reported the ability of CMRA to assess CAD using only the 8 proximal and middle coronary arteries and using all 15 coronary segments. When using all 15 coronary segments, the sensitivity of CMRA, when compared to ICA, was 69% (95% CI, 56% to 80%) and specificity was 74% (95% CI, 60% to 86%).[11] When compared with multislice computed tomography, the sensitivity of CMRA for both the 8 proximal vessels and all 15 coronary segments was significantly lower (74% and 69% vs. 92%; $P < .01$), but the specificity was not significantly different (75% and 74% vs. 79%; $P > .06$).[11]

In a patient-based analysis by Hamdan and colleagues,[16] CMRA and 64-slice computed tomography angiography had a similar ability to diagnose coronary artery stenosis of 50% more, with sensitivities of 54% and 56% ($P = .16$) and specificities of 83% and 77% ($P = .06$). CMRA and 64-slice computed tomography angiography also had a similar ability to predict subsequent coronary revascularization at 1 month after testing.[16]

In 52 adults referred for ICA, CMRA and 16-slice multidetector row computed tomography had a similar ability to detect CAD, defined as greater than 50% diameter stenosis.[20] The sensitivities were 75% and 82% ($P \geq .05$) and specificities 77% and 79% ($P \geq .05$).[20] However, it should be noted that 16-slice computed tomography would now be considered as old or obsolete technology, as machines with higher numbers of detector rows are now available.[73]

Klein and colleagues[22] compared different MRI parameters in 54 adults with suspected CAD. The authors found that, compared with ICA, CMRA had a sensitivity of 91% (95% CI, 69% to 98%) and a specificity of 54% (95% CI, 33% to 74%).

In 68 patients referred for ICA, Langer and colleagues[25] found that 16-slice multidetector row computed tomography was able to diagnose CAD significantly better than CMRA, with a higher specificity (95% vs. 77%; $P = .0008$) and a higher diagnostic accuracy (96% vs. 66%; $P < .0001$; sensitivity was not reported). Subgroup analysis focusing by heart rate, body mass index, age, and sex showed no significant differences between the subgroups with regard to the test used.[25] However, it should be noted that 16-slice computed tomography would now be considered as old or obsolete technology, as machines with higher numbers of detector rows are now available.[73]

Pouleur and colleagues[32] compared the use of CMRA and 40-slice or 60-slice multidetector computed tomography in 77 adults referred for ICA. On a per-patient basis, the sensitivity of CMRA and multidetector computed tomography was similar (100% vs. 94%; $P = .9$).[32] However, CMRA had a significantly lower specificity (72% vs. 88%; $P = .02$) and diagnostic accuracy (78% vs. 90%; $P = .04$) than multidetector computed tomography for the detection of diameter stenosis of 50% or more.[32]

Only 1 included study[42] reported on the intraobserver and interobserver reliability of CMRA. Using quantitative analysis, the observers were in almost perfect agreement[74] (intraobserver agreement, 0.84; 95% CI, 0.70 to 0.97; interobserver agreement, 0.81; 95% CI, 0.66 to 0.95).[42]

Using visual analysis, the observers were in substantial agreement[74] (intraobserver agreement, 0.77; 95% CI, 0.61 to 0.93; interobserver agreement, 0.71; 95% CI, 0.53 to 0.88).[42]

Diagnostic Performance From Studies Not Included in the Meta-Analysis

In the study by Bogaert and colleagues,[9] 19 patients underwent real-time navigator CMRA for the detection of significant coronary artery stenoses, with conventional ICA as the reference standard. The results were interpreted by 2 experienced readers, and consensus was not used to resolve any differences in interpretation.[9] When analyzed at a per-patient level, for reader 1 and reader 2 respectively, CMRA had a:

- Sensitivity of 70% and 50%
- Specificity of 89% and 45%
- Accuracy of 79% and 47%
- Positive predictive value (PPV) of 87% and 40%
- Negative predictive value (NPV) of 73% and 56%

In the CE-MARC study by Greenwood and colleagues,[14] 628 patients were scheduled for an integrated CMRA protocol and ICA. For the integrated protocol, comprising CMRA with adenosine stress perfusion, cine imaging, and LGE, the sensitivity was 87% (95% CI, 82% to 90%), specificity 83% (95% CI, 79% to 87%), PPV 77% (95% CI, 72% to 82%), and NPV 91% (87% to 93%).[14] The addition of CMRA to multiparameter MRI was also assessed within the CE-MARC study.[54] Overall, the use of CMRA within the full multiparametric protocol had no additional diagnostic benefit compared to the perfusion/function/LGE combination (overall accuracy, 85% vs. 84%; $P = .53$).[54]

In the study by Bettencourt and colleagues,[8] CMRA alone or integrated with stress perfusion and LGE was evaluated in 43 adults with suspected CAD and at least 2 cardiovascular risk factors or an inconclusive treadmill test (i.e., at intermediate to high risk pretest probability). The reference standard was combined ICA and fractional flow reserve; specifically, 90% or greater stenosis or fractional flow reserve of 0.80 or less in vessels greater than 2 mm.[8] In a per-patient based analysis:[8]

- CMRA had a sensitivity of 96% (95% CI, 82% to 100%) and a specificity of 68% (95% CI, 51% to 73%).
- Integrated CMRA, with stress perfusion and LGE, had a sensitivity of 96% (95% CI, 83% to 100%) and a specificity of 89% (95% CI, 73% to 94%).

When compared with a perfusion and LGE protocol, the additive value of CMRA resulted in a 17% increase in sensitivity (79% vs. 96%; $P = 0.13$) and a 5% decrease in specificity (95% vs. 90%; $P = 1.0$); neither of which were statistically significant.[8]

Clinical Utility

We did not find any RCTs or comparative NRSs evaluating the clinical utility (i.e., effectiveness) of CMRA in this population.

GRADE Summary of Findings

Table 5. GRADE Summary of Evidence: Diagnostic Performance of CMRA in Adults With Suspected CAD

Pooled Sensitivity (95% CI)	0.88 (0.84 to 0.91)
Pooled Specificity (95% CI)	0.72 (0.64 to 0.78)

Test Results	Number of Results per 1,000 Patients Tested (Range)			Number of Participants and Studies	Certainty of Evidence (GRADE)	Rationale
	Prevalence 53% Median of All Included Studies	Prevalence 44% Lower Bound of IQR	Prevalence 65% Upper Bound of IQR			
True positives (patients with CAD)	466 (445 to 482)	387 (370 to 400)	572 (546 to 592)	N = 1,367 23 studies	⨁⨁⨁⨁ HIGH	Not downgraded
False negatives (patients incorrectly classified as not having CAD)	64 (48 to 85)	53 (40 to 70)	78 (58 to 104)			
True negatives (patients without CAD)	338 (301 to 367)	403 (358 to 437)	252 (224 to 273)	N = 1,367 23 studies	⨁⨁⨁⨁ HIGH	Not downgraded
False positives (patients incorrectly classified as having CAD)	132 (103 to 169)	157 (123 to 202)	98 (77 to 126)			

Abbreviations. CAD: coronary artery disease; CI: confidence interval; CMRA: cardiac magnetic resonance angiography; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation; IQR: interquartile range.

Table 6. GRADE Summary of Evidence: Diagnostic Performance of CMRA in Adults With Suspected Coronary CAD

Participants (N) Number of Studies	Findings	Certainty of Evidence	Rationale
Outcome: Interobserver and Intraobserver Reliability			
N = 62 1 NRS[42]s	Using quantitative analysis, the observers were in almost perfect agreement Using visual analysis, the observers were in substantial agreement	⨁⨁⨁◯ MODERATE	Downgraded 1 level for imprecision (i.e., wide CIs)

Note. Nonrandomized diagnostic test accuracy studies start at HIGH in the GRADE framework.
Abbreviations. CAD: coronary artery disease; CI: confidence interval; CMRA: cardiac magnetic resonance angiography; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation; NRS: nonrandomized study.

B. Adults With Suspected Coronary Vessel Anomalies

We found 4 eligible studies that evaluated the diagnostic validity (i.e., accuracy) or clinical utility (i.e., effectiveness) of CMRA (with or without contrast) in adults with suspected coronary vessel anomalies (Table 7; Appendix C, Tables C2, C3, C11, and C12).[10,13,39,45] We rated the risk of bias in these studies as follows:

- Each of the 3 DTA studies were at high risk of bias due to concerns around patient selection, the lack of blinding, and the timing of tests.[10,13,39]
- The single NRS was at high risk of bias because there was no comparator group.[45]

We did not find any eligible RCTs evaluating the clinical utility of CMRA in this population.

Study Characteristics

We found 3 studies evaluating the diagnostic performance of CMRA (with or without contrast) in adults with suspected coronary vessel anomalies (Table 7).[10,13,39]

Table 7. Characteristics of Eligible Studies Evaluating the Diagnostic Performance of CMRA in Adults With Suspected Coronary Vessel Anomalies

Study Risk of Bias	Study Number and Name Setting	Population	CMRA	Magnet Strength	Comparator
Bunce et al., 2003[10] High risk of bias	NR Hospital, UK	26 adults with known or suspected coronary artery anomalies	CMRI protocol, comprising free-breathing 3D CMRA	1.5 T	ICA

Study Risk of Bias	Study Number and Name Setting	Population	CMRA	Magnet Strength	Comparator
Gharib et al., 2008[13] High risk of bias	NR University hospital, US	12 adults with symptoms and referred for evaluation of known or suspected anomalies	CMRI protocol, comprising scout imaging and 3D CMRA	3.0 T	ICA CCTA
Taylor et al., 2000[39] High risk of bias	NR Hospital, UK	25 adults with congenital heart disease, undergoing CMRA to identify the coronary artery origin and proximal course	CMRI protocol, respiratory-gated, with CMRA	1.5 T	ICA

Abbreviations. CCTA: coronary computed tomography angiography; CMRA: cardiac magnetic resonance angiography; ICA: invasive coronary angiography; NR: not reported; T: Tesla.

We also found 1 NRS without a control group evaluating the clinical utility (i.e., effectiveness) of CMRA (with or without contrast) in adults with suspected coronary vessel anomalies (Table 8).[45]

Table 8. Characteristics of Eligible NRSs Evaluating CMRA in Adults With Suspected Coronary Vessel Anomalies

Study Risk of Bias	Study Number and Name Setting	Population	CMRA	Magnet Strength
Casolo et al., 2005[45] High risk of bias	NR University hospital, Italy	19 adults identified with CAA, referred for suspected CAA or other cardiac indication for further diagnosis	CMRI protocol, comprising a spin-echo echo-planar T1 weighted scan, followed by repeated breath-hold cine-balanced fast field echo series, with 3D-turbo-field-echocardiogram as appropriate	1.5 T

Abbreviations. 3D: 3 dimensional; CAA: coronary artery anomalies; CMRA: cardiac magnetic resonance angiography; CMRI: cardiac magnetic resonance imaging; NR: not reported; NRS: nonrandomized study; T: Tesla.

Study Findings

Diagnostic Accuracy

Overall, 3 studies reported on the diagnostic performance of CMRA compared with other tests for the identification and assessment of coronary vessel anomalies.

- In the study by Bunce and colleagues[10]:
  - In 18 of 25 (72.0%) patients, CMRA and ICA were concordant for the origin of the vessel anomaly.
  - In 14 of 25 (56.0%) patients, CMRA and ICA were concordant for the proximal course of the vessel anomaly.

  - In 8 patients with anomalous arteries that coursed between the aortic root and the right ventricular outflow tract, identified using CMRA, ICA could not be used confidently to identify the proximal course.
- In the study by Gharib and colleagues[13]:
  - In 10 of 12 (83.3%) patients were diagnosed with coronary arterial anomalies and variants using CMRA.
  - 8 of 8 (100%) patients had concordant results for CMRA and ICA.
- Only 1 study reported data which allowed us to calculate the sensitivity and specificity of CMRA when compared with ICA.[39]
  - CMRA had a sensitivity of 88% (95% CI, 62% to 98%) and a specificity of 100% (95% CI, 66% to 100%).

Complications associated with CMRA were assessed in 2 studies[13,39]:

- 1 study reported no adverse events or complications.[39]
- 1 patient experienced diaphoresis and restlessness (no further details were reported) and was not able to complete CMRA.[13]

No studies reported on intraobserver or interobserver reliability.

Clinical Utility

Indications for Referral or Diagnosis

In the NRS by Casolo and colleagues,[45] 6 of 19 (31.5%) patients with coronary artery anomalies were referred for CMRA examination based on the results from prior tests. The remainder (13 of 19 [68.5%]) had coronary artery anomalies identified using CMRI for other purposes (unexplained ventricular arrhythmias in 7 patients, congenital heart disease in 3 patients, stable coronary artery disease with prior myocardial infarction in 1 patient and hypertrophic cardiomyopathy in 2 patients).[45]

Impact of Testing

In the NRS by Casolo and colleagues,[45] CMRA added the following clinical information to the prior cardiac tests:

- In the 5 patients who were studied after ICA, CMRA added some information on the origin and course of the anomalies.[45]
- In 1 patient whose coronary artery anomaly was suspected by transesophageal echocardiography, CMRA provided all the information useful for clinical management, thus avoiding the need for conventional angiography.[45]

Safety

No eligible studies reported on the safety of CMRA in this population.

GRADE Summary of Findings

Table 9. GRADE Summary of Evidence: Diagnostic Performance of CMRA in Adults With Suspected Coronary Vessel Anomalies

Participants (N) Number of Studies	Findings	Certainty of Evidence	Rationale
CMRA vs. Other Tests			
Outcome: Diagnostic Performance			
N = 63 3 NRSs[10,13,39]	CMRA was highly concordant with surgical and ICA findings, and may identify vessel anomalies that are not identified using other tests, including ICA	⨁⨁◯◯ LOW	Downgraded 1 level each for imprecision (i.e., not assessable and small sample sizes) and risk of bias (i.e., all studies were at high risk of bias)
N = 25 1 NRS[39]	When compared with ICA, CMRA had a sensitivity of 88% (95% CI, 62% to 98%) and a specificity of 100% (95% CI, 66% to 100%)	⨁⨁◯◯ LOW	Downgraded 1 level each for imprecision (i.e., wide confidence intervals) and risk of bias (i.e., high risk of bias and small sample size)
Outcome: Interobserver and Intraobserver Reliability			
Not reported			

Note. Nonrandomized diagnostic test accuracy studies start at HIGH in the GRADE framework.
Abbreviations. CI: confidence interval; CMRA: cardiac magnetic resonance angiography; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation; ICA: invasive coronary angiography; NRS: nonrandomized study.

Table 10. GRADE Summary of Evidence: Clinical Utility of CMRA in Adults With Suspected Coronary Vessel Anomalies

Participants (N) Number of Studies	Findings	Certainty of Evidence	Rationale
CMRA vs. No Comparator			
Outcome: Impact of Testing			
N = 19 1 NRS[45]	CMRA added information on the origin and course of the anomalies in 5 patients, and in one patient, CMRA provided all the information useful for clinical management, thus avoiding the need for conventional angiography	⨁◯◯◯ VERY LOW	Downgraded 1 level each for risk of bias (i.e. no comparator group) and imprecision (i.e., not assessable)

Note. Nonrandomized studies start at LOW in the GRADE framework.
Abbreviations. CMRA: cardiac magnetic resonance angiography; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation; NRS: nonrandomized study.

C. Adults Who Have Undergone CABG Surgery

We did not find any studies evaluating the diagnostic performance of CMRA (with or without contrast) in adults after CABG surgery. We did find 2 studies evaluating MRI in adults after CABG, but the CMRI protocol did not include angiography, so are not reported further.[75,76]

D. Adults Being Assessed For Cardiac Device Lead Placement

We found 2 studies that evaluated the ability of CMRA (with or without contrast) to identify the vein used for left ventricular cardiac device lead placement in adults (Table 11; Appendix C, Tables C2 and C3).[12,24] We rated the risk of bias in these studies as follows:

- 2 NRSs studies had a high risk of bias because of patient selection concerns, a lack of blinding, and small sample sizes.[12,24]

We did not find any eligible RCTs or NRSs evaluating the clinical utility of CMRA in this population.

Study Characteristics

We found 2 studies evaluating the ability of CMRA (with or without contrast) to identify the vein used for cardiac device lead placement in adults (Table 11).[12,24]

Table 11. Characteristics of Eligible Studies Evaluating the Ability of CMRA to Identify the Vein Used for Lead Placement in Adults

Study Risk of Bias	Study Number and Name Setting	Population	CMRA	Magnet Strength	Comparator
Duckett et al., 2011[12] High risk of bias	NR University hospital, UK	14 adults having a CMRA as part of assessment for CRT implants	CMRI protocol, comprising dynamic electrocardiogram-triggered inversion recovery scan subsequent to starting an ECG triggered respiratory-navigated 3D-SSFP scan with inversion recovery preparation	1.5 T	X-ray venography
Lam et al., 2015[24] High risk of bias	NR University hospital, US	19 adults scheduled to undergo CRT	CMRI protocol, comprising cine images and 3D-whole heart imaging	1.5 T	X-ray venography

Abbreviations. 3D: 3-dimensional; CMRA: cardiac magnetic resonance angiography; CMRI: cardiac magnetic resonance imaging; CRT: cardiac resynchronization therapy; ECG: electrocardiography; NCT: National Clinical Trial; NR: not reported; SSFP: steady-state free precession; T: Tesla.

Study Findings

Diagnostic Performance

In both studies, CMRA was able to identify the vein for lead placement in all patients.[12,24]

GRADE Summary of Findings

Table 12. GRADE Summary of Evidence: Ability of CMRA to Identify the Vein Used for Lead Placement in Adults

Participants (N) Number of Studies	Findings	Certainty of Evidence	Rationale
CMRA vs. X-ray Venography			
Outcome: Visualization of the Vein for Lead Placement			
N = 27 2 NRSs[12,24]	CMRA was able to visualize the vein for cardiac device lead placement in all patients	⨁⨁◯◯ LOW	Downgraded 1 level each for risk of bias (i.e. both studies at high risk of bias) and imprecision (i.e., not assessable)
Outcome: Interobserver and Intraobserver Reliability			
Not reported			

Note. Nonrandomized diagnostic test accuracy studies start at HIGH in the GRADE framework.
Abbreviations. CMRA: cardiac magnetic resonance angiography; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation; NRS: nonrandomized study.

E. Children With Suspected or Confirmed Congenital Heart Disease

We found 12 studies evaluating the diagnostic validity (i.e., accuracy) or clinical utility (i.e., effectiveness) of CMRA (with or without contrast) in children with suspected or confirmed congenital heart disease (Table 13; Appendix C, Tables C2, C3, C5, and C7).[6,7,15,28,33,38,43,44,46-48,51] We rated the risk of bias in these studies as follows:

- Each of the 6 DTA studies had a high risk of bias due to concerns about patient selection, the lack of blinding, and the timing between the index and reference tests.[6,7,15,28,33,38]
- Each of the 6 NRSs had a high risk of bias because of the lack of a comparator.[43,44,46-48,51]

We did not find any eligible RCTs evaluating the clinical utility of CMRA in this population.

Study Characteristics

We found 4 studies evaluating the diagnostic performance of CMRA (with or without contrast) in children with suspected or confirmed congenital heart disease (Table 13).[6,28,33,38] We also included 2 studies with both adults and children with congenital heart disease where the median age was under 18 years (Table 13).[7,15] We considered there to be possible overlap in the included populations in the studies by Geva and colleagues[77] and by Greil and colleagues[15] (i.e., same hospitals, same inclusion criteria, and substantial overlap in study dates) so we report only on the larger of the 2 studies.

Table 13. Characteristics of Eligible Studies Evaluating the Diagnostic Performance of CMRA in Children With Suspected or Confirmed Congenital Heart Disease

Study Risk of Bias	Study Number and Name Setting	Population	CMRA	Magnet Strength	Comparator
Albrecht et al., 2019[6] High risk of bias	NR Children's hospital, US	21 children referred for CMRA referred after inconclusive echocardiography	Prototype noncontrast, free-breathing, self-navigated 3D CMRA	1.5T	CCTA
Beerbaum et al., 2009[7] High risk of bias	NR Not clear	40 young adults and children who underwent CMRI for routine diagnostic assessment of congenital heart disease	MRI examination, which included ventricular volumetry, quantitative flow studies, and 3D contrast-enhanced CMRA	1.5T	ICA
Greil et al., 2002[15] High risk of bias	NR Children's hospital, US	61 adults and children with a diagnosis of pulmonary or systemic venous anomaly by any imaging modality	CMRI protocol, gadolinium enhanced and breath hold where possible	1.5 T	Other tests, including ICA
Nguyen et al., 2015[28] High risk of bias	NR University hospital, US	56 children who underwent CMRA for known or suspected congenital cardiovascular disorders	CMRI protocol, comprising cine sequence, and high resolution CMRA	3.0 T or 1.5 T	ICA Surgery
Prakash et al., 2007[33] High risk of bias	NR Children's hospital, US	28 infants who underwent contrast-enhanced CMRA, after echo testing	CMRI protocol, using gadopentetate dimeglumine	1.5 T	ICA Surgery
Tangcharoen et al., 2011[38] High risk of bias	NR University hospital, UK	100 children referred for CMRA with general anesthesia and 3D whole-heart data set indicated	CMRI protocol, comprising initial survey, rest cine, first-pass 3D angiography technique after injection of gadopentetate dimeglumine, and 3D-whole heart	1.5 T	Surgery

Abbreviations. 3D: 3-dimensional; CCTA: coronary computed tomography angiography; CMRA: cardiac magnetic resonance angiography; CMRI: cardiac magnetic resonance imaging; ICA: invasive coronary angiography; NR: not reported; T: Tesla.

We also found 5 NRSs evaluating the clinical utility (i.e., effectiveness) of CMRA (with or without contrast) in children with suspected or confirmed congenital heart disease[43,44,46-48,51] (Table 14). We also included 1 study with both adults and children with congenital heart disease where the median age was under 18 years.[43] None of the eligible studies included a comparator group.[43,44,46-48,51]

Table 14. Characteristics of Eligible NRSs Evaluating CMRA in Children With Suspected or Confirmed Congenital Heart Disease

Study Risk of Bias	Study Number and Name Setting	Population	CMRA	Magnet Strength
Albrecht et al., 2018[43] High risk of bias	NR Not clear	109 young adults and children who underwent CMRI for the evaluation of coronary anatomy	3D-CMRA, with protocol specific to the specific congenital malformation	1.5 T
Biko et al., 2015[44] High risk of bias	NR Children's hospital, US	14 children who underwent CMRA for suspected or known anomalous coronary artery, diagnosis of left coronary or right coronary artery originating from the contralateral sinus	CMRA protocol, comprising steady-state free precession sequence looking at the motion of the right atrioventricular groove/right coronary artery Scan parameters were adjusted accordingly for each patient	1.5 T or 3.0 T
Clemente et al., 2010[46] High risk of bias	NR University hospital, Italy	15 children with clinical and echocardiographic suspicion of AOCA	CMRI protocol, comprising a whole heart technique, using a navigator gated and corrected free breathing 3D steady-state free precession sequence	1.5 T
Holmqvist et al., 2001[47] High risk of bias	NR University hospital, Sweden	39 children with known or suspected congenital heart defect or thoracic vessel malformation	CMRI protocol, comprising contrast-enhanced 3D-CMRA, using gadoterate meglumine	1.5 T
Monney et al., 2015[48] High risk of bias	NR University hospital, Switzerland	111 young adults and children with congenital disease involving the heart or the great vessels	CMRI protocol, comprising a free-breathing 3D self-navigated sequence	1.5 T
Secchi et al., 2011[51] High risk of bias	NR National center, Italy	214 children with known or suspected congenital heart disease	CMRI protocol, comprising a series of ECG-gated sequences and gadolinium-enhanced 3D-angiography, using gadopentetate dimeglumine Protocol was adapted on a case-by-case basis	1.5 T

Abbreviations. 3D: 3-dimensional; AOCA: anomalous origin of the coronary artery; CMRA: cardiac magnetic resonance angiography; CMRI: cardiac magnetic resonance imaging; ECG: electrocardiography; NR: not reported; NRS: nonrandomized study; T: Tesla.

Study Findings

Diagnostic Accuracy

Overall, 6 studies reported on the diagnostic performance of CMRA compared with other tests or surgical findings for the identification and assessment of vessel anomalies in adults and children:

- Albrecht and colleagues[6] compared the diagnostic accuracy of CMRA and CCTA for the detection of coronary artery anomalies, reporting a:
  - Sensitivity of 92.8%
  - Specificity of 92.8%
  - PPV of 96.1%
  - NPV of 87.5%
- In the study by Beerbaum and colleagues,[7] CMRA detected congenital heart defects in 17 of 40 (42.5%) patients, with CMRA and ICA being concordant in 6 patients with a coronary anomaly and 6 patients with normal coronary anatomy.
- In the study by Greil and colleagues[15]:
  - All vessel anomalies confirmed using other methods, specifically ICA, surgery or autopsy, were diagnosed using CMRA.
  - In 3 patients, cardiac catheterization did not diagnose anomalies of the pulmonary veins that were subsequently demonstrated by MRA.
- In the study by Nguyen and colleagues,[28] there were no significant false-positive or false-negative findings in any patient when compared with anesthesia surgical or catheter angiographic findings.
- In the study by Prakash and colleagues,[33] no discrepancies were noted between the official magnetic resonance angiographic, x-ray angiographic, and operative reports.
- In the study by Tangcharoen and colleagues,[38] 58 of 100 (58.0%) underwent surgery and the origin and course of the suspected anomalous artery was correctly imaged with MRI and confirmed with surgery in all patients.

In the study by Greil and colleagues,[15] previously unsuspected diagnoses of venous anomalies were found by CMRA in 17 patients (28%), suspected diagnoses were confirmed by CMRA and additional clinically important information was provided for in another 28 patients (46%), and in the remaining 16 patients (26%), the referral diagnoses were confirmed by CMRA without additional information being provided. In the study by Prakash and colleagues,[33] the diagnostic questions at referral were accurately answered by MRA in each patient.

Only 1 of the included studies reported interobserver agreement at the patient level.[6] Albrecht and colleagues[6] reported a high interobserver agreement for CMRA in the visualization of coronary artery anomalies of 0.81 (95% CI; 0.55 to 0.92).

Safety related to testing was reported in 2 of the 5 studies. Overall, there were very few complications of CMRA testing in children and adults.[15,33] There were no complications associated with the CMRA procedures in 82 patients, reported in 2 studies[6,15] Prakash and colleagues monitored 28 infants who underwent CMRA over a minimum of 72 hours for patients who remained admitted to the hospital.[33] Infants who returned home were also followed-up to assess any longer-term effects of testing.[33] No adverse events were observed in either group.[33]

Clinical Utility

Indications for Referral or Diagnosis

In the 6 eligible NRSs of CMRA,[7,43,44,46-48,51] referrals for CMRA testing and confirmed diagnoses varied between studies. For example, in the study by Albrecht and colleagues, the largest group of patients, 31 of 109 (28.4%), were diagnosed with tetralogy of Fallot and 18 patients (16.5%) were diagnosed with tricuspid atresia status post Fontan (Appendix C, Tables C11 and C12).

Diagnostic Ability

The majority of the eligible NRSs reported on the diagnostic performance of CMRA; however, there was no direct comparison with a reference standard in all patients, so the findings are mainly descriptive in nature.

- In 2 studies[43,44] all completed CMRA studies were considered to be diagnostic, with no additional imaging required.
- In the study by Secchi and colleagues, fewer than 1% of CMRA tests were considered to be unreliable.[51]
- In 2 studies,[47,48] a minority of CMRA tests had limited image quality allowing for only partial or no diagnosis.
- In the study by Clemente and colleagues,[46] CMRA evaluation confirmed the anomalous origin of the coronary artery (AOCA) suspicion in 6 of 15 (40.0%) of patients, with 7 of 15 (60.0%) patients having normal vasculature confirmed; however, there were no ICA or surgical findings with which to compare the diagnoses.

Impact of Testing

In 2 studies[43,44] all completed CMRA studies were considered to be diagnostic, with no additional imaging required. In 1 study by Secchi and colleagues,[51] CMRA:

- Confirmed findings that were already known in fewer than 1% of examinations
- Identified new findings that did not result in a change of therapy or suggested lifestyle in 27.6% of examinations
- Identified new findings that resulted in a change of therapy or suggested lifestyle in 66.3% of examinations
- Identified new findings that resulted in a change of diagnosis in 4.7% of examinations

Safety

No studies reported on the harms associated with CMRA testing.

GRADE Summary of Findings

Table 15. GRADE Summary of Evidence: Diagnostic Performance of CMRA in Children With Suspected or Confirmed Congenital Heart Disease

Participants (N) Number of Studies	Findings	Certainty of Evidence	Rationale
CMRA vs. Other Tests			
Outcome: Diagnostic Performance			
N = 306 6 NRSs[6,7,15,28,33,38]	CMRA was highly concordant with surgical, ICA, and CCTA findings, and may identify vessel anomalies that are not identified using other tests, including ICA	⨁⨁◯◯ LOW	Downgraded 1 level each for imprecision (i.e., not assessable and small sample sizes) and risk of bias (i.e., all studies were at high risk of bias)
Outcome: Interobserver and Intraobserver Reliability			
N = 21 1 NRS[6]	There was high interobserver agreement for CMRA in the visualization of coronary artery anomalies	⨁⨁⨁◯ VERY LOW	Downgraded 1 level each for imprecision (i.e., not assessable and small sample sizes), risk of bias (i.e., study was at high risk of bias), and indirectness (i.e., coronary artery anomalies only)

Note. Nonrandomized diagnostic test accuracy studies start at HIGH in the GRADE framework.
Abbreviations. CCTA: coronary computed tomography angiography; CMRA: cardiac magnetic resonance angiography; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation; ICA: invasive coronary angiography; NRS: nonrandomized study.

Table 16. GRADE Summary of Evidence: Clinical Utility of CMRA in Children With Suspected or Confirmed Congenital Heart Disease

Participants (N) Number of Studies	Findings	Certainty of Evidence	Rationale
CMRA vs. No Comparator			
Outcome: Impact of Testing			
N = 502 6 NRSs[43,44,46-48,51]	CMRA was diagnostic in most cases, with no additional imaging needed CMRA also identified new findings or diagnosis in the majority of cases	⨁◯◯◯ VERY LOW	Downgraded 1 level each for risk of bias (i.e. no comparator group) and imprecision (i.e., not assessable)

Note. Nonrandomized studies start at LOW in the GRADE framework.
Abbreviations. CMRA: cardiac magnetic resonance angiography; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation; NRS: nonrandomized study.

Safety

We found 1 study evaluating the safety of CMRA (with or without contrast) in neonates and small infants (Table 17).[50] The study by Rangamani and colleagues[50] was assessed as having a high risk of bias, because of the lack of a comparator group.[50] We also included 1 further study reporting a single center's experience of anesthetizing pediatric patients with congenital heart disease for cardiac MRI, because of a lack of safety data for CMRA.[49] We assessed this study as being at high risk of bias because of the lack of a comparator group.[49]

Table 17. Characteristics of Eligible Studies Evaluating the Safety of CMRA in Children

Study Risk of Bias	Study Number and Name Setting	Population
Odegard et al., 2004[49] High risk of bias	NR Children's hospital, US	250 children who underwent general anesthesia for cardiac MRI for a variety of congenital conditions
Rangamani et al., 2012[50] High risk of bias	NR Children's hospital, US	143 infants who underwent CMRI with general anesthesia or deep sedation, including CMRA as appropriate, for the evaluation of congenital heart disease

Abbreviations. CMRA: cardiac magnetic resonance angiography; CMRI: cardiac magnetic resonance imaging; NR: not reported; MRI: magnetic resonance imaging.

In the study by Rangamani and colleagues,[50] 12 children (9%) had adverse events, 1 major and 11 minor, all related to general anesthesia or deep sedation. The single major adverse event was respiratory arrest after deep sedation in a neonate (resuscitated without sequelae).[50] Minor adverse events included desaturation, hypothermia, bradycardia, and bradycardia with hypoxemia events.[50] There were no major adverse events related to CMRA. Of 25 outpatients, 5 (20%) were admitted for overnight observation due to desaturations; all were discharged the next day with no further adverse events reported.[50] There was no gadolinium-contrast-related event recorded in any of the 136 children who underwent CMRA.[50] None of the children demonstrated a significant change in hepatic function or other adverse effects.[50]

In the study reporting on the safety of general anesthesia in children with congenital heart disease undergoing cardiac MRI,[49] no patients were admitted overnight to the hospital because of complications resulting from general anesthesia.[49]

The safety of CMRA was reported in 8 of the included studies in adults.[11,13,14,18,21,31,34,39] Overall, CMRA appeared to be safe, with few complications associated with the procedure or the associated pharmacological agents.

- In 5 studies,[13,14,18,21,39] CMRA was completed in all patients without any complications.
- Dewey and colleagues[11] observed 7 adverse events, which occurred in 6 of the 129 patients. None of the adverse events were related to the CMRA.
- In the study by Plein and colleagues,[31] patients underwent a multiparametric protocol, including CMRA. No adverse events occurred, and the adenosine infusion was well tolerated by all patients.[31]

- Regenfus and colleagues[34] observed that CMRA was performed without complications in all patients. None of the patients experienced nausea or other adverse reactions to the contrast agent.[34]

The safety of CMRA was reported in 2 of the included studies in children.[15,33] No complications were observed with CMRA.[15,33] The use of general anesthesia for MRI in children also appeared to be safe.[49]

GRADE Summary of Findings

Table 18. GRADE Summary of Evidence: Safety of CMRA in Adults and Children

Participants (N) Number of Studies	Findings	Certainty of Evidence	Rationale
Outcome: Safety			
N = 1,005 8 NRSs[11,13,14,18,21,31,34,39]	In adults, CMRA appeared to be a safe procedure, with few adverse events related to the procedure or to the pharmacological agents	⨁⨁◯◯ LOW	Not downgraded
N = 339 3 NRSs[15,33,49]	In children, CMRA appeared to be a safe procedure, with few adverse events related to the procedure or to general anesthesia	⨁⨁◯◯ LOW	Not downgraded

Note. Nonrandomized studies start at LOW in the GRADE framework.
Abbreviations. CMRA: cardiac magnetic resonance angiography; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation; NRS: nonrandomized study.

FDA-Reported Harms for CMRA

We also searched the US FDA MAUDE database for the last 5 years and the Medical Device Recall reports (Appendix F, Tables F1 and F2). We found 253 entries in the MAUDE database, including voluntary, user facility, distributor, and manufacturer reports of adverse events relating to magnetic resonance imaging (MRI) scanner use in the last 5 years. We were not able to analyze the reports by condition and many of the entries were not specific to the use of CMRA alone. The types of adverse events were very different to those reported in our eligible studies for CMRA across the selected populations of interest. Common adverse events included burns, hearing loss or tinnitus, and adverse consequences due to unknown metal implants in patients.

We also found 2 entries in the Medical Device Recall database related to other devices or components of devices used for MRI (Appendix F, Tables F1 and F2), neither of which were specific to the use of CMRA.

KQ3

A. Adults With Suspected CAD

Women

In the CE-MARC study,[14,53] a multiparametric CMRA protocol when compared with ICA had a sensitivity of 89% in women and 86% in men (P = .57) and a specificity of 83% in women and 83% in men (P = .86). When only the CMRA component was evaluated, again, the results did not

statistically differ by sex (sensitivity, 67% vs. 72%; specificity, 88% vs. 90%; *P* value not reported).[53]

Single-Vessel and Multi-Vessel Disease

In the CE-MARC study,[14,53] a multiparametric CMRA protocol, when compared with ICA, did not differ in performance (i.e., sensitivity or specificity) for single-vessel or multi-vessel disease when evaluated in women and in men.

Heart Rate

In a study of 127 adults with suspected CAD, the diagnostic performance of CMRA did not differ significantly between patients with a heart rate of less than 70 beats per minute and patients with a heart rate of 70 or more beats per minute.[19]

Body Mass Index

In a study of 127 adults with suspected CAD, the diagnostic performance of CMRA did not differ significantly between patients with a body mass index of less than 25 kg/m^2 and patients with a body mass index of 25 kg/m^2 or more.[19]

Pretest Probability

In patients at intermediate pretest probability,[8] according to the modified Diamond-Forrester score[78]:

- CMRA had a sensitivity of 100% (95% CI, 75% to 100%) and a specificity of 73% (95% CI, 55% to 73%)
- Integrated CMRA, with stress perfusion and LGE, had a sensitivity of 91% (95% CI, 67% to 91%) and a specificity of 100% (95% CI, 74% to 100%)

B. Adults With Suspected Coronary Vessel Anomalies

We did not find any information on variation by subgroup in this population.

C. Adults Who Have Undergone CABG Surgery

We did not find any information on variation by subgroup in this population.

D. Adults Being Assessed For Cardiac Device Lead Placement

We did not find any information on variation by subgroup in this population.

E. Children With Suspected or Confirmed Congenital Heart Disease

We did not find any information on variation by subgroup in this population.

Safety

We did not find any information on variation in harms by subgroup.

KQ4

A. Adults With Suspected CAD

We did not identify any eligible studies for this population.

B. Adults With Suspected Coronary Vessel Anomalies

We did not identify any eligible studies for this population.

C. Adults Who Have Undergone CABG Surgery

We did not identify any eligible studies for this population.

D. Adults Being Assessed For Cardiac Device Lead Placement

We did not identify any eligible studies for this population.

E. Children With Suspected or Confirmed Congenital Heart Disease

We did not identify any eligible studies for this population.

Ongoing Studies

We did not identify any ongoing studies of CMRA in a population of interest.

Summary

A. Adults With Suspected CAD (e.g., symptomatic patients)

- CMRA has a sensitivity of 88% (95% CI, 84% to 91%) and a specificity of 72% (95% CI, 64% to 78%), based on pooled data from 23 studies (high CoE, based on 23 NRSs; Table 5).
    - In a population of 1,000 adults with a 53% prevalence of CAD (the median prevalence of the included studies), CMRA testing would result in:
        - 466 patients being diagnosed correctly as having CAD
        - 64 patients incorrectly classified as not having CAD
        - 338-patients being diagnosed correctly as not having CAD
        - 132 patients incorrectly classified as having CAD
- CMRA has high levels of observer agreement, both within reviewers (intraobserver) and between observers (interobserver; moderate CoE, based on 1 NRS; Table 6).

B. Adults With Suspected Coronary Vessel Anomalies

- CMRA is highly concordant with surgical and ICA findings, and may identify vessel anomalies that are not identified using other tests, including ICA (low CoE, based on 3 NRSs; Table 9).
- When compared with ICA, CMRA had a sensitivity of 88% (95% CI, 62% to 98%) and a specificity of 100% (95% CI, 66% to 100%) (low CoE, based on 1 NRS; Table 9).
- CMRA may add information on the origin and course of the anomalies and can provide the information needed for clinical management, thus avoiding the need for conventional angiography (very low CoE, based on 1 NRS; Table 10).

C. Adults Who Have Undergone CABG Surgery

- No eligible studies were identified.

D. Adults Being Assessed For Cardiac Device Lead Placement

- CMRA may be useful to visualize the appropriate vein for cardiac device lead placement (low CoE, based on 2 NRSs; Table 12).

E. Children With Suspected or Confirmed Congenital Heart Disease

- CMRA was highly concordant with surgical, ICA, and CCTA findings, and may identify vessel anomalies that are not identified using other tests, including ICA (low CoE, based on 6 NRSs; Table 15).
- There was high interobserver agreement for CMRA in the visualization of coronary artery anomalies (very low CoE, based on 1 NRS; Table 15).
- CMRA can be diagnostic in most cases, with no additional imaging needed. CMRA also identifies new findings or new diagnoses in the majority of cases where they are present (very low CoE, based on 6 NRSs; Table 16).

Safety

- In adults, CMRA appears to be a safe procedure, with few adverse events related to the procedure or to the pharmacological agents (low CoE, based on 8 NRSs; Table 18).
- In children, CMRA appears to be a safe procedure, with few adverse events related to the procedure or to general anesthesia (low CoE, based on 4 NRSs; Table 18).

FDA-Reported Harms

We did not identify any harms associated specifically with CMRA; however, patients and providers have reported burns, hearing loss or tinnitus, and issues with metal implants associated with MRI for any indication.

Economic Outcomes

We did not identify any economic studies assessing the cost-effectiveness of CMRA for any of the populations of interest.

Clinical Practice Guidelines

We identified 1 clinical practice guideline[59] and 2 appropriateness criteria documents developed by the American College of Radiology (ACR) [57,58] on the use of CMRA in adults with suspected CAD (Table 19). We also identified 2 guidelines for the use of CMRA in adults with congenital heart disease, which we have included as being relevant to the subgroup of adults with suspected coronary vessel anomalies.[55,56] We assessed 2 of the guidelines as being of good methodological quality[55,59] and 3 as being of moderate methodological quality.[56-58] We did not identify any eligible clinical practice guidelines on the use of CMRA for adults who have undergone CABG surgery, adults being assessed for cardiac device lead placement, or for children with suspected or confirmed congenital heart disease.

Table 19. Clinical Practice Recommendations on CMRA in Adults

Organization Methodological Quality	Excerpted Recommendation(s)	Status
A. Adults With Suspected CAD		
National Institute for Health and Care Excellence (NICE) [59] Good	• Do not use MR coronary angiography for diagnosing stable angina	Current
Expert Panel on Cardiac Imaging, American College of Radiology[57] Moderate	• MRA coronary arteries without and with IV contrast may be appropriate in patients with chronic chest pain and with a high probability of CAD	Current
Expert Panel on Cardiac Imaging, American College of Radiology[58] Moderate	• MRA coronary arteries without and with IV contrast may be appropriate in patients with chronic chest pain in whom a noncardiac etiology is unlikely and who have a low to intermediate probability of CAD	Current
B. Adults With Suspected Coronary Vessel Anomalies		
American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines[55] Good	• CMR can be useful in the initial evaluation and serial assessment of selected patients [adults] with congenital heart disease based on anatomic complexity and clinical status. • Imaging studies should be performed and interpreted by individuals with expertise in CHD imaging. • In patients with ACHD who have or who are at risk of developing RV enlargement and dysfunction, serial CMR is recommended for quantitative assessment of RV size and function. • CMR or CTA is recommended for evaluation of partial anomalous pulmonary venous connection • Initial and follow-up aortic imaging using CMR or CTA is recommended in adults with coarctation of the aorta, including those who have had surgical or catheter intervention • CMR is useful to quantify ventricular size and function, pulmonary valve function, pulmonary artery anatomy, and left heart abnormalities in patients with repaired tetralogy of Fallot • Baseline and serial imaging with either echocardiography or CMR should be performed in adults with d-TGA with arterial switch who have neoaortic dilation, valve dysfunction or PA or branch PA stenosis or ventricular dysfunction • It is reasonable to perform anatomic evaluation of coronary artery patency (catheter angiography, or CT or MR angiography) in asymptomatic adults with d-TGA with arterial switch • Adults after Fontan palliation should be evaluated annually with either echocardiography or CMR. • CMR is reasonable in adults with CCTGA to determine systemic RV dimensions and systolic function	Current

Organization Methodological Quality	Excerpted Recommendation(s)	Status
	• Coronary angiography, using catheterization, CT, or CMR, is recommended for evaluation of anomalous coronary artery	

Expert Panel on Cardiac Imaging, American College of Radiology[56]
Moderate
	• MRA chest without and with IV contrast is usually appropriate for adults with suspected or known congenital heart disease
	  ○ This procedure is complementary to the transthoracic echocardiogram and may be performed as an alternative to MRI heart function and morphology if only great-vessel anatomical information is needed and no information is needed about intracardiac anatomy, heart function, and flow
	  ○ Occasionally, it may be complementary to MRI heart function and morphology without IV contrast
	• MRA chest without IV contrast may be appropriate for adults with suspected or known congenital heart disease
	  ○ This procedure is complementary to the transthoracic echocardiogram and may be performed as an alternative to MRA chest without and with IV contrast or CTA chest with IV contrast
		Current

Abbreviations. ACHD: adult congenital heart disease; CAD: coronary artery disease; CCTGA: congenitally corrected transposition of the great arteries; CHD: coronary heart disease; CMR: cardiac magnetic resonance; CMR: cardiac magnetic resonance angiography; CT: computed tomography; CTA: computed tomography angiography; d-TGA; d-transposition of the great arteries; IV: intravenous; MR: magnetic resonance; MRA: magnetic resonance angiography; MRI: magnetic resonance imaging; PA: pulmonary artery; RV: right ventricle.

In patients with chronic chest pain and with a high probability of CAD, the ACR Expert Panel also noted that CMRA should be limited to treatment sites where there are staff with appropriate capabilities and extensive experience in the use of CMRA.[57]

In summary, recommendations from good-quality and moderate-quality methodological guidelines support the use of CMRA in adults with congenital heart disease, including coronary vessel anomalies. Support for the use of CMRA in adults with suspected CAD is less clear, with only conditional recommendations from the ACR[57,58] and a 'do not do' recommendation from NICE.[59]

Selected Payer Coverage Determinations

We did not identify any current Medicare national coverage determinations or any local coverage determinations relevant to Washington State on the use of CMRA in a population of interest.

Each of the 3 private payers that we reviewed (Aetna, Cigna, and Regence) had coverage policies for CMRA.[60-62]

Aetna considers CMRA medically appropriate when it can replace a more invasive test (e.g., contrast angiography) and reduce risk for its members. Aetna specifically considers CMRA to be medically necessary for[60]:

- Diagnosis, treatment planning, and post-operative surgical shunt evaluation in members with congenital heart disease or developmental anomalies of the thoracic vasculature (e.g., atresia or hypoplasia of the pulmonary arteries, coarctation of the aorta, double aortic arch, interrupted inferior vena cava, partial anomalous venous connection, persistent left superior vena cava, right-sided aortic arch, total anomalous pulmonary venous connection, and truncus arteriosus)

Cigna cover the use of CMRA for a number of indications of interest[61]:

- Preoperative and postoperative congenital heart disease assessment
  - CMRA may be added if the aorta or pulmonary artery need to be visualized beyond the root
- CMRA can be performed in certain situations (e.g., suspected dissection, coarctation, known or suspected aortic aneurysm)
- Imaging that only requires aortic arch imaging, does not require intracardiac CMR, only CMRA
- Anomalous pulmonary venous connections
  - Initial studies-for diagnosis, clinical changes, and consideration of surgery
    - Echocardiogram at time of diagnosis
    - CMRI, CMRA, or cardiac computed tomography, or cardiac computed angiography at time of diagnosis if any issues with pulmonary veins or right ventricular volume
- Coarctation of the aorta
  - Initial studies-for diagnosis, clinical changes, and consideration of surgery
    - If echocardiogram and exam are equivocal or positive ONE of the following is indicated:
      - Cardiac computed angiography
      - CMRA
    - Individuals with coarctation of the aorta do not require intracardiac MR unless issue cannot be resolved on echocardiogram
- Tetralogy of Fallot
  - Initial studies-for diagnosis, clinical changes, and consideration of surgery
    - CMRA or cardiac computed angiography at the time of diagnosis
- Right ventricle–to-pulmonary artery conduit
  - Initial studies-for diagnosis, clinical changes, and consideration of surgery
    - CMRA or cardiac computed angiography
    - Prior to interventions or surgery may repeat imaging
- Transposition of the great arteries
  - Initial studies-for diagnosis, clinical changes, and consideration of surgery
    - Baseline CMRA or cardiac computed angiography
    - Perfusion or CMRA
- Congenitally corrected transposition of the great arteries
  - Initial studies for diagnosis, clinical changes, and consideration of surgery
    - Baseline CMRI imaging and CMRA

- Congenital heart disease imaging in pregnancy
  - CMRA or cardiac computed angiography of arch if known disease with aortic involvement or if known dilation

Regence cover CMRA as recommended in AIM Specialty Health guidelines.[62] Based on these guidelines, CMRA is considered medically necessary for congenital or developmental vascular anomalies.

In summary, the private payer policies cover the use of CMRA for congenital heart disease or vessel anomalies, but do not consider the use of CMRA for other indications to be medically necessary.

Conclusions

When compared with ICA, CMRA is a good test for adults with suspected CAD, with an overall estimated accuracy of 89%. Pooled estimates of sensitivity and specificity are 88% and 72%. However, there is no direct evidence on the effectiveness of CMRA in changing clinical practice or in improving outcomes for patients with CAD. The economic impact of CMRA in patients with suspected CAD when compared to standard care is also unknown.

In other populations, where anatomical imaging of the vessels is clinically important for diagnosis, evaluation, or monitoring, CMRA does appear to be a useful test. CMRA often performs as well as ICA, and may be able to identify anomalies that are not identified using ICA. However, it should be noted that ICA is not usually considered to be the reference standard for the diagnosis of coronary anomalies. CMRA also appears to be a useful tool in informing and changing clinical pathways and actions in adults and children whose vascular anatomy needs to be visualized, which would be expected to lead to improved surgical and other outcomes. However, no evidence on patient outcomes was identified. Overall, there is a lot of uncertainty around these findings given the paucity of clinical outcome studies.

Adverse events appear to be minimal in both adults and children. However, patients may be exposed to harm (e.g., burns, loss of hearing, tinnitus) through the use of MRI and other procedures associated with MRI (e.g., general anesthesia or sedation in young children, gadolinium contrast agents in people with diminished renal function). MRI may also not be suitable for people who are unable to tolerate the MRI procedure (e.g., people with severe claustrophobia). In general, the use of MRI is considered a safe procedure; patients are not exposed to the harmful effects of ionizing radiation of other imaging modalities, such as computed tomography. Patients may also avoid the risks associated with invasive testing, including radiation exposure and test-related complications, or with unnecessary surgery when CMRA is used as an alternative.

Clinical practice guidelines and payer policies are also in agreement on the use of CMRA in adults with congenital heart disease, including coronary vessel anomalies; however, there is no clear consensus on the use of CMRA for adults with suspected CAD.

In summary, CMRA performs well as a test to visualize the cardiac vessels, and can therefore be a useful test when clinicians need to understand the vascular anatomy of the heart. CMRA also appears to be a safe alternative for most patients. However, there is a lack of data on the impact

on patient outcomes and clinical decision-making of using CMRA, and on the cost-effectiveness of CMRA in the populations of interest. Overall, there is a lot of uncertainty around the clinical impact of the findings given the paucity of clinical outcome studies.

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Appendix A. Search Strategy

Databases

- Ovid MEDLINE and Epub Ahead of Print, In-Process & Other NonIndexed Citations and Daily: from January 1, 2000 to May 3, 2021
- Cochrane Library databases (Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials): from January 1, 2000 to May 3, 2021

Search Terms for Ovid MEDLINE

1 ((cardio* or cardiac or coronary or whole heart or whole-heart or myocardi*) adj4 (magnetic resonance angiograph* or MRA or x-ray angiograph*)).mp.

2 ((MR or magnetic resonance) adj3 (cardio* or cardiac or coronary or whole heart or whole-heart or myocardi*) adj4 angiograph*).mp.

3 ((cardio* or cardiac or coronary or whole heart or whole-heart or myocardi*) adj5 (perfusion adj4 (magnetic resonance or MRI or angiograph*))).mp.

4 ((cardio* or cardiac or coronary or whole heart or whole-heart or myocardi*) adj5 (Magnetic Resonance adj2 Perfusion Imaging)).mp.

5 or/1-4

6 Magnetic Resonance Angiography/mt [Methods]

7 cardio*.ab. /freq=3 or cardiac.ab. /freq=3 or coronary.ab. /freq=3 or whole heart.ab. /freq=3 or whole-heart.ab. /freq=3 or myocardi*.ab. /freq=3

8 and/6-7

9 5 or 8

10 (animals/ not (animals/ and humans/)) or (animal or animals or bovine or canine or cat or cats or chimpanzee$1 or dog or dogs or hens or mice or mouse or pig or pigs or porcine or rabbit or rabbits or rat or rats or rattus or rhesus or monkey$1 or non-human or veterinary or zebrafish).ti.

11 9 not 10

12 limit 11 to (english language and yr="2000 -Current")

13 limit 12 to (case reports or randomized controlled trial, veterinary)

14 12 not 13

Appendix B. Additional Methods

Table B1. Risk of Bias Assessment: Diagnostic Test Accuracy Studies

Domain	Domain Elements[a]
Patient Selection and Inclusion	• Selection criteria are clearly described • A consecutive or random sample of patients were enrolled • A case-control design was not used • The study avoided inappropriate exclusions
Patient Representation	• The spectrum of patients is representative of the patients who will receive the test in practice • The index test, its use, and interpretation are similar to the review question
Study Design	• The study avoided the use of a case-control design
Reference Standard	• The reference standard is likely to classify the condition correctly
Test Timing	• The period between the reference standard and index test is short enough to be reasonably sure that the target condition did not change between the 2 tests
Verification	• The whole sample, or a random selection of the sample, received verification using the same diagnostic reference standard
Use of Reference Standard	• All patients received the same reference standard, regardless of the index test result
Test Independence	• The reference standard was independent of the index test (i.e., the index test did not form part of the reference standard)
Interpretation of the Index Test	• Index test results were interpreted without knowledge of the results of the reference standard • If a threshold was used, it was pre-specified
Interpretation of the Reference Standard	• Reference standard results were interpreted without knowledge of the results of the index test
Uninterpretable or Intermediate Test Results	• Uninterpretable or intermediate test results are reported
Withdrawals	• All patients enrolled were included in the analysis • An explanation is provided for all withdrawals or losses from the study
Interest Disclosure	• Disclosures of interest are provided for authors/funders/commissioners of the study • Interests are unlikely to significantly affect study validity
Funding Source	• There is a description of source(s) of funding • Funding source is unlikely to have a significant impact on study validity

Note. [a] The elements included in each domain are assessed and rated as Yes, No, Unclear, *or* Not Applicable *based on performance and documentation of the individual elements in each domain. The overall risk of bias for the study is assessed as* High, Moderate, *or* Low *based on assessment of how well the overall study methods and processes were performed to limit bias and ensure validity.*

Table B2. Risk of Bias Assessment: Randomized Controlled Trials

Domain	Domain Elements[a]
Randomization	• An appropriate method of randomization is used to allocate participants or clusters to groups, such as a computer random number generator
Allocation Concealment	• An adequate concealment method is used to prevent investigators and participants from influencing enrollment or intervention allocation
Baseline Characteristics	• Baseline characteristics between groups or clusters are similar • If they are not similar, then these factors should be statistically adjusted for in analyses
Intervention	• Intervention and comparator intervention applied equally to groups • Co-interventions appropriate and applied equally to groups • Control selected is an appropriate intervention
Outcomes	• Outcomes are measured using valid and reliable measures • Investigators use single outcome measures and do not rely on composite outcomes, or the outcome of interest can be calculated from the composite outcome • The trial has an appropriate length of follow-up and groups are assessed at the same time points • Outcome reporting of entire group or subgroups is not selective
Masking (Blinding) of Investigators and Participants	• Investigators and participants are unaware (masked or blinded) of intervention status
Masking (Blinding) of Outcome Assessors	• Outcome assessors are unaware (masked or blinded) of intervention status
Intention to Treat Analysis	• Participants are analyzed based on random assignment (intention-to-treat analysis)
Statistical Analysis	• Participants lost to follow-up unlikely to significantly bias the results (i.e., complete follow-up of ≥ 80% of the participants overall and nondifferential, ≤ 10% difference between groups) • The most appropriate summary estimate (e.g., risk ratio, hazard ratio) is used • Paired or conditional analysis used for crossover RCT • Clustering appropriately accounted for in a cluster-randomized trial (e.g., use of an intraclass correlation coefficient)
Other Biases (as appropriate)	List others in table footnote and describe, such as: • Sample size adequacy • Interim analysis or early stopping • Recruitment bias, including run-in period used inappropriately • Use of unsuitable crossover intervention in a crossover RCT
Interest Disclosure	• Disclosures of interest are provided for authors/funders/commissioners of the study • Interests are unlikely to significantly affect study validity
Funding	• There is a description of source(s) of funding • Funding source is unlikely to have a significant impact on study validity

Note. [a] *The elements included in each domain are assessed and rated as* Yes, No, Unclear, *or* Not Applicable *based on performance and documentation of the individual elements in each domain. The overall risk of bias for the study is assessed as* High, Moderate, *or* Low *based on assessment of how well the overall study methods and processes were performed to limit bias and ensure validity.*
Abbreviation. RCT: randomized controlled trial.

Table B3. Risk of Bias Assessment: Nonrandomized Studies

Domain	Domain Elements[a]
Participant Selection	For cohort studies: • The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation, or statistical adjustment is used appropriately to achieve this • The study indicates how many of the people asked to take part did so, in each of the groups being studied • The likelihood that some eligible participants might have the outcome at the time of enrolment is assessed and taken into account in the analysis • Fewer than 20% of individuals or clusters in each arm of the study dropped out before the study was completed For case-control studies: • Cases and controls are clearly specified and defined, with the inclusion and exclusion criteria applied appropriately • Cases may be selected by meeting inclusion criteria, controls may be selected by meeting inclusion criteria and then being matched to cases • Sampling selection (ratio of cases to control) is justified • Cases and controls selected from the same population and same timeframe. When not all cases and controls are selected from the same population, they are randomly selected • Among cases, investigators confirm that the exposure occurred before the development of the disease being studied and/or the likelihood that some eligible participants might have the outcome at the time of enrolment is assessed and taken into account in the analysis
Intervention	• The assessment of exposure to the intervention is reliable • Exposure level or prognostic factors are assessed at multiple times across the length of the study, if appropriate • For case-control studies assessors of (intervention) exposure status are unaware (masked or blinded) to the case or control status of participants there is a method to limit the effects of recall bias on the assessment of exposure to the intervention
Control	• Control condition represents an appropriate comparator
Outcome	• There is a precise definition of the outcomes used • Outcomes are measured using valid and reliable measures, evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable • Investigators use single outcome measures and do not rely on composite outcomes, or the outcome of interest can be calculated from the composite outcome • The study has an appropriate length of follow-up for the outcome reported and groups are assessed at the same time points • Outcome reporting of entire group or subgroups is not selective • When patient-reported outcomes are used there is a method for validating the measure
Masked Outcome Assessment	• The assessment of outcome(s) is made blind to exposure status. Where outcome assessment blinding was not possible, there is recognition that knowledge of exposure status could have influenced the assessment of outcome • For case-control study: assessors of exposure status are unaware (masked or blinded) of the case or control status of participant)

Domain	Domain Elements[a]
Confounding	• The main potential confounders are identified and taken into account in the design and analysis of the study
Statistical Analysis	• Comparison is made between full participants and those who dropped out or were lost to follow-up, by exposure status • If the groups were not followed for an equal length of time, the analysis was adjusted for differences in the length of follow-up • All major confounders are adjusted for using multiple variable logistic regression or other appropriate statistical methods • Confidence intervals (or information with which to calculate them) are provided • For case-control studies that use matching, conditional analysis is conducted or matching factors are adjusted for in the analysis
Other Biases (as appropriate)	• List others in table footnote and describe, e.g., • Sample size adequacy
Interest Disclosure	• Disclosures of interest are provided for authors/funders/commissioners of the study • Interests are unlikely to significantly affect study validity
Funding Source	• There is a description of source(s) of funding • Funding source is unlikely to have a significant impact on study validity

Note. [a] The elements included in each domain are assessed and rated as Yes, No, Unclear, or Not Applicable based on performance and documentation of the individual elements in each domain. The overall risk of bias for the study is assessed as High, Moderate or Low, based on assessment of how well the overall study methods and processes were performed to limit bias and ensure validity.

Table B4. Risk of Bias Assessment: Economic Studies

Domain	Domain Elements[a]
Target Population	• Target population and care setting described • Describe and justify basis for any target population stratification, identify any a priori identifiable subgroups • If no subgroup analyses were performed, justify why they were not required
Perspective	• State and justify the analytic perspective (e.g., societal, payer, etc.)
Time Horizon	• Describe and justify the time horizon(s) used in the analysis
Discount Rate	• State and justify the discount rate used for costs and outcomes
Comparators	• Describe and justify selected comparators • Competing alternatives appropriate and clearly described
Modeling	• Model structure (e.g., scope, assumptions made) is described and justified • Model diagram provided, if appropriate • Model validation is described (may involve validation of different aspects such as structure, data, assumptions, and coding and different validation models such as comparison with other models) • Data sources listed and assumptions for use justified • Statistical analyses are described
Effectiveness	• Estimates of efficacy/effectiveness of interventions are described and justified • The factors that are likely to have an impact on effectiveness (e.g., adherence, diagnostic accuracy, values, and preferences) are described and an explanation of how they were factored into the analysis is included • The quality of evidence for the relationship between the intervention and outcomes, and any necessary links, is described
Outcomes	• All relevant outcomes are identified, measured, and valued appropriately (including harms/adverse events) for each intervention, and the justification for information/assumptions is given • Any quality of life measures used in modeling are described and their use justified • Any other outcomes that were considered, but rejected, are described with the rationale for rejection • Ethical and equity-related outcomes are considered and included when appropriate
Resource Use/Costs	• All resources used are identified, valued appropriately, and included in the analyses • Methods for costing are reporting (e.g., patient level) • Resource quantities and unit costs are both reported • Methods for costing time (e.g., lost time, productivity losses) are appropriate and a justification is provided if time costs are not considered
Uncertainty	• Sources of uncertainty in the analyses are identified and justification for probability distributions used in probabilistic analyses are given • For scenario analyses, the values and assumptions tested are provided and justified
Results	• All results are presented in a disaggregated fashion, by component, in addition to an aggregated manner • All results are presented with undiscounted totals prior to discounting and aggregation • Natural units are presented along with alternative units (e.g., QALYs) • The components of the ICER are shown (e.g., mean costs of each intervention in numerator and mean outcomes of each intervention in denominator)

Domain	Domain Elements[a]
	• Results of scenario analyses, including variability in factors such as practice patterns and costs, are reported and described in relation to the reference (base) case
Interest Disclosure	• Disclosures of interest are provided for authors/funders/commissioners of the study • Interests are unlikely to significantly affect study validity
Funding Source	• There is a description of source(s) of funding • Funding source is unlikely to have a significant impact on study validity

Note. [a] The elements included in each domain are assessed and rated as Yes, No, Unclear, *or* Not Applicable *based on performance and documentation of the individual elements in each domain. The overall risk of bias for the study is assessed as* High, Moderate, *or* Low *based on assessment of how well the overall study methods and processes were performed to limit bias and ensure validity.*
Abbreviations. ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Table B5. Methodological Quality Assessment: Clinical Practice Guidelines

Domain	Domain Elements[a]
Rigor of Development: Evidence	• Systematic literature search that meets quality standards for a systematic review (i.e., comprehensive search strategy with, at a minimum, 2 or more electronic databases) • The criteria used to select evidence for inclusion is clear and appropriate • The strengths and limitations of individual evidence sources is assessed and overall quality of the body of evidence assessed
Rigor of Development: Recommendations	• Methods for developing recommendations clearly described and appropriate • There is an explicit link between recommendations and supporting evidence • The balance of benefits and harms is considered in formulating recommendations • The guideline has been reviewed by external expert peer reviewers • The updating procedure for the guideline is specified in the guideline or related materials (e.g., specialty society website)
Editorial Independence	• There is a description of source(s) of funding and the views of the funder(s) are unlikely to have influenced the content or validity of the guideline • Disclosures of interests for guideline panel members are provided and are unlikely to have a significant impact on the overall validity of the guideline (e.g., a process for members to recuse themselves from participating on recommendations for which they have a significant conflict is provided)
Scope and Purpose	• Objectives specifically described • Health question(s) specifically described • Target population(s) for guideline recommendations is specified (e.g., patients in primary care) and target users for the guideline (e.g., primary care clinicians)
Stakeholder Involvement	• Relevant professional groups represented • Views and preferences of target population(s) sought (e.g. clinicians and patients)
Clarity and Presentation	• Recommendations are specific and unambiguous • Different management options are clearly presented • Key recommendations are easily identifiable
Applicability	• Provides advice and/or tools on how the recommendation(s) can be put into practice • Description of facilitators and barriers to its application • Potential resource implications considered • Criteria for implementation monitoring, audit, and/or performance measures based on the guideline are presented

Note. [a] Assessment indicates how well the guideline methodology and development process were performed to limit bias and ensure validity for elements in domain (each domain rated as Good, Fair, or Poor overall based on performance and documentation of elements).

Appendix C. Evidence Tables

See attachment for detailed study characteristics and results for included studies (pages C1–C59).

Appendix D. Risk of Bias Assessments

Table D1. Risk of Bias: Diagnostic Test Accuracy Studies, Part 1

Study	Patient Selection	Patient Representation	Patient Inclusion	Case-Control Design Avoided	Reference Standard	Interpretation of Reference Standard	Test Independence	Verification
A. Adults with Suspected Coronary Artery Disease								
Bettencourt et al., 2013[8]	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes
Bogaert et al., 2003[9]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Dewey et al., 2006[11]	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes
Greenwood et al., 2012[14]	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes
Hamdan et al., 2011[16]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Heer et al., 2013[17]	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes
Ikonen et al., 2003[18]	Unclear	Yes	Yes	Yes	Yes	Unclear	Yes	Yes
Kato et al., 2010[19]	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Kefer et al., 2005[20]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Kim et al., 2001[21]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Klein et al., 2008[22]	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Kunimasa et al., 2009[23]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Langer et al., 2009[25]	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes

Study	Patient Selection	Patient Representation	Patient Inclusion	Case-Control Design Avoided	Reference Standard	Interpretation of Reference Standard	Test Independence	Verification
Maintz et al., 2007[26]	Unclear	Yes	No	Yes	Yes	Yes	Yes	Yes
Nagata et al., 2011[27]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ogawa et al., 2020[29]	Unclear	Unclear	No	Yes	Yes	Yes	Yes	Yes
Piccini et al., 2014[30]	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Plein et al., 2002[31]	No	No	No	Yes	Yes	Yes	Yes	Yes
Pouleur et al., 2008[32]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Regenfus et al, 2000[34]	Unclear	Yes	Yes	Yes	Yes	Unclear	Yes	Yes
Sakuma et al., 2005[36]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Sakuma et al., 2006[35]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Sardanelli et al., 2000[37]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Wagner et al., 2011[40]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Yang et al., 2003[41]	Unclear	Yes	No	Yes	Yes	Yes	Yes	Yes
Yonezawa et al., 2014[42]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
B. Adults With Suspected Coronary Vessel Anomalies								
Bunce et al., 2003[10]	No	No	No	Yes	Yes	Unclear	Yes	No
Gharib et al., 2008[13]	No	No	No	No	Yes	Unclear	Yes	No

Study	Patient Selection	Patient Representation	Patient Inclusion	Case-Control Design Avoided	Reference Standard	Interpretation of Reference Standard	Test Independence	Verification
Taylor et al., 2000[39]	Yes	Yes	No	Yes	Yes	No	No	No
C. Adults Who Have Undergone Coronary Artery Bypass Graft Surgery								
No eligible studies identified								
D. Adults Being Assessed For Cardiac Device Lead Placement								
Duckett et al., 2011[12]	Unclear	Unclear	Yes	Yes	Yes	Unclear	Yes	No
Lam et al., 2015[24]	No	No	No	Yes	Yes	Unclear	Yes	Yes
E. Children With Suspected or Confirmed Congenital Heart Disease								
Beerbaum et al., 2009[7]	No	Yes	No	Yes	Yes	Yes	Yes	No
Greil et al., 2002[15]	Unclear	Yes	No	Yes	Yes	Unclear	Yes	Yes
Nguyen et al., 2015[28]	No	Yes	No	Yes	Unclear	Unclear	No	Unclear
Prakash et al., 2007[33]	No	Yes	No	Yes	Yes	Unclear	Yes	Yes
Tangcharoen et al., 2011[38]	No	Yes	No	Yes	Unclear	Yes	Yes	No

Table D1. Risk of Bias: Diagnostic Test Accuracy Studies, Part 2

Study	Interpretation of Index Test	Threshold Determination	Uninterpretable or Intermediate Test Results	Test Timing	Withdrawals	Interest Disclosure	Funding Source	Overall Risk of Bias Assessment Comments
A. Adults With Suspected Coronary Artery Disease								
Bettencourt et al., 2013[8]	Yes	Yes	Unclear	Yes	Yes	No	No	**Low**
Bogaert et al., 2003[9]	Yes	No	Unclear	Yes	Yes	No	No	**Moderate** Conflicts of interest not reported and small sample size
Dewey et al., 2006[11]	Yes	Yes	Yes	Unclear	Yes	No	No	**Moderate** Some uncertainty around blinding and conflicts of interest
Greenwood et al., 2012[14]	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	**Moderate** Some uncertainty around blinding
Hamdan et al., 2011[16]	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	**Low**
Heer et al., 2013[17]	Yes	Yes	Unclear	Yes	Yes	No	Yes	**Moderate** Some uncertainty around conflicts of interest and blinding
Ikonen et al., 2003[18]	Yes	Yes	Unclear	Yes	Yes	No	Yes	**Moderate** Some uncertainty around blinding and conflicts of interest not reported
Kato et al., 2010[19]	Unclear	Yes	Unclear	Unclear	Yes	Yes	No	**Moderate** Some uncertainty around patient selection and blinding

Study	Interpretation of Index Test	Threshold Determination	Uninterpretable or Intermediate Test Results	Test Timing	Withdrawals	Interest Disclosure	Funding Source	Overall Risk of Bias Assessment Comments
Kefer et al., 2005[20]	Yes	Yes	Unclear	Yes	Yes	No	Yes	**Moderate** Conflicts of interest not reported
Kim et al., 2001[21]	Yes	Yes	Unclear	Yes	Yes	No	Yes	**Low**
Klein et al., 2008[22]	Yes	Yes	Unclear	Yes	Yes	No	No	**Moderate** Some uncertainty around patient selection and conflicts of interest
Kunimasa et al., 2009[23]	Yes	Yes	Unclear	Yes	Yes	Unclear	Unclear	**Moderate** Funding and conflicts of interest not reported
Langer et al., 2009[25]	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	**Moderate** Some uncertainty around blinding
Maintz et al., 2007[26]	Yes	Yes	Yes (by segment)	Yes	Yes	No	No	**High** Some uncertainty around patient selection, funding and conflicts of interest not reported, and small sample size
Nagata et al., 2011[27]	Yes	Yes	Unclear	Yes	Yes	Yes	No	**Low**
Ogawa et al., 2020[29]	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	**High** Some uncertainty around patient selection and small sample size

Study	Interpretation of Index Test	Threshold Determination	Uninterpretable or Intermediate Test Results	Test Timing	Withdrawals	Interest Disclosure	Funding Source	Overall Risk of Bias Assessment Comments
Piccini et al., 2014[30]	Yes	No	Unclear	Yes	Yes	Yes	No	**High** Some uncertainty around patient selection and small sample size
Plein et al., 2002[31]	Yes	Yes	Unclear	No	Yes	No	Yes	**High** Some uncertainty around patient selection, conflicts of interest not reported, and small sample size
Pouleur et al., 2008[32]	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	**Low**
Regenfus et al, 2000[34]	Yes	Yes	Unclear	Yes	Yes	No	Yes	**Moderate** Some uncertainty around blinding
Sakuma et al., 2005[36]	Yes	Yes	Unclear	Unclear	Yes	No	No	**High** Some uncertainty around the timing of tests, funding and conflicts of interest not reported, and small sample size
Sakuma et al., 2006[35]	Unclear	Yes	Unclear	Unclear	Yes	No	No	**Moderate** Some uncertainty around blinding and the timing of tests
Sardanelli et al., 2000[37]	Yes	Yes	Unclear	Yes	Yes	No	No	**Moderate** Funding and conflicts of interest not reported

Study	Interpretation of Index Test	Threshold Determination	Uninterpretable or Intermediate Test Results	Test Timing	Withdrawals	Interest Disclosure	Funding Source	Overall Risk of Bias Assessment Comments
Wagner et al., 2011[40]	Yes	Yes	Unclear	Yes	Yes	No	No	**Moderate** Funded by contrast manufacturer and no conflicts of interest reported; also small sample size
Yang et al., 2003[41]	Yes	Yes	Unclear	Yes	Yes	No	Yes	**Moderate** Some uncertainty around blinding and conflicts of interest not reported
Yonezawa et al., 2014[42]	Yes	No	Unclear	Yes	Yes	Yes	No	**Low**
B. Adults With Suspected Coronary Vessel Anomalies								
Bunce et al., 2003[10]	Unclear	Yes	Unclear	Unclear	No	No	No	**High** Some concerns about patient selection, lack of blinding, and timing of tests not clear
Gharib et al., 2008[13]	Unclear	Yes	Unclear	Unclear	No	No	No	**High** Lack of reporting on most aspects of study conduct, concerns about patient selection, small numbers, and blinding not reported
Taylor et al., 2000[39]	Yes	Yes	Unclear	Unclear	Unclear	No	No	**High** Index test is part of the consensus

Study	Interpretation of Index Test	Threshold Determination	Uninterpretable or Intermediate Test Results	Test Timing	Withdrawals	Interest Disclosure	Funding Source	Overall Risk of Bias Assessment Comments
								reference, and a small sample size
C. Adults Who Have Undergone Coronary Artery Bypass Graft Surgery								
No eligible studies identified								
D. Adults Being Assessed for Cardiac Device Lead Placement								
Duckett et al., 2011[12]	Unclear	Yes	Unclear	Unclear	No	No	No	**High** Some concerns about patient selection, lack of blinding, and timing of tests not clear
Lam et al., 2015[24]	Unclear	Yes	Unclear	Yes	Yes	No	Yes	**High** Some concerns about patient selection, lack of blinding, and a small sample size
E. Children With Suspected or Confirmed Congenital Heart Disease								
Beerbaum et al., 2009[7]	Yes	Yes	Unclear	Unclear	No	No	No	**High** Some concerns about patient selection, lack of blinding, and timing of tests not clear
Greil et al., 2002[15]	Unclear	Yes	Unclear	Unclear	Yes	No	No	**High** Some concerns about patient selection, lack of blinding, and timing of tests not clear

Study	Interpretation of Index Test	Threshold Determination	Uninterpretable or Intermediate Test Results	Test Timing	Withdrawals	Interest Disclosure	Funding Source	Overall Risk of Bias Assessment Comments
Nguyen et al., 2015[28]	Yes	Yes	Unclear	Unclear	No	No	No	**High** Some concerns about patient selection, possible conflicts of interest, and not all patients received the reference standard
Prakash et al., 2007[33]	Yes	Yes	Unclear	Yes	Yes	No	No	**High** Some concerns around patient selection, the inclusion criteria, and the lack of blinding
Tangcharoen et al., 2011[38]	Unclear	Yes	Unclear	Unclear	No	No	Yes	**High** Some concerns around patient selection, a lack of blinding, and not all patients undergoing a reference standard

Table D2. Risk of Bias: Nonrandomized Studies

None of the included studies had a comparator group, so were all assessed as being at high risk of bias.

Table D3. Methodological Quality: Guidelines

Guideline Developer Year	Rigor of Development: Evidence	Rigor of Development: Recommendations	Editorial Independence	Scope and Purpose	Stakeholder Involvement	Clarity and Presentation	Applicability	Overall Assessment
American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines[55] 2019	Yes	Yes	Yes	Yes	No	Yes	Yes	**Good** Patient involvement not clear; barriers to implementation not clear
Expert Panel on Cardiac Imaging, American College of Radiology[57] 2017	Yes	Yes	Unclear	Yes	No	Yes	Yes	**Moderate** Patient involvement not clear; barriers to implementation not clear; editorial process unclear
Expert Panel on Cardiac Imaging, American College of Radiology[56] 2017	Yes	Yes	Unclear	Yes	No	Yes	Yes	**Moderate** Patient involvement not clear; barriers to implementation not clear; editorial process unclear
Expert Panel on Cardiac Imaging, American College of Radiology[58] 2018	Yes	Yes	Unclear	Yes	No	Yes	Yes	**Moderate** Patient involvement not clear; barriers to implementation not clear; editorial process unclear

Guideline Developer Year	Rigor of Development: Evidence	Rigor of Development: Recommendations	Editorial Independence	Scope and Purpose	Stakeholder Involvement	Clarity and Presentation	Applicability	Overall Assessment
National Institute for Health and Care Excellence[59] 2016	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**Good**

Appendix E. GRADE Certainty of Evidence

Diagnostic Test Accuracy

Table E1. GRADE Profile: Diagnostic Performance of CMRA in Adults With Suspected CAD

Sensitivity	0.88 (95% CI, 0.84 to 0.91)
Specificity	0.72 (95% CI, 0.64 to 0.78)
Prevalences	53% (median of included studies; 44% (lower interquartile bound of included studies); 65% (lower interquartile bound of included studies); 65%

Outcome	Number of Studies and Participants	Study Design	Factors That May Decrease Certainty of Evidence					Effect Per 1,000 Patients Tested (95% CI)			Test Accuracy CoE
			Risk of Bias	Indirectness	Inconsistency	Imprecision	Publication Bias	PTP of 53%	PTP of 44%	PTP of 65%	
True positives (patients with CAD)	23 studies 1,367 participants	Cross-sectional (cohort type accuracy study)	Not serious	Not serious	Not serious	Not serious	Not Assessed	466 (445 to 482)	387 (370 to 400)	572 (546 to 592)	⊕⊕⊕⊕ HIGH
False negatives (patients incorrectly classified as not having CAD)								64 (48 to 85)	53 (40 to 70)	78 (58 to 104)	
True negatives (patients without CAD)	23 studies 1,367 participants	Cross-sectional (cohort type accuracy study)	Not serious	Not serious	Not serious	Not serious	Not Assessed	338 (301 to 367)	403 (358 to 437)	252 (224 to 273)	⊕⊕⊕⊕ HIGH
False positives (patients incorrectly classified as having CAD)								132 (103 to 169)	157 (123 to 202)	98 (77 to 126)	

Note. Nonrandomized diagnostic test accuracy studies start at HIGH in the GRADE framework.
Abbreviations. CAD: coronary artery disease; CI: confidence interval; CMRA: cardiac magnetic resonance angiography; CoE: certainty of evidence; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation; PTP: pretest probability.

Table E2. GRADE Profile: Diagnostic Performance of CMRA in Adults With Suspected With Suspected CAD

Number of Participants and Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Comments	Effect	Overall CoE Rating
CMRA vs. Other Tests								
Outcome: Interobserver and Intraobserver Reliability								
N = 62 1 NRS[42]s	Not serious	Not assessable Single study	Not serious	Serious (-1)	Not assessed	Downgraded 1 level for imprecision (i.e., wide CIs)	Using quantitative analysis, the observers were in almost perfect agreement Using visual analysis, the observers were in substantial agreement	⊕⊕◯◯ MODERATE

Note. Nonrandomized diagnostic test accuracy studies start at HIGH in the GRADE framework.
Abbreviations. CAD: coronary artery disease; CI: confidence interval; CMRA: cardiac magnetic resonance angiography; CoE: certainty of evidence; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation NRS: nonrandomized study.

Table E3. GRADE Profile: Diagnostic Performance of CMRA in Adults With Suspected Coronary Vessel Anomalies

Number of Participants and Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Comments	Effect	Overall CoE Rating
CMRA vs. Other Tests								
Outcome: Diagnostic Performance								
N = 63 3 NRSs[10,13,39]	Serious (-1) See Risk of Bias Assessment, Table D1	Not serious	Not serious	Serious (-1) Not assessable	Not assessed	Downgraded 1 level each for imprecision (i.e., not assessable and small sample sizes) and risk of bias (i.e., all studies were at high risk of bias)	CMRA was highly concordant with surgical and ICA findings, and may identify vessel anomalies that are not identified using other tests, including ICA	⊕⊕◯◯ LOW
N = 25 1 NRS[39]	Serious (-1) See Risk of Bias Assessment, Table D1	Not assessable Single study	Not serious	Serious (-1) Wide confidence intervals	Not assessed	Downgraded 1 level each for imprecision (i.e., wide confidence intervals) and risk of bias (i.e., high risk of bias and small sample size)	When compared with ICA, CMRA had a sensitivity of 88% (95% CI, 62% to 98%) and a specificity of 100% (95% CI, 66% to 100%)	⊕⊕◯◯ LOW
Outcome: Interobserver and Intraobserver Reliability								
Not reported								

Note. Nonrandomized diagnostic test accuracy studies start at HIGH in the GRADE framework.
Abbreviations. CI: confidence interval; CMRA: cardiac magnetic resonance angiography; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation; ICA: invasive coronary angiography; NRS: nonrandomized study.

Table E4. GRADE Profile: Diagnostic Performance of CMRA in Adults Being Assessed for Cardiac Device Lead Placement

Number of Participants and Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Comments	Effect	Overall Certainty of Evidence Rating
CMRA vs. X-ray Venography								
Outcome: Visualization of the Vein for Lead Placement								
N = 27 2 NRSs[12,24]	Serious (-1) See Risk of Bias Assessment, Table D1	Not serious	Not serious	Serious (-1) Not assessable	Not assessed	Downgraded 1 level each for risk of bias (i.e. both studies at high risk of bias) and imprecision (i.e., not assessable)	CMRA was able to visualize the vein for cardiac device lead placement in all patients	⨁⨁◯◯ LOW
Outcome: Interobserver and Intraobserver Reliability								
Not reported								

Note. Nonrandomized diagnostic test accuracy studies start at HIGH in the GRADE framework.
Abbreviations. CMRA: cardiac magnetic resonance angiography; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation; NRS: nonrandomized study.

Table E5. GRADE Profile: Diagnostic Performance of CMRA in Children With Suspected or Confirmed Congenital Heart Disease

Number of Participants and Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Comments	Effect	Overall Certainty of Evidence Rating
CMRA vs. Other Tests								
Outcome: Diagnostic Performance								
N = 306 6 NRSs[6,7,15,28,33,38]	Serious (-1) See Risk of Bias Assessment, Table D1	Not serious	Not serious	Serious (-1) Not assessable	Not assessed	Downgraded 1 level each for imprecision (i.e., not assessable and small sample sizes)	CMRA was highly concordant with surgical, ICA, and CCTA findings, and may identify	⨁⨁◯◯ LOW

Number of Participants and Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Comments	Effect	Overall Certainty of Evidence Rating
						and risk of bias (i.e., all studies were at high risk of bias)	vessel anomalies that are not identified using other tests	
Outcome: Diagnostic Performance								
N = 21 1 NRS[6]	Serious (-1) See Risk of Bias Assessment, Table D1	Not assessable Single study	Not serious	Serious (-1) Not assessable	Not assessed	Downgraded 1 level each for imprecision (i.e., not assessable and small sample sizes), risk of bias (i.e., study was at high risk of bias), and indirectness (i.e., coronary artery anomalies only)	There was high interobserver agreement for CMRA in the visualization of coronary artery anomalies	⨁⨁⨁◯ VERY LOW

Number of Participants and Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Comments	Effect	Overall Certainty of Evidence Rating
CMRA vs. Other Tests								
Outcome: Impact of Testing								
N = 502 6 NRSs[43,44,46-48,51]	Serious (-1) See Risk of Bias Assessment, Table D1	Not serious	Not serious	Serious (-1) Not assessable	Not assessed	Downgraded 1 level each for risk of bias (i.e. no comparator group) and imprecision (i.e., not assessable)	CMRA was diagnostic in most cases, with no additional imaging needed CMRA also identified new findings or diagnosis in the majority of cases	⊕◯◯◯ VERY LOW

Note. Nonrandomized diagnostic test accuracy studies start at HIGH in the GRADE framework.
Abbreviations. CMRA: cardiac magnetic resonance angiography; ICA: invasive coronary angiography; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation; NRS: nonrandomized study.

Clinical Utility

Table E6. GRADE Profile: Clinical Utility of CMRA in Adults With Suspected Coronary Vessel Anomalies

Number of Participants and Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Comments	Effect	Overall Certainty of Evidence Rating
CMRA vs. No Comparator								
Outcome: Impact of Testing								
N = 19 1 NRS[45]	Serious (-1) See Risk of Bias Assessment, Table D2	Not assessable Single study	Not serious	Serious (-1) Not assessable	Not assessed	Downgraded 1 level each for risk of bias (i.e. no comparator group) and imprecision (i.e., not assessable)	CMRA added information on the origin and course of the anomalies in 5 patients, and in one patient, CMRA provided all the information useful for clinical management, thus avoiding the need for conventional angiography	⨁◯◯◯ VERY LOW

Note. Nonrandomized studies start at LOW in the GRADE framework.
Abbreviations. CMRA: cardiac magnetic resonance angiography; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation; NRS: nonrandomized study.

Table E7. GRADE Profile: Clinical Utility of CMRA in Children With Suspected or Confirmed Congenital Heart Disease

Number of Participants and Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Comments	Effect	Overall Certainty of Evidence Rating
CMRA vs. No Comparator								
Outcome: Impact of Testing								
N = 502 6 NRSs[43,44,46-48,51]	Serious (-1) See Risk of Bias Assessment, Table D2	Not serious	Not serious	Serious (-1) Not assessable	Not assessed	Downgraded 1 level each for risk of bias (i.e. no comparator group) and imprecision (i.e., not assessable)	CMRA was diagnostic in most cases, with no additional imaging needed CMRA also identified new findings or diagnosis in the majority of cases	⨁◯◯◯ VERY LOW

Note. Nonrandomized studies start at LOW in the GRADE framework.
Abbreviations. CMRA: cardiac magnetic resonance angiography; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation; NRS: nonrandomized study.

Harms

Table E8. GRADE Profile: Harms of CMRA in Adults and Children

Number of Participants and Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Comments	Effect	Overall Certainty of Evidence Rating
Outcome: Adverse Events								
N = 1,005 8 NRSs[11,13,14,18,21,31,34,39]	Not serious	Not serious	Not serious	Not serious	Not assessed	Not downgraded	In adults, CMRA appeared to be a safe procedure, with few adverse events related to the procedure or to the pharmacological agents	⨁⨁◯◯ LOW
N = 339 3 NRSs[15,33,49]	Not serious	Not serious	Not serious	Not serious	Not assessed	Not downgraded	In children, CMRA appeared to be a safe procedure, with few adverse events related to the procedure or to general anesthesia	⨁⨁◯◯ LOW

Note. Nonrandomized studies start at LOW in the GRADE framework.
Abbreviations. CMRA: cardiac magnetic resonance angiography; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation; NRS: nonrandomized study.

Appendix F. MAUDE and Medical Device Recall Reports

Table F1. Reports on Magnetic Resonance Scanners from the FDA MAUDE Database

See attachment for results from the US Food and Drug Administration (FDA) Manufacturer and User Facility Device Experience (MAUDE) database (pages F1–F198).

Table F2. Reports on CMRA and Associated Devices from the FDA Medical Device Recall Database

Device Name and Description	Manufacturer	Recall Class	Classification Date	Reason for Recall
Chest Pneumograph NM 3160 Monitors bellows-derived respiration by detecting abdominal or chest wall motion	Philips North America, LLC	2	2020/06/02	The labeling of the Philips Chest Pneumograph does not include a statement indicating that the product contains natural rubber latex.
MEDRAD MRXerion MR Injection System Angiographic Injector and Syringe, MEDRAD MRXperion MR Injection System, MEDRAD MRXperion Sterile Disposable MR Imaging Kit	Philips North America, LLC	2	2016/07/19	Bayer Healthcare is initiating this recall due to complaints that were received from customer sites describing a 4205 error message when the injector is used with a 3T scanner.

Abbreviations. CMRA: cardiac magnetic resonance angiography; FDA: US Food and Drug Administration; MR: magnetic resonance.

Appendix G. Excluded Studies

See attachment for a list of excluded studies, with reasons for exclusion (pages G1-G66).