# Coronary computed tomography angiography (with or without functional evaluation) for the diagnosis of chronic coronary heart disease[1]

## EXTRACT

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According to §139b (3) No. 2 of Social Code Book (SGB) V, Statutory Health Insurance, external experts who are involved in the Institute's research commissions must disclose "all connections to interest groups and contract organizations, particularly in the pharmaceutical and medical devices industries, including details on the type and amount of any remuneration received". The Institute received the completed Form for disclosure of potential conflicts of interest from each external expert. The information provided was reviewed by a Committee of the Institute specifically established to assess conflicts of interests. The information on conflicts of interest provided by the external experts and external reviewers is presented in Chapter A9 of the full report. No conflicts of interest were detected that could endanger professional independence with regard to the work on the present commission.

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

**Patient and family involvement**

Patients or family members were consulted during the preparation of the report. One person participated in the discussion. Its aim was to obtain information on the following topics: experiences, wishes and concerns regarding the diagnostic procedures, impact of the disease on life and everyday life, and coping with the disease.

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

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## Key statement

### *Research question*

The following 2 questions are part of this report:

- Question 1: The objective is to assess the benefit of diagnostic strategies using contrast enhanced coronary computed tomography angiography (shortened to CCTA) compared with diagnostic strategies with the same goal, but without CCTA.

- Question 2: The objective is to assess the benefit of diagnostic strategies using CCTA with the option of subsequent computed tomography (CT)-based functional evaluation compared with diagnostic strategies with the same goal, but without the option of CT-based functional evaluation. If the benefit of CCTA is at least comparable according to Question 1, the diagnostic comparator strategies may also include CCTA.

The tests to be assessed aim to establish a diagnosis in patients with suspected chronic coronary heart disease (CHD) who, after basic diagnostic tests, have a clinical indication for further non-invasive diagnostic tests. The assessment focused on selected patient-relevant outcomes.

In addition, the incorporation of both the test and control interventions of the assessed tests into the upstream and downstream diagnostic procedures is presented.

### *Conclusion*

#### Question 1

Depending on the control intervention, the conclusion for Question 1 is divided into:

#### CCTA versus FDTs

To answer the question about the comparison of CCTA vs. functional diagnostic tests (FDTs), a total of 11 studies were analysed.

For the outcome of myocardial infarction, a diagnostic strategy using CCTA was shown to be superior to a diagnostic strategy using FDTs in the medium and long term (proof of benefit). For the outcome of unnecessary invasive diagnostic tests, it was shown that after CCTA, patients in the intervention group were less likely to have undergone invasive diagnostic tests with the result “no obstructive CHD” than patients who had undergone FDTs (proof of less harm).

In contrast, the analysis for the outcome of unstable angina pectoris provided an indication of less benefit of CCTA compared to FDTs in the long term.

For all other outcomes, there were no relevant differences between the diagnostic tests or no usable data were available. There were hardly any usable data on adverse events (AEs).

Since the role of unstable angina pectoris and potential adverse effects in the form of AEs is considered to be less important than that of myocardial infarctions and unnecessary invasive diagnostic tests, across all outcomes there is proof of a greater benefit of a diagnostic strategy using CCTA vs. a diagnostic strategy using FDTs in patients who are suspected of having chronic CHD after basic diagnostic tests.

**CCTA versus direct ICA**

To answer Question 1, the comparison between CCTA and invasive coronary angiography (ICA), a total of 4 studies were analysed.

For the outcome of stroke, the analysis showed that in the long term, fewer events occurred in the CCTA group than in the direct ICA group (indication of a benefit). In addition, for the outcome of unnecessary invasive diagnostic tests, it was shown that a lower proportion of patients in the CCTA group underwent invasive diagnostic tests with the result of "no obstructive CHD" than in the direct ICA group (proof of less harm). For the outcome of AEs, the CCTA group was also shown to have fewer periprocedural AEs (indication of less harm).

For all other outcomes, there were no relevant differences between the comparisons or no usable data were available.

Overall, based on the outcomes of stroke, unnecessary invasive diagnostic tests and AEs, there is proof across outcomes of a greater benefit of the diagnostic strategy using CCTA compared with direct ICA in patients suspected of having chronic CHD after basic diagnostic tests.

**Question 2: CCTA with the option of CT-based functional evaluation versus strategies without the option of CT-based functional evaluation**

A total of 3 studies were analysed for this question. These studies investigated 2 different functional evaluation methods as a possible adjunct to CCTA: CT-based measurement of fractional flow reserve (CT-FFR) and CT-based measurement of myocardial perfusion (CTP).

The study results show that both CT-FFR and CTP, as optional add-ons to CCTA, help to avoid unnecessary invasive diagnostic tests (indication of less harm). With the exception of the case described below, for all other outcomes there were either no relevant differences between the comparisons or no usable data were available. No data were available on AEs.

The reduction in unnecessary invasive diagnostic tests is contrasted by conspicuous numerical trends in the CT-FFR from the included study (as well as from another study reported as supplementary information) for the outcome of myocardial infarction, to the disadvantage of

the intervention. Because of these numerical group differences, there is concern that harm could be associated with a reduction in invasive diagnostic tests.

In the two studies on CTP, there were no numerically conspicuous group differences, but there was also no effect in favour of the intervention for any other outcome. As CTP is associated with additional procedural risks due to the injection of drugs and contrast agents, there is no advantage of the option of CT-based functional evaluation using CTP.

Overall, there is no benefit or potential of CCTA with CT-based functional evaluation compared with CCTA without CT-based functional evaluation in patients with suspected chronic CHD after basic diagnostic tests, because of concerns about potential harm (CT-FFR), or because no advantage is apparent after weighing the potential benefits and harms (CTP).

# Table of contents

## List of tables

**Page**

## List of abbreviations

| Abbreviation | Meaning |
|---|---|
| ACS | acute coronary syndrome(s) |
| AE | adverse event |
| AHRQ | Agency for Healthcare Research and Quality |
| ASSIGN | Assessing cardiovascular risk using SIGN (Scottish Intercollegiate Guidelines Network) |
| CCS | chronic coronary syndrome(s) |
| CCTA | coronary computed tomography angiography |
| CHD | coronary heart disease |
| CI | confidence interval |
| CT | computed tomography |
| CT-FFR | computed tomography-based measurement of fractional flow reserve |
| CTP | computed tomography-based measurement of myocardial perfusion |
| ECG | electrocardiogram |
| EQ-5D | European Quality of Life – 5 Dimensions |
| ESC | European Society of Cardiology |
| FDT | functional diagnostic test |
| FFR | fractional flow reserve |
| G-BA | Gemeinsamer Bundesausschuss (Federal Joint Committee) |
| HR | hazard ratio |
| HTA | health technology assessment |
| ICA | invasive coronary angiography |
| IQWiG | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care) |
| ITT | intention to treat |
| MACE | major adverse cardiovascular event |
| MCS | Mental Component Summary Score |
| MD | mean difference |
| MRI | magnetic resonance imaging |
| mSv | millisievert |
| NICE | National Institute for Health and Care Excellence |
| NVL | Nationale VersorgungsLeitlinie (National Care Guideline) |
| OR | odds ratio |
| PCS | Physical Component Summary Score |

| Abbreviation | Meaning |
|---|---|
| PET | positron emission tomography |
| PHQ-9 | Patient Health Questionnaire |
| RCT | randomized controlled trial |
| SAE | serious adverse event |
| SAQ | Seattle Angina Questionnaire |
| SF-12 | 12-Item Short Form Health Survey |
| SF-36 | 36-Item Short Form Health Survey |
| SHI | statutory health insurance |
| SPECT | single photon emission computed tomography |
| SPS | Stanford Presenteeism Scale |
| SR | systematic review |
| VAS | Visual Analogue Scale |

# 1 Background

Coronary heart disease (CHD) is defined as arteriosclerosis in the coronary arteries. In these arteries, there are various types of deposits in the vessel walls. Depending on the extent of these deposits, CHD is divided into 2 stages. If there is no imbalance between oxygen demand and supply in the heart muscle due to the arteriosclerosis, it is called non-stenosing or non-obstructive CHD, which is asymptomatic. If, on the other hand, the stenosis has already progressed so far that there is a reduction in blood flow to the heart muscle, i.e. ischaemia, this is stenosing or obstructive CHD, which typically manifests itself in angina pectoris, i.e. chest pain with a feeling of tightness [1]. In 2018, as in previous years, chronic CHD was the most common cause of death among men and women in Germany [2].

The leading clinical symptom of chronic CHD, also known as chronic coronary syndrome (CCS), is stable angina pectoris, which occurs in response to physical exertion because the increased oxygen demand of the heart muscle triggered by the exertion can no longer be adequately met. Stable angina pectoris, in contrast to acute coronary syndrome (ACS), usually subsides at rest or after medication. Unstable angina pectoris can be classified as ACS if it manifests as pain at rest and for longer than 20 minutes, new onset moderate to severe angina, or angina that gradually increases in intensity and severity [3]. However, as people with chronic CHD may also be asymptomatic, may periodically present with symptoms of unstable angina pectoris or may suffer from dyspnoea without the typical chest pain, a clear diagnosis is essential [1].

In the case of pectanginal symptoms, if both ACS and other causes can be ruled out by means of an electrocardiogram (ECG) and laboratory tests plus medical history and physical examination, and if stable obstructive CHD is thus the most likely suspected diagnosis, various non-invasive and invasive imaging procedures are available depending on the pre-test probability [1].

Non-invasive procedures include single photon emission computed tomography (SPECT), determination of coronary calcification using calcium scoring (without contrast agents), exercise ECG, stress echocardiography, stress magnetic resonance imaging (stress MRI), dobutamine stress MRI and positron emission tomography (PET) [1]. In addition, the computed tomographic procedures relevant to this report also belong to non-invasive diagnostic tests. These include contrast-enhanced computed tomography (CT) coronary angiography (CCTA), CT-based measurement of fractional flow reserve (CT-FFR), and CT-based measurement of myocardial perfusion (CTP). Both CT-FFR and CTP are downstream of CCTA [4,5]. CTP can be divided into static ("snapshot") and dynamic (multiple image sequences) measurement of perfusion. In contrast to SPECT, exercise ECG and stress echocardiography, CCTA, CT-FFR, CTP as well as calcium scoring, MRI and PET procedures are currently not included in the scope of the services reimbursed by the statutory health insurance (SHI).

The invasive procedures for the diagnosis or exclusion of CHD include invasive coronary angiography (ICA) using a left heart catheter. This can be performed with or without measurement of the FFR [6].

Depending on the target mechanism, the above procedures can be divided into anatomical and functional diagnostic tests (FDTs). While FDTs such as stress echocardiography, exercise ECG and SPECT detect the effects of stenosis on myocardial perfusion, anatomical tests such as ICA and CCTA are used for direct detection of stenosis [1,3]. ICA is the gold standard for diagnosing CHD caused by a stenosis [6]. If the result is unclear, the two procedures can be supplemented by a functional evaluation by measuring the FFR (invasive FFR during ICA or CT-FFR after CCTA) or, in the case of CCTA, also by a functional evaluation using CTP [1].

The National Care Guideline (Nationale VersorgungsLeitlinie, NVL) "Chronic CHD" and the corresponding guideline of the European Society of Cardiology (ESC) on the diagnosis and management of CCS make positive recommendations for all non-invasive procedures mentioned so far - with the exception of CTP [1,3]. The choice of non-invasive procedure is mainly based on the pre-test probability of obstructive CHD, which is determined according to age, sex and type of symptoms. Other factors that influence the choice of procedure are the suitability of the patient (e.g. existing intolerances), the risks (e.g. radiation exposure) and the equipment and expertise on site [1]. The current guideline of the National Institute for Health and Clinical Excellence (NICE) recommends CCTA as the primary diagnostic tool for new onset chest pain and suspected CHD [7]. The NVL recommends non-invasive procedures for a mean pre-test probability of obstructive CHD of 15% to 85%; CCTA is only recommended for a pre-test probability in the low-intermediate range of 15% to 50% and thus primarily for the exclusion of chronic CHD [1]. CTP is not mentioned in the corresponding guidelines. In contrast, FFR measurement is currently recommended in the ESC guideline only for use in combination with ICA. Here, the guideline advocates its use for:

1) symptomatic patients with a high clinical risk profile;
2) asymptomatic patients in whom non-invasive risk stratification indicates a high risk of cardiovascular mortality (> 3% annually) and revascularisation is being considered to improve prognosis;
3) patients with unclear or conflicting results from non-invasive diagnostic tests [3].

Despite a strong negative recommendation in the current NVL against ICA for low and intermediate pre-test probability, the number of ICAs in Germany has been steadily increasing for years. In 2019, approximately 510,000 ICAs were performed. In about 30% of cases, the ICAs showed no pathological results [1,8]. A possible reason for the increase is that CCTA – in contrast to ICA (with and without measurement of FFR) – is not included in the scope of services reimbursed by SHI [1,3,7].

## 2 Research questions

The following 2 questions are part of this report:

- Question 1: The objective is to assess the benefit of diagnostic strategies using contrast enhanced coronary computed tomography angiography (shortened to CCTA) compared with diagnostic strategies with the same goal, but without CCTA.
- Question 2: The objective is to assess the benefit of diagnostic strategies using CCTA with the option of subsequent computed tomography (CT)-based functional evaluation compared with diagnostic strategies with the same goal, but without the option of CT-based functional evaluation. If the benefit of CCTA is at least comparable according to Question 1, the diagnostic comparator strategies may also include CCTA.

The tests to be assessed aim to establish a diagnosis in patients with suspected chronic heart disease (CHD) who, after basic diagnostic tests, have a clinical indication for further non-invasive diagnostic tests. The assessment focused on selected patient-relevant outcomes.

In addition, the incorporation of both the test and control interventions of the assessed tests into the upstream and downstream diagnostic procedures is presented.

# 3 Methods

For both questions, patients with suspected chronic CHD who, after basic diagnostic tests, had a clinical indication for further non-invasive diagnostic tests were the target population for the benefit assessment. The test intervention was diagnostic strategies using CCTA (Question 1) and diagnostic strategies using CCTA with the option of an additional CT-based functional evaluation (Question 2). Diagnostic strategies of the same objective without CCTA (Question 1) or without the option of a CT-based functional evaluation (Question 2) were considered as control interventions. The procedures used as control interventions are part of the scope of services reimbursed by SHI. In the case of at least comparable benefit of CCTA according to Question 1, the diagnostic comparator strategies for Question 2 could also include CCTA (see Section A2 of the full report).

The following patient-relevant outcomes were considered for the investigation:

- Mortality
- Morbidity
- Health-related quality of life
- Adverse effects

Only randomized controlled trials (RCTs) were included in the benefit assessment for both questions. There were no restrictions regarding the study duration of the RCTs. If necessary, according to the commission of the Federal Joint Committee (G-BA), diagnostic accuracy was also to be assessed.

In parallel to the preparation of the protocol (“report plan”), a search for systematic reviews (SRs) was conducted in the MEDLINE database (also includes the Cochrane Database of Systematic Reviews) and the Health Technology Assessment (HTA) Database, as well as on the websites of NICE and the Agency for Healthcare Research and Quality (AHRQ). The working paper GA20-01 by the Institute for Quality and Efficiency in Health Care (IQWiG) was also reviewed for relevant SRs based on RCTs [9].

It was examined whether at least 1 high-quality and current SR was available for each research question whose information retrieval could be used as the basis for the assessment (hereinafter: basic SR).

If such a basic SR was available, a supplementary search for studies for the period not covered by the basic SR was carried out in a second step. Otherwise, the search for studies was carried out without restricting the search period.

The systematic literature search for studies was conducted in the databases MEDLINE, Embase and Cochrane Central Register of Controlled Trials.

In addition, the following information sources and search techniques were considered: study registries, manufacturer enquiries, documents submitted by the G-BA, review of reference lists, author enquiries, and documents provided from hearing procedures.

The selection of relevant studies was carried out by 2 persons independently of each other. Discrepancies were resolved by discussion. Data were extracted into standardized tables. Across-outcome and outcome-specific risk-of-bias criteria were assessed to assess the qualitative certainty of results (shortened to “certainty of results” in the following text), and the risk of bias was rated as low or high in each case. The results of the individual studies were described according to outcomes.

In addition to the comparison of the results of the individual studies, metaanalyses and sensitivity analyses were performed and effect modifiers examined, provided that the methodological requirements were met.

For each outcome, a conclusion on evidence of (greater) benefit and (greater) harm was made in 4 grades regarding the respective certainty of conclusions: either proof (highest certainty of conclusions), an indication (medium certainty of conclusions), a hint (weakest certainty of conclusions), or none of these 3 situations was present. The latter case occurred when no data were available or the available data did not allow any of the other 3 conclusions. In this case, the conclusion “There is no hint of (greater) benefit or (greater) harm” was drawn.

Finally, an assessment of benefit and harm across outcomes was performed.

# 4 Results

## 4.1 Results of information retrieval

For Question 1, 1 SR was considered as a basic SR for the purpose of identifying primary studies. For Question 2, no basic SRs were identified.

The information retrieval identified 15 relevant RCTs for Question 1 (11 studies comparing CCTA vs. FDTs and 4 studies comparing CCTA vs. direct ICA) and 3 relevant and 2 supplementary RCTs for Question 2. For 1 of the 2 RCTs presented as supplementary information, the PRECISE study, unpublished data were submitted by the manufacturer.

For Question 1, 3 planned and 3 ongoing studies were identified. Furthermore, 3 studies with unclear status were identified for this question. For Question 2, there were 2 ongoing studies. In addition, 1 study with unclear status was identified.

The last search took place on 20 September 2022 (Question 1) and on 30 June 2022 (Question 2).

Table 1: Study pool of the benefit assessment

| Study | Full publication (in scientific journals) | Available documents | | |
|---|---|---|---|---|
| | | Registry entry / results report from study registry | Documents from manufacturer (not publicly accessible) | Other documents |
| **Question 1: CCTA** | | | | |
| ***CCTA vs. FDTs*** | | | | |
| CAPP | yes [10,11] | yes [12] / no | no | no |
| CARE-CCTA | yes [13] | yes [14] / no | no | no |
| CATCH | yes [15,16] | yes [17] / no | no | no |
| CT-STAT | yes [18] | yes [19] / no | no | no |
| Goldstein 2007 | yes [20] | yes [21] / no | no | no |
| IAEA-SPECT/CTA | yes [22] | yes [23,24] / no | no | no |
| Min 2012 | yes [25] | no / no | no | no |
| Nabi 2016 | yes [26] | no / no | no | no |
| PERFECT | yes [27] | yes [28] / no | no | no |
| PROMISE | yes [29-39] | yes [40] / yes | no | no |
| SCOT-HEART | yes [41-48] | yes [49] / no | no | no |
| ***CCTA vs. direct ICA*** | | | | |
| CAD-MAN | yes [50,51] | yes [52] / no | no | no |
| CONSERVE | yes [53,54] | yes [55] / no | no | no |
| DISCHARGE | yes [56,57] | yes [58] / no | no | no |
| Reis 2022 | yes [59] | no / no | no | no |
| **Question 2: CCTA with functional evaluation** | | | | |
| CATCH-2 (CTP) | yes [60,61] | yes [62] / no | no | no |
| FORECAST (CT-FFR) | yes [63,64] | yes [65] / no | no | no |
| PRECISE (CT-FFR)[a] | yes [66][b] | yes [67] / no | Study protocol [68]<br>Presentation (scientific meeting) [69]<br>Full-text manuscript [70] | no |
| TARGET (CT-FFR)[a] | yes [71,72] | yes [73] / no | no | no |
| Yu 2020 (CTP) | yes [74] | no / no | no | no |

a. This study does not sufficiently meet the inclusion criteria of this assessment. Therefore, the information on this study is only reported in as supplementary information.
b. The full-text publication is a publication on methods, not results.

CCTA: coronary computed tomography angiography; CT-FFR: computed tomography-based measurement of fractional flow reserve; CTP: computed tomography-based measurement of myocardial perfusion; ICA: invasive coronary angiography

## 4.2 Diagnostic strategies using CCTA (Question 1)

The assessment of Question 1 included studies that compared CCTA with FDTs, but also studies whose control treatment consisted of direct ICA, i.e. without further upstream diagnostic tests after randomization. For all patients from studies comparing CCTA with direct ICA, there is a clinical indication for invasive diagnostic tests, but based on the existing symptoms or the results of non-invasive FDTs, it is probably not urgent. For such patients, there is therefore also a clinical indication for a further non-invasive diagnostic test, in this case the CCTA applied in the intervention arm. Therefore, studies comparing CCTA with direct ICA also meet the inclusion criteria of the report. In the following text, the characteristics and results of the studies for Question 1 are thus presented separately for each control intervention.

### 4.2.1 Characteristics of studies included in the assessment

Of the 15 included studies related to Question 1, 11 referred to the comparison with non-invasive FDTs (CAPP [11], CARE-CCTA [13], CATCH [16], CT-STAT [18], Goldstein 2007 [20], IAEA-SPECT/CTA [22], Min 2012 [25], Nabi 2016 [26], PERFECT [27], PROMISE [38] and SCOT-HEART [45]) and 4 studies referred to the comparison with direct ICA (CAD-MAN [51], CONSERVE [53], DISCHARGE [57] and Reis 2022 [59]) (see Section A3.2.1.1 of the full report).

**Comparison of CCTA vs. FDTs**

The CAPP study is a multicentre RCT from Northern Ireland and was conducted in two specialist chest pain clinics between 2010 and 2011. It included 500 patients aged over 40 years with stable chest pain. Patients with known CHD or suspected unstable angina pectoris were explicitly excluded. After randomization (1 : 1), CCTA was preceded by calcium scoring in the intervention arm. An exercise ECG was performed in the control arm. Further diagnostic tests, based on the results of the CCTA or the exercise ECG, were carried out according to the judgement of the treating physician. The possible further diagnostic tests included an ICA and a SPECT. The follow-up period of the study was 12 months.

The CARE-CCTA study is a multicentre RCT from South Korea and was conducted in three outpatient clinics between 2011 and 2014. A total of 965 patients between 30 and 80 years of age with stable chest pain were enrolled in the study. Patients with known CHD or suspected ACS were excluded. After randomization (1 : 1), CCTA was performed in the intervention arm and SPECT was performed in the control arm. In case of unclear results, the test from the other study arm followed in a few cases. Further diagnostic tests in case of positive results of CCTA or SPECT consisted of ICA. The follow-up period of the study was 12 months.

The CATCH study is a single-centre RCT from Denmark and was conducted between 2010 and 2013. It included 600 patients over 18 years of age with suspected ACS, but with two normal troponin values and a normal resting ECG, and who could be discharged from hospital after

24 hours without recurrence of chest pain. Patients with known CHD were also included, but accounted for less than 15% of the total population. After randomization (1 : 1), CCTA with upstream calcium scoring was performed in the intervention arm. An exercise ECG was performed in the control arm. If the ECG result was unclear or physical fitness was low, a SPECT was performed. To conceal group allocation, both interventions were performed in all patients. CCTA results were not available in the control arm and ECG/SPECT results were not considered for clinical decision-making in the intervention arm. Further diagnostic tests in both arms in case of unclear or positive results usually consisted of ICA. The median follow-up period of the study was 18.7 months.

The CT-STAT and Goldstein 2007 studies differ mainly in the number of study centres. CT-STAT is a multicentre RCT from the USA and was conducted between 2007 and 2008. Goldstein 2007 is a single-centre RCT from the USA, conducted in 2005. 749 (CT-STAT) and 203 (Goldstein 2007) inpatients over 25 years of age with acute chest pain, but normal troponin values and a normal resting ECG, were included. Patients with known CHD were excluded. After randomization (1 : 1), CCTA with upstream calcium scoring was performed in the intervention arm. SPECT was performed in the control arm. SPECT was also performed in the intervention arm if the CCTA results were unclear. Further diagnostic tests in both arms in case of unclear or positive results usually consisted of ICA. The follow-up period of the studies was 6 months.

The IAEA-SPECT/CTA study is a multicentre RCT and was conducted between 2011 and 2014 in Brazil, India, Mexico, Slovenia and the Czech Republic as well as in Turkey. A total of 303 patients over 21 years of age with stable chest pain or an asymptomatic course, but with an intermediate to high pre-test probability, were included. Patients with known CHD were explicitly excluded. After randomization (1 : 1), CCTA with upstream calcium scoring was performed in the intervention arm. SPECT was performed in the control arm. In the intervention arm, SPECT was usually performed if the CCTA findings were unclear. Otherwise, ICA was usually performed in both arms in case of unclear or positive results. The follow-up period of the study was 12 months.

The Min 2012 study is a multicentre RCT from the USA and was conducted between 2008 and 2009 in two outpatient cardiology clinics. It included 180 patients over 40 years of age with stable chest pain and suspected CHD. Patients with known CHD or suspected ACS were not allowed to participate. After randomization (1 : 1), CCTA was performed in the intervention arm and SPECT was performed in the control arm. Subsequently, in case of positive or unclear results of CCTA or SPECT, ICA was usually performed. The mean follow-up period of the study was 1.8 months.

The Nabi 2016 study is a single-centre RCT from the USA and was conducted between 2009 and 2011. It included 598 patients over 18 years of age with acute chest pain, but with a

normal troponin level. Patients with known CHD were excluded. After randomization (1 : 1), CCTA with upstream calcium scoring was performed in the intervention arm. SPECT was performed in the control arm. In case of positive or unclear results of CCTA or SPECT, ICA was usually performed. The median follow-up period of the study was 6.5 months.

The PERFECT study is a single-centre RCT from the USA and was conducted between 2011 and 2013. A total of 411 patients over 45 years of age with acute chest pain, but normal troponin values and resting ECG results, were included. Patients with known CHD were excluded. After randomization (1 : 1), CCTA with upstream calcium scoring was performed in the intervention arm. Further diagnostic tests in the intervention arm, based on unclear results of CCTA, usually included stress echocardiography or SPECT. In the control arm, stress echocardiography or SPECT was performed, depending on the judgement of the treating physician. If the results were positive or unclear, ICA was usually performed in both arms. The follow-up period of the study was 12 months.

The PROMISE study is a multicentre RCT from the USA and was conducted between 2010 and 2013. It included 10,003 patients (female patients over 65 years of age and male patients over 55 years of age) with stable chest pain. This makes PROMISE the largest study included in the study pool. Patients with known CHD or suspected ACS were explicitly excluded. After randomization (1 : 1), CCTA with upstream calcium scoring was performed in the intervention arm. Stress echocardiography, exercise ECG or SPECT was performed in the control arm. The choice of FDT in the control arm was determined by the treating physician before randomization. Apart from that, ICA was usually performed in both arms in case of unclear or positive results. The median follow-up period of the study was 25 months.

The SCOT-HEART study is a multicentre RCT from Scotland and was conducted between 2010 and 2014. A total of 4146 patients between 18 and 75 years of age with stable chest pain were included in the study. Patients with known CHD were included, but accounted for less than 10% of the total population. Patients with an ACS within the last 3 months were excluded. Before randomization, all patients had received the standard of care according to the NICE guideline, consisting of an exercise ECG and, depending on the result, further functional or invasive tests. After randomization (1 : 1), a CCTA with upstream calcium scoring was performed in the intervention arm. The ASSIGN (Assessing cardiovascular Risk using SIGN [Scottish Intercollegiate Guidelines Network]) score was calculated in the control arm. Calculation of the ASSIGN score in the intervention arm was possible at the request of the treating physician, but was not regularly provided for. In contrast to other pre-test probabilities, the ASSIGN score also includes socioeconomic status by documenting place of residence and family history. In case of unclear or positive results, ICA was usually performed in both arms. The median follow-up period of the study was 4.8 years.

**Comparison CCTA vs. direct ICA**

The CAD-MAN study is a single-centre RCT from Germany and was conducted between 2009 and 2015. It included 340 patients over 30 years of age with suspected CHD and a clinical indication for ICA due to atypical symptoms. Overall, 12% (intervention arm) and 18% (control arm) of patients showed no reduction in chest pain with medication or rest and thus had suspected ACS. In the 6 months prior to randomization, 50% (intervention arm) and 57% (control arm) of patients had undergone at least 1 FDT. Patients with known CHD were explicitly excluded. After randomization (1 : 1), CCTA with upstream calcium scoring was performed in the intervention arm and ICA was performed in the control arm. Subsequently, if the CCTA results were positive, an ICA was performed in the intervention arm. The median follow-up period of the study was 3.3 years.

The CONSERVE study is a multicentre RCT from North America, East Asia, Europe and India and was conducted between 2012 and 2015 in hospitals and cardiology practices. It included 1631 patients over 18 years of age with stable chest pain, suspected CHD and a clinical indication for ICA. Prior to inclusion in the study, 28% (control arm) and 29% (intervention arm) of patients had undergone at least 1 FDT. Patients with known CHD or known ACS were excluded. In the intervention arm, CCTA with prior calcium scoring was performed after randomization (1 : 1). In the control arm, ICA was performed. Subsequently, in case of unclear or positive results of CCTA or ICA, (further) ICA, exercise ECG or resting echocardiography was usually performed, depending on the judgement of the treating physician. The median follow-up period of the study was 12.3 months.

The DISCHARGE study is a multicentre RCT from Germany, Austria, Czech Republic, Denmark, Hungary, United Kingdom, Ireland, Italy, Latvia, Lithuania, Poland, Portugal, Romania, Serbia, Spain and Finland and was conducted between 2015 and 2019. It included 3667 patients over 30 years of age with stable chest pain, suspected CHD and a clinical indication for ICA. Prior to inclusion in the study, 35% (control arm) and 33% (intervention arm) of patients had undergone at least 1 FDT. After randomization (1 : 1), CCTA with upstream calcium scoring was performed in the intervention arm. ICA was performed in the control arm. In the intervention arm, if the CCTA results were positive, further diagnostic tests (FDTs and / or ICA) were decided on by a local heart team consisting of cardiologists, heart surgeons and radiologists. The median follow-up period of the study was 3.5 years.

The Reis 2022 study is a single-centre RCT from Portugal and was conducted between 2015 and 2018. It included 220 patients over 18 years of age with suspected stable CHD and a clinical indication for ICA. All patients had undergone at least 1 FDT prior to inclusion in the study. Patients with known CHD or known ACS were explicitly excluded. After randomization (1 : 1), CCTA with upstream calcium scoring was performed in the intervention arm. ICA was performed in the control arm. Subsequently, if the CCTA results were unclear or positive, an

ICA was performed in the intervention arm. The follow-up period of the study was at least 12 months.

### 4.2.2 Overview of patient-relevant outcomes

Table 2: Matrix of patient-relevant outcomes (Question 1: CCTA) (multi-page table)

| Study | Outcomes | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mortality | | MACE | Morbidity | | | | | | | | QoL | | | | | Adverse effects |
| | All-cause mortality | Cardiovascular mortality | | Myocardial infarction | Stroke | Unstable angina pectoris | Angina pectoris | Health state (EQ-5D VAS) | Depressive symptoms (PHQ-9) | Health-related work productivity (SPS) | Unnecessary invasive diagnostic tests | Physical summary score (SF-36) | Mental summary score (SF-36) | Physical summary score (SF-12) | Mental summary score (SF-12) | Disease-specific quality of life (SAQ) | Adverse events |
| **CCTA vs. FDTs** | | | | | | | | | | | | | | | | | |
| CAPP | ● | – | ○[b] | ● | ○[c] | ● | ●[d] | – | – | – | – | – | – | – | – | ● | ●[e] |
| CARE-CCTA | ● | – | – | ● | ● | ● | – | ● | – | – | ● | – | – | – | – | – | – |
| CATCH | ● | ● | ○[b] | ● | – | ● | – | – | – | – | ● | ● | ● | – | – | – | – |
| CT-STAT | ● | ● | ○[b] | ● | – | ● | – | – | – | – | – | – | – | – | – | – | – |
| Goldstein 2007 | ● | ● | ● | ● | – | ● | – | – | – | – | – | – | – | – | – | – | ●[e] |
| IAEA-SPECT/CTA | ● | – | ○[b] | ○[f] | – | – | – | – | – | – | – | – | – | – | – | – | – |
| Min 2012 | ● | ● | – | ● | – | – | – | – | – | – | – | – | – | – | – | ● | – |
| Nabi 2016 | – | ● | – | ○[f] | – | ○[f] | – | – | – | – | – | – | – | – | – | – | – |
| PERFECT | ● | ●[g] | – | ●[g] | – | ●[g] | – | – | – | – | – | – | – | – | – | – | – |
| PROMISE | ● | – | ● | ● | ● | ● | – | ● | ● | ● | ● | – | – | ○[h] | ○[h] | ●[i] | ●[j] |
| SCOT-HEART | ● | ● | ● | ● | ● | – | ●[d] | – | – | – | ● | – | – | ● | ● | ●[k] | ● |
| **CCTA vs. direct ICA** | | | | | | | | | | | | | | | | | |
| CAD-MAN | ●[l] | ● | ○[b] | ● | ● | ● | – | – | – | – | ● | – | – | × | × | – | ●[e] |
| CONSERVE | ● | – | ○[b] | ● | ● | ● | – | × | – | – | ● | – | – | – | – | – | ●[e] |

Table 2: Matrix of patient-relevant outcomes (Question 1: CCTA) (multi-page table)

| Study | Outcomes | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mortality | | | Morbidity | | | | | | | | QoL | | | | | Adverse effects |
| | All-cause mortality | Cardiovascular mortality | MACE | Myocardial infarction | Stroke | Unstable angina pectoris | Angina pectoris | Health state (EQ-5D VAS) | Depressive symptoms (PHQ-9) | Health-related work productivity (SPS) | Unnecessary invasive diagnostic tests | Physical summary score (SF-36) | Mental summary score (SF-36) | Physical summary score (SF-12) | Mental summary score (SF-12) | Disease-specific quality of life (SAQ) | Adverse events |
| DISCHARGE | ● | ● | ●[m] | ● | ● | – | ● | ● | – | – | ● | – | – | ●[n] | – | – | ●[g] |
| Reis 2022 | ● | ● | ○[b] | ● | ● | ● | ● | – | – | – | ● | – | – | – | – | – | – |

●: Data were reported and were usable.

○: Data were reported but were not usable for the benefit assessment.

x: Data were not reported despite planned collection.

-: No data were reported (no further information) / the outcome was not recorded.

a. Proportion of patients without obstructive CHD diagnosed by ICA.
b. Data not usable because individual components are not of comparable clinical severity.
c. It is not clear from the publication whether events occurred.
d. Only hospitalized cases, i.e. primarily serious events, were recorded.
e. Only a defined catalogue of AEs was recorded that were assessed as a "complication" of the interventions.
f. Data not usable, as results not shown per group.
g. No results reported at the planned time of analysis of 30 days after discharge.
h. Data not usable as not all subscales were recorded and therefore no summary score could be formed.
i. No results reported at the planned time of analysis of 24 months.
j. Only the number of events was documented, but not the number of patients with an event.
k. The outcome is assigned to morbidity because only the response threshold used for the subscales "angina stability" and "disease perception" is at least 15% of the scale range of the data collection instrument used.
l. No results reported at the planned time of analysis of 3.3 years (median).
m. MACE includes results for single components reported at 3.5 years. Results for single components at the periprocedural time of analysis of 48 hours were assigned to AEs.
n. The outcome is assigned to the morbidity category, as only the PCS subscale was recorded.

Table 2: Matrix of patient-relevant outcomes (Question 1: CCTA) (multi-page table)

| Study | Outcomes | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mortality | | MACE | Morbidity | | | | | | | | QoL | | | | | Adverse effects |
| | All-cause mortality | Cardiovascular mortality | | Myocardial infarction | Stroke | Unstable angina pectoris | Angina pectoris | Health state (EQ-5D VAS) | Depressive symptoms (PHQ-9) | Health-related work productivity (SPS) | Unnecessary invasive diagnostic tests | Physical summary score (SF-36) | Mental summary score (SF-36) | Physical summary score (SF-12) | Mental summary score (SF-12) | Disease-specific quality of life (SAQ) | Adverse events |
| AE: adverse event; CCTA: coronary computed tomography angiography; CHD: coronary heart disease; EQ-5D: European Quality of Life – 5 Dimensions, 3 Level Version; QoL: quality of life; ICA: invasive coronary angiography; MACE: major adverse cardiovascular events; PCS: Physical Component Scale; PHQ-9: Patient Health Questionnaire-9; SAQ: Seattle Angina Questionnaire; SF-36: 36-Item Short Form Health Survey; SF-12: 12-Item Short Form Health Survey; SPS: Stanford Presenteeism Scale; VAS: Visual Analogue Scale | | | | | | | | | | | | | | | | |

Data on patient-relevant outcomes could be extracted from all 15 included studies. Table 2 shows an overview of the available data on patient-relevant outcomes from the included studies.

For the comparison CCTA vs. FDTs, usable data on all-cause mortality were available from all studies except the Nabi 2016 study.

For the comparison of CCTA vs. direct ICA, usable data on all-cause mortality were available from all 4 studies. In the CAD-MAN study, data collection at a long-term time of analysis was planned, but no results were reported.

Results for the outcome of cardiovascular mortality were available for the comparison CCTA vs. FDTs from 7 studies. In the PERFECT study, no results were reported at the planned periprocedural time of analysis.

For the comparison CCTA vs. direct ICA, cardiovascular mortality data were available from 3 studies. For the Reis 2022 and DISCHARGE studies, the result on cardiovascular mortality could be derived at the periprocedural time of analysis, as no events occurred for the outcome of all-cause mortality.

Composite outcomes that were composed of patient-relevant individual components were assigned to the outcome of major adverse cardiovascular events (MACE); these were assessed as usable if the individual components did not differ considerably in their severity and relevance for patients. Since effects were already evident at the level of the individual components, the MACE outcome was not used to answer Question 1.

Results on the outcome of myocardial infarction were available from all 9 included studies comparing CCTA vs. FDTs. However, data on myocardial infarction from the Nabi 2016 study were not usable, as they were not reported per group. Likewise, the results of the IAEA-SPECT/CTA study were not usable because myocardial infarction was only reported as a sub-event of a composite outcome, but not separately. In the PERFECT study, results were not reported at the planned periprocedural time of analysis. For the comparison CCTA vs. direct ICA, usable data on myocardial infarction were available in all 4 studies.

For the outcome of stroke, results were available from 3 of the included studies for the comparison CCTA vs. FDTs. Data from the CAPP study were not usable because it was not clear from the publication whether no strokes occurred or whether the outcome was not reported at the planned time of analysis. For the comparison of CCTA vs. direct ICA, usable data were available for the outcome of stroke in all 4 studies.

For the outcome of unstable angina pectoris, data from 7 studies were available for the comparison CCTA vs. FDTs. The results of the Nabi 2016 study were not usable as they were

not reported per group. Data on unstable angina pectoris were not reported in the PERFECT study at the planned periprocedural time of analysis. For the comparison CCTA vs. direct ICA, data were usable from all 3 studies in which the outcome was reported.

For the outcome of angina pectoris, usable data for the comparison CCTA vs. FDTs were available from the two studies CAPP and SCOT-HEART, in which only hospitalized cases, i.e. primarily serious events, were recorded. For the comparison of CCTA vs. direct ICA, usable results on angina pectoris were available from the DISCHARGE and Reis 2022 studies.

For health state, measured by the European Quality of Life - 5 Dimensions Visual Analogue Scale (EQ-5D VAS), usable data were available from the CARE-CCTA and PROMISE studies for the CCTA vs. FDTs comparison. For the comparison CCTA vs. direct ICA, results on health state were reported in the DISCHARGE study, which could be used for the present analysis. Even though data collection was planned, no results on health state were reported in the CONSERVE study. Results on depressive symptoms using the Patient Health Questionnaire (PHQ-9) were only available for the PROMISE study for the comparison CCTA vs. FDTs. Data on health-related work productivity, measured by the Stanford Presenteeism Scale (SPS), were only available from the PROMISE study for the comparison of CCTA vs. FDTs, whose results were usable.

Usable results on unnecessary invasive diagnostic tests could be calculated for 4 of the 11 included studies comparing CCTA vs. FDTs and for all 4 studies comparing CCTA vs. direct ICA.

Quality of life, measured by the two subscales physical (PCS) and mental (MCS) component summary scores of the 36-item Short Form Health Survey (SF-36), was recorded for the comparison CCTA vs. FDTs only in the CATCH study, whose results were usable. Results on quality of life, measured by the two subscales PCS and MCS of the 12-item Short Form Health Survey (SF-12), were available from the PROMISE study, but could not be used because not all subscale data were collected and thus no analysis of the summary scores was possible. In contrast, results for the two subscales of the SF-12 in the SCOT-HEART study were reported as planned and could be used.

For the comparison CCTA vs. direct ICA, no results on the SF-12 were reported in the CAD-MAN study even though data collection was planned. In the DISCHARGE study, only the PCS of the SF-12 was recorded, which, considered alone, was only usable under the category of morbidity. Usable results for the outcome of disease-specific quality of life, measured by the Seattle Angina Questionnaire (SAQ), were available from 4 of 11 included studies comparing CCTA vs. FDTs. Of these, however, only the subscales “angina stability” and “disease perception” (called quality of life in the publication) in the SCOT-HEART study used a suitable response threshold and were therefore usable; individually, these subscales are assigned to

the morbidity category. For the comparison of CCTA vs. direct ICA, no measurement of disease-specific quality of life was performed using the SAQ in any study.

Few data on adverse events (AEs) were available in the studies. If such data were available, mostly only a defined catalogue of AEs was recorded, which were assessed as "complications" of the interventions.

### 4.2.3 Assessment of the risk of bias of results

The risk of bias (see Section A3.2.1.2 of the full report) for the CCTA vs. FDTs comparison was rated as low across outcomes for 4 studies (CATCH, IAEA-SPECT/CTA, PROMISE and SCOT-HEART) and as high for the remaining 7 studies (CAPP, CARE-CCTA, CT-STAT, Goldstein 2007, Min 2012, Nabi 2016 and PERFECT). In the CT-STAT and Goldstein 2007 studies, concealment of group allocation was unclear. In addition, the remaining studies with a high risk of bias (CAPP, CARE-CCTA, Min 2012, Nabi 2016 and PERFECT) showed unclear generation of the randomization sequence.

For the 7 studies (CAPP, CARE-CCTA, CT-STAT, Goldstein 2007, Min 2012, Nabi 2016 and PERFECT), for which the risk of bias across outcomes had already been rated as high, there was consequently a high outcome-specific risk of bias for all assessed outcomes, so that no further outcome-specific assessment was performed for these studies. For the IAEA-SPECT/CTA study, only one outcome was considered, which had been rated as having a low outcome-specific risk of bias. For the 3 other studies with a low risk of bias across outcomes, some of the assessed outcomes were rated as having a high outcome-specific risk of bias: CATCH (health-related quality of life), PROMISE (health state, depressive symptoms, disease-specific quality of life, health-related work productivity) and SCOT-HEART (unnecessary invasive diagnostic tests, health-related quality of life, disease-specific quality of life). The reasons for this classification were an inadequate implementation of the intention-to-treat (ITT) principle and / or the lack of blinding of the outcome assessors for subjective outcomes.

The risk of bias for the comparison of CCTA vs. direct ICA was assessed as low for 3 studies (CAD-MAN, DISCHARGE and CONSERVE) across outcomes. A high risk of bias was found for the Rice 2022 study due to unclear concealment of group allocation.

For the Rice 2022 study, for which the risk of bias across outcomes had already been rated as high, a high outcome-specific risk of bias was consequently found for all assessed outcomes, so that no further outcome-specific assessment was performed for this study. For the CAD-MAN study, all assessed outcomes were rated as having a low outcome-specific risk of bias. For the 2 other studies with a low risk of bias across outcomes, the outcomes under assessment were rated as having a high outcome-specific risk of bias: CONSERVE (all outcomes) and DISCHARGE (angina pectoris, health state, health-related quality of life). The

reasons for this rating were an inadequate implementation of the ITT principle and / or the lack of blinding of the outcome assessors for subjective outcomes.

### 4.2.4 Results on patient-relevant outcomes

For the analysis of the data in this report, 3 analysis periods were defined to which the results were assigned. The times of analysis were assigned to the periprocedural (up to 30 days after the intervention), medium-term (6 to 24 months) and long-term (2 to 5 years) analysis period. Accordingly, the usable data for the derivation of effects were presented grouped according to the 3 analysis periods, but a conclusion on benefit across times of analysis was drawn for each outcome. If data were available in a study at several times of analysis within the medium-term analysis period, only 1 time of analysis, preferably after 12 months, was considered. If a study had data at several times of analysis within the long-term analysis period, only the last time of analysis was considered. Results at times of analysis outside the pre-specified periods were not considered if data were already available at a periprocedural, medium-term or long-term time of analysis. The results of the Min 2012 study were reported as supplementary information, as these data were evaluated exclusively at times of analysis outside the periods defined above (1.8 months).

#### 4.2.4.1 Results for the outcome of all-cause mortality

**Comparison CCTA vs. FDTs**

For the comparison of CCTA vs. FDTs, data on the outcome of all-cause mortality were available from 10 studies with a moderate and high certainty of results. Only the Nabi 2016 study did not assess all-cause mortality. Results were available for periprocedural, medium- and long-term times of analysis (see Table 23 of the full report).

For the periprocedural analysis period, usable data were available from 3 studies (CT-STAT, Goldstein 2007 and PERFECT) with a moderate certainty of results. As no deaths had occurred in either treatment group in all 3 studies, neither the calculation of an effect nor a meta-analytical summary of the results was performed.

For the medium-term analysis period, usable data from 4 studies with a high certainty of results (CATCH, IAEA-SPECT/CTA, PROMISE and SCOT-HEART) were available, which could be summarized meta-analytically. No statistically significant difference was found in the meta-analysis (odds ratio [OR]: 0.77; 95% confidence interval [CI]: [0.40; 1.50]; p = 0.303). The meta-analytic summary of the studies with a high certainty of results and the studies with a moderate certainty of results (CAPP, CARE-CCTA, CT-STAT, Goldstein 2007 and PERFECT) showed no statistically significant difference (OR: 0.75; 95 % CI: [0.45; 1.27]; p = 0.226). As no deaths occurred in the CT-STAT, Goldstein 2007 and PERFECT studies, an analysis using a beta-binomial model was calculated to take these studies into account. Again, no statistically significant difference was found (OR: 0.79; 95 % CI: [0.44; 1.40]; p = 0.411).

For the long-term analysis period, usable data were available from the SCOT-HEART and PROMISE studies, each with a high certainty of results. The meta-analytical summary showed no statistically significant difference (OR: 0.99; 95% CI: [0.77; 1.28]; p = 0.956).

No analysis period could be assigned to the results of the Min 2012 study with a moderate certainty of results after 55 ± 34 days, in which no deaths had occurred and thus no difference between the groups was detectable.

Overall, no hint of a benefit or harm from CCTA vs. FDTs was derived for the outcome of all-cause mortality at any of the 3 analysis periods (periprocedural, medium-term or long-term).

**Comparison CCTA vs. direct ICA**

For the comparison of CCTA vs. direct ICA, data from all 4 studies with a moderate and high certainty of results were available for the outcome of all-cause mortality. Results were available for the periprocedural and medium-term analysis period (see Table 23 of the full report). It was planned to collect data on the long-term analysis period in the CAD-MAN study. However, these were not reported.

For the periprocedural analysis period, usable data were available from the CAD-MAN and DISCHARGE studies with a high certainty of results. As no deaths occurred in either treatment group, no common effect estimate was calculated.

For the medium-term analysis period, data from the two studies CONSERVE and Rice 2022 with a moderate certainty of results were available. Since no deaths occurred in the Rice 2022 study and only 3 (2 vs. 1) occurred in the CONSERVE study, no common effect estimate was calculated here either.

Overall, no hint of a benefit or harm from CCTA vs. direct ICA was derived with regard to the outcome of all-cause mortality for any of the analysis periods.

#### 4.2.4.2 Results on the outcome of cardiovascular mortality

**Comparison CCTA vs. FDTs**

For the comparison of CCTA vs. FDTs, usable data on the outcome of cardiovascular mortality were available from 7 studies with a moderate and high certainty of results. Results were available at periprocedural, medium-term and long-term times of analysis (see Table 25 of the full report).

For the periprocedural period, usable data were available from the two studies CT-STAT and Goldstein 2007 with a moderate certainty of results. As no cardiovascular deaths occurred in either study, no common effect estimate was calculated.

For the medium-term period, data from 6 studies with a high and moderate certainty of results were available and could be summarized meta-analytically. Since no events occurred in the CT-STAT, Goldstein 2007, Nabi 2016 and PERFECT studies (with a moderate certainty of results), only the results of the studies CATCH and SCOT-HEART (with a high certainty of results) were included in the common effect estimate. The meta-analysis showed no statistically significant difference (OR: 0.53; 95% CI: [0.17; 1.66]; p = 0.277). In order to take into account the studies in which no cardiovascular deaths had occurred (CT-STAT, Goldstein 2007, Nabi, 2016 and PERFECT), a beta-binomial model was calculated for all studies. Again, there was no statistically significant difference (OR: 0.50; 95% CI: [0.15; 1.68]; p = 0.261).

For the long-term period, data from the SCOT-HEART study with a high certainty of results were available. There was no statistically significant difference (hazard ratio [HR]: 0.43; 95% CI: [0.15; 1.22]).

The data of the Min 2012 study with a moderate certainty of results after 55 ± 34 days could not be assigned to any of the 3 analysis periods. In this study, no cardiovascular deaths had occurred in either treatment group and thus there was no difference between the groups.

Overall, no hint of benefit or harm from CCTA vs. FDTs was derived with regard to the outcome of cardiovascular mortality for any of the 3 analysis periods (periprocedural, medium-term or long-term).

**Comparison CCTA vs. direct ICA**

For the comparison of CCTA vs. direct ICA, usable data on the outcome of cardiovascular mortality were available from the CAD-MAN, DISCHARGE and Reis 2022 studies with a moderate and high certainty of results. Results were available at periprocedural, medium-term and long-term times of analysis (see Table 25 of the full report).

For the periprocedural analysis period, data from the CAD-MAN and DISCHARGE studies with a high certainty of results were available. Since no cardiovascular deaths occurred in either treatment group, no common effect estimate was calculated.

For the medium-term analysis period, data from the Reis 2022 study with a moderate certainty of results were available. As no cardiovascular deaths occurred in either treatment group in this study, there was no difference between the groups.

For the long-term analysis period, usable data were available from the CAD-MAN and DISCHARGE studies with a high certainty of results, which could be summarized meta-analytically. The results showed no statistically significant difference (OR: 0.47; 95% CI: [0.19; 1.12]; p = 0.088).

Overall, no hint of a benefit or harm from CCTA vs. direct ICA was derived with regard to the outcome of cardiovascular mortality for any of the 3 analysis periods (periprocedural, medium-term or long-term).

#### 4.2.4.3 Results on the outcome of major adverse cardiovascular events

The composite outcome MACE was collected in many studies and operationalized very differently. In this assessment, outcomes were only to be considered if MACE was composed of two or more of the following individual components: death (all-cause or cardiovascular), myocardial infarction, stroke, unstable angina pectoris. The outcome MACE was not to be used if it included measures (e.g. revascularisation or hospitalization) whose causes differed considerably from those mentioned above in their severity and relevance for patients. The criteria for the consideration of MACE were fulfilled for the comparison CCTA vs. FDTs in the Goldstein 2007, PROMISE and SCOT-HEART studies and for the comparison CCTA vs. direct ICA in the DISCHARGE study (see Table 27 of the full report).

However, statistically significant effects were already shown in this assessment at the level of individual outcomes, namely for the outcomes of myocardial infarction (CCTA vs. FDTs) and stroke (CCTA vs. ICA), primarily due to the results of the large PROMISE and SCOT-HEART studies and the DISCHARGE study. Since it can be assumed that the differences found in the individual outcomes are also evident in combination with other individual outcomes, an analysis of the composite outcome was not performed.

#### 4.2.4.4 Results on the outcome of myocardial infarction

**Comparison CCTA vs. FDTs**

For the comparison of CCTA vs. FDTs, usable data were available for the outcome of myocardial infarction from 9 studies with a moderate and high certainty of results. Results were available at the periprocedural, medium-term and long-term times of analysis (see Table 29 of the full report).

For the periprocedural analysis period, data from the CT-STAT and Goldstein 2007 studies with a moderate certainty of results were available. As no myocardial infarctions occurred in either treatment group in the Goldstein 2007 study, no meta-analytical summary of the data from the two studies was performed. The results of the CT-STAT study showed no statistically significant difference (OR: 0.19; 95% CI: [0.02; 1.59]; p = 0.095).

Data from 3 studies with a high certainty of results (CATCH, PROMISE and SCOT-HEART) were available for the medium-term analysis period, for which a common effect estimate was not calculated. The estimate using Knapp and Hartung was not statistically significant. It was therefore examined whether the estimate according to DerSimonian and Laird yielded a statistically significant result; this was not the case. Therefore, a qualitative assessment was

made. The effects were not conclusive. Furthermore, a meta-analysis of all 8 studies with a moderate and high certainty of results showed a statistically significant difference (OR: 0.61; 95% CI: [0.41; 0.89]; p = 0.021) in favour of CCTA. Since no myocardial infarctions occurred in the CARE-CCTA and Goldstein 2007 studies, a beta-binomial model was calculated to take these studies into account. There was no statistically significant difference between CCTA and FDTs (OR: 0.58; 95% CI: [0.26; 1.33]; p = 0.199). Overall, a hint of an effect in favour of CCTA at the medium-term point was derived, as the conclusions on statistical significance differed.

For the long-term analysis period, usable data were available from the SCOT-HEART and PROMISE studies with a high certainty of results, which could be summarized meta-analytically. There was a statistically significant difference (OR: 0.65; 95% CI: [0.48; 0.87]; p = 0.004) in favour of CCTA.

The results of the Min 2012 study with a moderate certainty of results after 55 ± 34 days (during which no myocardial infarctions had occurred in either treatment group) could not be assigned to any of the 3 analysis periods and were not analysed for any other period.

Overall, proof of a benefit of CCTA vs. FDTs was derived with regard to the outcome of myocardial infarction.

**Comparison CCTA vs. direct ICA**

For the comparison of CCTA vs. direct ICA, data from all 4 studies with a high and moderate certainty of results were available for the outcome of myocardial infarction. Results were available at periprocedural, medium-term and long-term times of analysis (see Table 29 of the full report).

For the periprocedural analysis period, data from the two studies CAD-MAN and DISCHARGE with a high certainty of results were available, which could be summarized meta-analytically. The results showed no statistically significant difference (OR: 0.41; 95% CI: [0.14; 1.25]; p = 0.119).

For the medium-term analysis period, the results of the CONSERVE and Rice 2022 studies with a moderate certainty of results could be summarized meta-analytically. The results showed no significant difference (OR: 0.66; 95% CI: [0.13; 3.38]; p = 0.622).

For the long-term analysis period, data from the CAD-MAN and DISCHARGE studies with a high certainty of results were available, and their meta-analytical summary showed no statistically significant difference (OR: 1.16; 95% CI: [0.64; 2.09]; p = 0.620).

Overall, no hint of a benefit or harm from CCTA vs. direct ICA was derived with regard to the outcome of myocardial infarction.

#### 4.2.4.5 Results on the outcome of stroke

**Comparison CCTA vs. FDTs**

For the comparison of CCTA vs. FDTs, usable data from 3 studies with a moderate and high certainty were available for the outcome of stroke. Results were available for the periprocedural, medium-term and long-term times of analysis (see Table 31 of the full report).

For the periprocedural analysis period, only data from the PROMISE study with a high certainty of results were available. The results showed no statistically significant difference (Peto-OR: 0.51; 95% CI: [0.05; 4.95]; p = 0.681).

For the medium-term analysis period, data were available from the CARE-CCTA studies with a moderate certainty of results and the SCOT-HEART study with a high certainty of results. At the level of the SCOT-HEART study, there was no statistically significant difference (HR: 0.73; 95% CI: [0.23; 2.32]; p = 0.590). The results of the meta-analytical summary of the data from the CARE-CCTA studies and the SCOT-HEART study showed no statistically significant difference (OR: 0.72; 95% CI: [0.29; 1.78]; p = 0.473).

For the long-term analysis period, data were available from the SCOT-HEART study with a high certainty of results. The results of this study did not show a statistically significant difference (HR: 0.74; 95% CI: [0.38; 1.44]).

Overall, no hint of a benefit or harm from CCTA vs. FDTs was derived with regard to the outcome of stroke.

**Comparison CCTA vs. direct ICA**

For the comparison of CCTA vs. direct ICA, usable data were available for the outcome of stroke from all 4 studies with a moderate and high certainty of results. Results were available for the periprocedural, medium-term and long-term times of analysis (see Table 31 of the full report).

For the periprocedural analysis period, data from the CAD-MAN and DISCHARGE studies with a high certainty of results were available. As no strokes had occurred in either treatment group of the CAD-MAN study, a common effect was not calculated. The results of the DISCHARGE study showed no statistically significant difference (HR: 0.32; 95% CI: [0.01; 7.93]; p = 0.369).

For the medium-term analysis period, data from the CONSERVE and Reis 2022 studies with a moderate certainty of results were available, which could be summarized meta-analytically. The results showed no statistically significant difference (OR: 0.65; 95 % CI: [0.13; 3.32]; p = 0.608).

For the long-term analysis period, data from the CAD-MAN and DISCHARGE studies with a high certainty of results were available, which could be summarized meta-analytically. The pooled results showed a statistically significant difference in favour of CCTA (OR: 0.47; 95% CI: [0.22; 0.99]; p = 0.046).

Overall, an indication of a benefit of CCTA vs. direct ICA was derived with regard to the outcome of stroke. Although the result is based on 2 RCTs with a high certainty of results, no proof can be derived here for the following reason: The result is almost completely dominated by the DISCHARGE study, which included more than 10 times as many patients as the CAD-MAN study. Only 1 of the 31 stroke events in the two groups that were included in the meta-analysis came from the CAD-MAN study.

#### 4.2.4.6 Results on the outcome of unstable angina pectoris

**Comparison CCTA vs. FDTs**

For the comparison of CCTA vs. FDTs, data from 7 studies with a moderate and high quality certainty of results were available for the outcome of unstable angina pectoris. Results were available at periprocedural, medium-term and long-term times of analysis (see Table 33 of the full report).

For the periprocedural analysis period, only data from the CT-STAT study with a moderate certainty of results were available. The results showed no statistically significant difference (Peto OR: 0.94; 95% CI: [0.19; 4.67]; p = 0.997).

Data from all 7 studies were available for the medium-term analysis period. The meta-analytic summary of data from the CATCH and PROMISE studies with a high certainty of results showed no statistically significant difference (OR: 1.34; 95% CI: [0.88; 2.04]; p = 0.167). The meta-analytic summary of the data from the studies with a high (CATCH and PROMISE) and moderate (CAPP, CARE-CCTA, CT-STAT, Goldstein 2007 and PERFECT) certainty of results also showed no statistically significant difference (OR: 1.35; 95% CI: [0.87; 2.08]; p = 0.139). As no events had occurred in either treatment group in the Goldstein 2007 study, an analysis was conducted using the beta-binomial model to consider this study. Again, there was no statistically significant difference (OR: 1.34; 95% CI: [0.92; 1.95]; p = 0.128).

For the long-term analysis period, only data from the PROMISE study with a high certainty of results were available. The results of the study at the long-term time of analysis showed a statistically significant difference to the disadvantage of CCTA compared to FDTs (OR: 1.50; 95% CI: [1.01; 2.23]; p = 0.046).

Overall, an indication of a lower benefit of CCTA vs. FDTs was derived with regard to the outcome of unstable angina pectoris.

**Comparison CCTA vs. direct ICA**

For the comparison of CCTA vs. direct ICA, data from 3 studies with a moderate and high certainty of results were available for the outcome of unstable angina pectoris. Results were available for the medium-term and long-term times of analysis (see Table 33 of the full report).

For the medium-term analysis period, data from the CONSERVE and Rice 2022 studies with a moderate certainty of results could be meta-analysed. The results showed no statistically significant difference (OR: 1.13; 95% CI: [0.47; 2.74]; p = 0.786).

For the long-term analysis period, data from the CAD-MAN study with a high certainty of results were available. The results of this study also showed no statistically significant difference (OR: 4.91; 95% CI: [0.23; 103.05]; p = 0.211).

Overall, no hint of a benefit or harm from CCTA vs. direct ICA was derived for the outcome of unstable angina pectoris.

#### 4.2.4.7 Results on the outcome of angina pectoris

**Comparison CCTA vs. FDTs**

For the comparison of CCTA vs. FDTs, usable data were available from the CAPP and SCOT-HEART studies. Data were available at the medium-term time of analysis.

At the level of the single SCOT-HEART study with a high certainty of results, there was no statistically significant difference (HR: 1.12; 95% CI: [0.81; 1.55]; p = 0.513). The meta-analytical summary of the two studies (SCOT-HEART with a high and CAPP with a moderate certainty of results) showed significant heterogeneity (p < 0.001; see Figure 17 of the full report), which is why no pooled effect was calculated. The qualitative summary showed that the effects of the 2 studies were non-conclusive.

Overall, no hint of a benefit or harm from CCTA vs. direct ICA was derived with regard to the outcome of angina pectoris.

**Comparison CCTA vs. direct ICA**

For the comparison of CCTA vs. direct ICA, data on the outcome of angina pectoris were available from 2 studies with a moderate certainty of results. Results were available for the medium-term and long-term times of analysis (see Table 35 of the full report).

For the medium-term analysis period, results from the studies DISCHARGE and Rice 2022 with a moderate certainty of results were usable and could be summarized meta-analytically. The results showed no statistically significant difference (OR: 1.21: 95% CI: [0.98; 1.50]; p = 0.077).

For the long-term analysis period, only data from the DISCHARGE study with a moderate certainty of results were available. The results of this study also showed no statistically significant difference (OR: 1.17; 95% CI: [0.92; 1.48]).

Overall, no hint of a benefit or harm from CCTA vs. direct ICA was derived for the outcome of angina pectoris.

#### 4.2.4.8 Results on the outcome of health state (EQ-5D VAS)

**Comparison CCTA vs. FDTs**

For the outcome of health state, data for the comparison CCTA vs. FDTs were available from the studies CARE-CCTA and PROMISE with a moderate certainty of results. Results were available for the medium-term time of analysis (see Table 37 of the full report). The meta-analytic summary showed no statistically significant difference (mean difference [MD]: -0.70 [95% CI]: [-1.50; 0.10]; p = 0.086).

Overall, no hint of a benefit or harm from CCTA vs. FDTs was derived with regard to health state as measured by the EQ-5D VAS.

**Comparison CCTA vs. direct ICA**

For the comparison of CCTA vs. direct ICA, data from one study (DISCHARGE) with a moderate certainty of results were available for the outcome of health state for the medium-term and long-term times of analysis (see Table 37 of the full report).

For the medium-term analysis period, the results of the DISCHARGE study showed no statistically significant difference (OR: -0.20; 95% CI: [-1.25; 0.87]). The same applied to the long-term analysis period (OR: 0.31; 95% CI: [-0.76; 1.38]).

Overall, no hint of a benefit or harm from CCTA vs. direct ICA was derived with regard to the outcome of health state measured by the EQ-5D VAS.

#### 4.2.4.9 Results on the outcome of depressive symptoms (PHQ-9)

**Comparison CCTA vs. FDTs**

For the outcome of depressive symptoms, data for the comparison CCTA vs. FDTs were available from the PROMISE study with a moderate certainty of results. Results were available for the medium-term analysis period (see Table 39 of the full report).

The results of this study showed no statistically significant difference at 12 months (OR: 1.15; 95% CI: [0.97; 1.36]; p = 0.110).

Overall, no hint of a benefit or harm from CCTA vs. FDTs was derived with regard to the outcome of depressive symptoms.

**Comparison CCTA vs. direct ICA**

For the comparison CCTA vs. direct ICA, no data were available for the outcome of depressive symptoms.

#### 4.2.4.10 Results on the outcome of health-related work productivity (SPS)

**Comparison CCTA vs. FDTs**

For the outcome of health-related work productivity, measured by SPS, data for the comparison CCTA vs. FDTs were available from the PROMISE study with a moderate certainty of results. Data were available for the medium-term analysis period (see Table 41 of the full report). The results showed no statistically significant difference (MD: 0.10; 95% CI: [-0.24; 0.44]; p = 0.568).

Overall, no hint of a benefit or harm from CCTA vs. FDTs was derived with regard to health-related work productivity.

**Comparison CCTA vs. direct ICA**

For the comparison CCTA vs. direct ICA, no data were available for the outcome of health-related work productivity.

#### 4.2.4.11 Results on the outcome of unnecessary invasive diagnostic tests

The outcome of unnecessary invasive diagnostic tests in this report was the proportion of patients in whom no obstructive CHD was detected by ICA. If such an analysis was not available in the studies themselves, the proportion of ICAs performed and the number of patients without obstructive CHD were calculated. Since no time of analysis was reported for the majority of ICAs, this outcome was not assigned to an analysis period.

**Comparison CCTA vs. FDTs**

For the comparison CCTA vs. FDTs, data from 4 studies with a high and moderate certainty of results were available for the outcome of unnecessary invasive diagnostic tests (see Table 43 of the full report).

The meta-analytical summary of the data from the studies with a high certainty of results (CATCH and PROMISE) showed a statistically significant difference (OR: 0.77; 95% CI: [0.64; 0.94]; p = 0.011) in favour of CCTA. In the meta-analytic summary of the data from the studies with a high (CATCH and PROMISE) and moderate (CARE-CCTA and SCOT-HEART) certainty of results, no common effect was calculated due to relevant heterogeneity of the results. The two studies with a high certainty of results had already shown proof of an effect, so that overall proof of an effect was derived.

Overall, proof of less harm from CCTA vs. FDTs was derived with regard to the outcome of unnecessary invasive diagnostic tests.

**Comparison CCTA vs. direct ICA**

For the comparison of CCTA vs. direct ICA, data were available from 4 studies with a moderate (CONSERVE and Rice 2022) and a high (CAD-MAN and DISCHARGE) certainty of results for the outcome of unnecessary invasive diagnostic tests (see Table 43 of the full report). For the two studies with a high certainty of results (CAD-MAN and DISCHARGE), no pooled effect was calculated due to relevant heterogeneity of the results. Here, the qualitative summary of the results showed that the effects are clearly conclusive in favour of CCTA. A pooled analysis of all studies with a moderate and high certainty of results also showed relevant heterogeneity; the effects are conclusive. All 4 studies show strikingly large effects in favour of CCTA with OR effect estimates in the range of 0.01 to 0.03.

Overall, proof of less harm from CCTA vs. direct ICA was derived with regard to the outcome of unnecessary invasive diagnostic tests.

#### 4.2.4.12 Results on the outcome of health-related quality of life (SF-12 and SF-36)

**Comparison CCTA vs. FDTs**

For the comparison of CCTA vs. FDTs, data were available for the outcome of quality of life, measured by the SF-12 or SF-36 questionnaires on PCS and MCS. Results from the 2 studies CATCH (SF-36) and SCOT-HEART (SF-12) with a moderate certainty of results were available for the medium-term time of analysis (see Table 45 of the full report).

The data from the two studies CATCH and SCOT-HEART were combined meta-analytically. For the outcome of health-related quality of life, measured by the PCS of the SF-12 or SF-36, there was no statistically significant difference (Hedges' g: -0.07; 95% CI: [-0.13; 0.00]; p = 0.054). Likewise, there was no statistically significant difference for this outcome measured by the MCS of the SF-12 or SF-36 (Hedges' g: -0.05; 95% CI: [-0.12; 0.02]; p = 0.150).

Overall, no hint of a benefit or harm from CCTA vs. FDTs was derived with regard to the outcome of health-related quality of life, measured by PCS and MCS.

**Comparison CCTA vs. direct ICA**

For the comparison of CCTA vs. direct ICA, usable data from the DISCHARGE study with a moderate certainty of results were available for the medium- and long-term analysis periods (see Table 45 of the full report). The results did not show a statistically significant difference either for the medium-term (MD: 0.12; 95% CI: [-0.37; 0.61]) or long-term time of analysis (MD: 0.26; 95% CI: [-0.27; 0.78]). Since only the PCS and thus not the data on the entire SF-12 had been recorded in this study, the results were assigned to the domain of morbidity.

Overall, no hint of a benefit or harm from CCTA vs. direct ICA was derived with regard to the PCS recorded with the SF-12.

#### 4.2.4.13 Results on the outcome of disease-specific quality of life (SAQ)

**Comparison CCTA vs. FDTs**

For the outcome of disease-specific quality of life measured using the SAQ, data from the CAPP and PROMISE studies with a moderate certainty of results were usable for the comparison of CCTA vs. FDTs for the medium-term time of analysis. Furthermore, data from the Min 2012 study with a moderate certainty of results were available, but their time of analysis of 55 ± 34 days could not be assigned to any of the defined analysis periods (see Table 47 of the full report).

The results of the CAPP and PROMISE studies with a moderate certainty of results could be summarized meta-analytically for the medium-term analysis period. The meta-analytical summary of the data from both studies for the subscale “physical limitation” (OR: -0.77; 95% CI: [-1.56; 0.02]; p = 0.056) showed no statistically significant difference. For the subscale “angina stability”, the meta-analytical summary showed a statistically significant difference (OR: -0.80; 95% CI: [-1.60; -0.01]; p = 0.047) to the disadvantage of CCTA. In order to check the clinical relevance of the result, the standardized MD was calculated in the form of Hedges' g. The 95% CI is not completely above or below the irrelevance threshold of 0.2 and -0.2, respectively (Hedges' g: -0.05; 95% CI: [-0.11; -0.0003]) [75]. Thus, it cannot be deduced that this effect is relevant. For the subscale “angina frequency”, the meta-analytical summary of the data from both studies showed no statistically significant difference (OR: -0.14; 95% CI: [-0.73; 0.46]; p = 0.649). Likewise, no statistically significant difference was found for the subscales “treatment satisfaction” (OR: 0.81; 95% CI: [-0.25; 1.87]; p = 0.133) and “disease perception” (called quality of life in the publications) of the SAQ based on the meta-analytical summary of the results of both studies (OR: -0.71; 95% CI: [-1.73; 0.32]; p = 0.175).

The results of the Min 2012 study with a moderate certainty of results were reported using a model adjusted for clinical risk factors. There was no statistically significant difference for the subscale “physical limitation” (p = 0.58). There was also no statistically significant difference for the subscale “angina stability” (p = 0.11), as well as for the subscales “angina frequency” (p = 0.31), “treatment satisfaction” (p = 0.26) and “disease perception” (called quality of life in the publication) (p = 0.80).

In addition, a responder analysis of the SCOT-HEART study was available with usable data on the subscales “angina stability” and “disease perception” (called quality of life in the publication). Only for these 2 dimensions does the response threshold used correspond to at least 15% of the scale range. Since not all domains of the SAQ were usable in this study, the

results are assigned to the morbidity domain. Results were available for the medium-term analysis period.

The results of the SCOT-HEART study with a moderate certainty of results showed no statistically significant difference for the subscale “angina stability” for the medium-term analysis period (OR: 1.12; 95% CI: [0.98; 1.28]; p = 0.086). Likewise, for the subscale “disease perception”, the results of the SCOT-HEART study showed no statistically significant difference (OR: 0.95; 95% CI: [0.84; 1.08]; p = 0.431).

Overall, no hint of a benefit or harm was derived for CCTA vs. FDTs with regard to the outcome of health-related quality of life,

**Comparison CCTA vs. direct ICA**

No data were available for the outcome of health-related quality of life for the comparison CCTA vs. direct ICA.

#### 4.2.4.14 Results on the outcome of adverse events

AEs (often referred to as "complications" in the publications) that were recorded on the basis of a predefined catalogue bear the risk of selective data collection. Since it can be assumed that only such a selective choice of AEs was recorded in all included studies, these data were considered as supplementary information in this assessment and limited to serious and severe events. A quantitative analysis was not performed as only isolated events occurred. Periprocedural mortality and morbidity outcomes (all-cause mortality, myocardial infarction, stroke) are considered in the respective sections of this report.

**Comparison CCTA vs. FDTs**

For the comparison CCTA vs. FDTs, results from the Goldstein 2007 study with a moderate certainty of results and the PROMISE study with a high certainty of results were available for the periprocedural analysis period (see Table 50 of the full report). In the Goldstein 2007 study, AEs had not occurred in either treatment group after the intervention. In the PROMISE study, severe bleeding occurred in 3 patients in both treatment groups. In the control group, 9 additional serious AEs (SAEs) had occurred, including 5 ventricular tachycardias and 4 hospital admissions due to symptoms such as chest pain and nausea, for which it was not stated how many patients were affected.

Data on AEs were available from the CAPP and Goldstein 2007 studies with a moderate certainty of results and from the SCOT-HEART study with a high certainty of results for the medium-term analysis period. In each of the 3 studies, no SAEs occurred in either treatment group after the intervention.

Overall, the data on AEs provided no hint of a benefit or harm from CCTA vs. FDTs with regard to this outcome.

**Comparison CCTA vs. direct ICA**

For the comparison of CCTA vs. direct ICA, data were available from 3 studies with a high and moderate certainty of results. Results were available for the periprocedural and medium-term analysis period (see Table 50 of the full report).

For the periprocedural analysis period, data from the CAD-MAN and DISCHARGE studies with a high certainty of results were available. In the CAD-MAN study, no SAEs occurred in either treatment group. In the DISCHARGE study, SAEs occurred in 6 patients in the intervention group (4 patients with prolonged hospitalization and 2 patients with a dissection) and in 22 patients in the control group (6 patients with cardiac arrhythmia, 11 patients with prolonged hospitalization, 2 patients with a dissection, 2 patients with cardiac arrest, and 1 patient with a cardiac tamponade). Thus, there was a statistically significant difference in favour of CCTA for the outcome of AEs (OR: 0.26; 95% CI: [0.11; 0.64]; p = 0.002).

Data from the CONSERVE study with a moderate certainty of results were available for the medium-term analysis period. No SAEs had occurred in the intervention group and 2 patients in the control group had experienced serious bleeding, of which 1 patient required a transfusion.

Overall, the data on AEs provide an indication of less harm from CCTA vs. direct ICA.

## 4.3 Diagnostic strategies using CCTA with a functional evaluation (Question 2)

### 4.3.1 Characteristics of the studies included in the assessment

Of the 5 studies identified for Question 2, the CATCH-2 [61] and Yu 2020 [74] studies investigated functional evaluation using CTP and the FORECAST [63], PRECISE [76] and TARGET [71] studies investigated functional evaluation using CT-FFR. The PRECISE and TARGET studies did not sufficiently meet the inclusion criteria of this assessment and were therefore not included. However, they are presented below as supplementary information. The characteristics of the studies are described below (see Section A3.3.1.1 of the full report).

The CATCH-2 study [61] is a multicentre RCT from Denmark and was conducted between 2013 and 2017. It included 600 patients over 50 years of age with acute chest pain, but normal troponin values and a normal resting ECG. After randomization (1 : 1), CCTA with upstream calcium scoring was performed in the intervention arm and in the control arm. Initially, a diagnostic decision was made in all randomized patients without knowledge of the group allocation on the basis of CCTA alone. Only then did the treating physicians in the intervention group additionally receive the results of a static CTP. Further diagnostic tests in both arms in

case of positive results consisted of an ICA. The median follow-up period of the study was 18 months.

The FORECAST study [63] is a multicentre RCT from the UK and was conducted in several specialist chest pain clinics between 2017 and 2019. It included 1400 patients over 18 years of age with stable chest pain. Patients with an ACS were excluded. After randomization (1 : 1), only CCTA with upstream calcium scoring was performed in the intervention arm. Subsequently, if CCTA was positive, computerized analysis of CT images was performed to measure FFR. This affected 31% of the patients. For CT-FFR, a US CE-certified software was used, based on a "computational fluid dynamics" simulation, cloud-based, involving a mainframe computer (offsite) [77]. In the case of a positive CT-FFR finding, ICA was usually performed. In the control arm, the standard of care according to the NICE guideline [7] applied, consisting of CCTA with upstream calcium scoring (but without measurement of FFR), stress echocardiography, exercise ECG, SPECT, exercise MRI and direct ICA. Although this NICE guideline calls for CCTA as the primary diagnostic test, only a total of 63% of patients in the control group received CCTA as the first diagnostic test. According to the study authors, this was due to the still developing equipment and capacities of the participating study centres. The follow-up period of the study was 9 months.

The PRECISE study [66] is a multicentre RCT from North America and Europe conducted between 2018 and 2021. It included 2103 patients over 18 years of age with stable chest pain. Patients with an ACS and acute chest pain were excluded. After randomization (1:1), low-risk patients in the intervention arm were selected and deferred using the PROMISE Minimal Risk Tool [78]. Thus, no further tests were performed in 16% of the patients. With 79% of patients, the majority of all participants in the intervention arm underwent CCTA. If the result of the CCTA was positive, the CT images were then analysed by computer to measure the FFR. This affected 31% of the patients. The CT-FFR used the same US software as in the FORECAST study. In the control arm, a standard treatment consisting of stress echocardiography, exercise ECG, SPECT, PET, exercise MRI and direct ICA was used; 12% received a treatment not reimbursable by the SHI (stress MRI, PET). The median follow-up period of the study was 11.8 months. Since in the PRECISE study the CCTA was explicitly not allowed to be included in the diagnostic strategy of the control arm and the PROMISE Risk Tool was used exclusively in the intervention arm to select patients, no reliable conclusion on the benefit of CT-FFR is possible on the basis of the comparison of this study, since the study arms differ considerably in the diagnostic tests used in addition. Therefore, this study is only reported as supplementary information.

The TARGET study [71] is a multicentre RCT from China conducted between 2019 and 2022. It included 1216 patients without age restriction with stable chest pain and a stenosis in at least one main coronary artery (diameter > 2.5 mm) between 30% and 90%, based on upstream CCTA, and intermediate to high pre-test probability assessed by the CAD Consortium Score. Patients with ACS were explicitly excluded. After randomization (1 : 1), the FFR was

determined in the intervention arm based on the images of the CCTA by computer-controlled analysis with the CE-certified software DEEPVESSEL FFR. This is an on-site product from China based on a machine learning algorithm [77]. Patients in the control arm underwent an FDT (stress echocardiography, exercise ECG or SPECT). Further diagnostics in both arms in case of positive results consisted of ICA. The median follow-up period of the study was 12.2 months. Since 41% of the patients in the intervention arm and 37% in the control arm had a stenosis grade of 70% to 90%, combined with the high pre-test probability of the study population, which was on average 74.6% in the entire study population (see Table 54 of the full report), too large a proportion did not correspond to the population relevant for this report, i.e. a clinical indication for further non-invasive diagnostic testing. The fact that this part of the study population has no clinical indication for further non-invasive diagnostic tests is also shown by the fact that in this study, 69% of patients in the intervention arm and 79% in the control arm ultimately received invasive diagnostics. In contrast, this rate in the other studies was between 14% (CATCH 2) and 33% (Yu, 2020) in the intervention arm and between 25% (FORECAST) and 48% (Yu, 2020) in the control arm. While the CCTA was thus used in other studies to exclude a CHD diagnosis (rule-out) in a population with a low to intermediate pre-test probability, in the TARGET study the CCTA was used more for rule-in with a considerably higher pre-test probability, which in turn is shown by the high rate of invasive diagnostic tests. Thus, the diagnostic strategy of TARGET falls short of the use of CCTA as a rule-out diagnostic test recommended in the ESC and NVL guidelines. Thus, the results of the study, i.e. the investigation of an additional CT-FFR, which would have been dispensable here, cannot be transferred to the approach in Germany. An enquiry to authors for a subgroup analysis according to stenosis grade (see Table 13 of the full report) remained unanswered, which is why this study is only reported as supplementary information.

The Yu 2020 study [74] is a single-centre RCT from China conducted between 2016 and 2018. It included 250 patients with stable chest pain or angina-like symptoms with no stated age restriction. Patients with an ACS were explicitly excluded. After randomization (1 : 1), CCTA with upstream calcium scoring was performed in the intervention arm and the control arm. In contrast to the CATCH-2 study, in the Yu 2020 study a dynamic CTP was performed between calcium scoring and CCTA in all patients in the intervention arm. Further diagnostic tests in both arms in case of positive results consisted of ICA. The follow-up period of the study was 12 months.

### 4.3.2 Overview of patient-relevant outcomes

Data on patient-relevant outcomes could be extracted from all 5 identified studies. Table 3 shows the overview of the available data on patient-relevant outcomes.

Table 3: Matrix of patient-relevant outcomes (Question 2: CCTA with functional evaluation)

| Study | Outcomes | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mortality | | | Morbidity | | | | | | QoL | Adverse effects |
| | All-cause mortality | Cardiovascular mortality | MACE | Myocardial infarction | Stroke | Unstable angina pectoris | Angina pectoris | Health state (EQ-5D VAS) | Unnecessary invasive diagnostic tests | Disease-specific quality of life (SAQ) | Adverse events |
| CATCH-2 | ● | ● | ○[a] | ● | – | ● | ●[b] | – | ● | – | – |
| FORECAST | ● | – | ○[a] | ● | ● | – | – | ○[c] | ● | ●[d,e] | × |
| PRECISE | ●[f] | ●[f] | ●[f] | ●[f] | – | ●[f] | – | × | ●[f] | ○[g] | – |
| TARGET | – | ●[f, h] | ○[a] | ●[f] | – | ●[f] | – | – | ●[f] | ●[d,f] | × |
| Yu 2020 | ● | ● | ○[a] | ● | – | – | – | – | – | – | – |

●: Data were reported and were usable.

○: Data were reported but were not usable for the benefit assessment.

x: Data were not reported despite planned collection.

-: No data were reported (no further information) / the outcome was not recorded.

a. Outcome not usable because individual components are not of comparable clinical severity.
b. Only hospitalized cases, i.e. primarily serious events, were recorded.
c. The present analysis of the utility values is assessed as not relevant to patients, as the underlying tariff was not generated on the basis of a patient population suitable for the question.
d. It is a short version of the SAQ, the SAQ-7, which contains 7 items instead of 19.
e. Only the total score was reported in the publication.
f. The results of this study are reported only as supplementary information.
g. Outcome not usable as not all domains of the SAQ were presented separately.
h. In the study, deaths due to unknown causes and unobserved deaths were counted towards the outcome of cardiovascular mortality.

EQ-5D: European Quality of Life – 5 Dimensions, 3 Level Version; QoL: quality of life: MACE: major adverse cardiovascular events; SAQ: Seattle Angina Questionnaire; VAS: Visual Analogue Scale

As the PRECISE and TARGET studies did not sufficiently meet the inclusion criteria of this assessment (see Section 4.3.1), these two studies are only reported as supplementary information in this report. Therefore, the presentation of the assessment of the risk of bias and of the results on outcomes of these studies was omitted in the following Sections 4.3.3 and 4.3.4. The corresponding data can be found in Sections A3.3.1.2 and A3.3.2 of the full report.

For the comparison of CCTA with functional evaluation vs. CCTA without functional evaluation, usable results were available for the outcome of all-cause mortality from all included studies.

Usable data for the outcome of cardiovascular mortality were available from the CATCH-2 study and could be calculated for the Yu 2020 study based on the results for all-cause mortality, in which no events had occurred. The data for the outcome MACE from the studies for Question 2 could not be used, as the individual components differed considerably in their severity and in their relevance for the patients.

For the outcome of myocardial infarction, usable results were available from all included studies. For the outcome of stroke, data were only available from the FORECAST study. Results for the outcome of unstable angina pectoris were available from the CATCH-2 study and could be used. Usable results for the outcome of angina pectoris were also available from the CATCH-2 study. In this study, only hospitalized cases of angina pectoris were recorded, i.e. mainly serious events. Results on health state, measured by the EQ-5D VAS, were only available from the FORECAST study, but were not usable because the results on the VAS had not been reported. Usable data on the outcome of unnecessary invasive diagnostic tests could be calculated from the number of patients diagnosed with obstructive CHD by ICA for the CATCH-2 and FORECAST studies. Data on disease-specific quality of life were available from the FORECAST study. No data on AEs were available in any of the 3 studies relevant to answering Question 2.

### 4.3.3 Assessment of the risk of bias

The risk of bias (see Section A3.3.1.2 of the full report) for Question 2 on CCTA with the option of functional evaluation was rated as low across outcomes for the CATCH-2 and FORECAST studies and high for the Yu 2020 study. In the Yu 2020 study, both the adequate generation of the randomization sequence and the concealment of group allocation were partly unclear.

For the Yu 2020 study, in which the risk of bias across outcomes had already been rated as high, there was consequently a high outcome-specific risk of bias for all assessed outcomes, so that no further outcome-specific assessment was carried out for this study. For the CATCH-2 and FORECAST studies, all assessed outcomes were rated as having a low outcome-specific risk of bias. Only the outcome of disease-specific quality of life (SAQ-7) of the FORECAST study was rated as having a high risk of bias due to the lack of blinding in the recording of subjective outcomes.

### 4.3.4 Results on patient-relevant outcomes

As for Question 1, usable data were classified according to their time of analysis as periprocedural, medium-term or long-term. Thus, the results of the studies for Question 2 were also assigned to the periprocedural (up to 30 days after the procedure), medium-term (6 to 24 months), and long-term (2 to 5 years) analysis period. For Question 2, only data on the medium-term period were available. The two functional evaluation methods investigated in the studies, CT-FFR and CTP, are not technically comparable. Therefore, a meta-analytical

summary across all outcomes of the FORECAST study on CT-FFR and the CATCH-2 and Yu 2020 studies on CTP was not meaningful.

#### 4.3.4.1 Results on the outcome of all-cause mortality

For the comparison of CCTA without functional evaluation vs. CCTA with functional evaluation, data were available from 3 included studies with a high (CATCH-2 and FORECAST) and moderate (Yu 2020) certainty of results. Only results for the medium-term analysis time of analysis were available (see Table 57 of the full report).

For the CATCH-2 (Peto OR: 1.00; 95% CI: [0.20; 4.99]; p > 0.999) and FORECAST (OR: 5.02; 95% CI: [0.24; 104.78]; p = 0.171) studies with a high certainty of results, there was no statistically significant difference between the treatment groups. In the Yu 2020 study with a moderate certainty of results, no deaths had occurred in either treatment group. A meta-analytical summary of the results of the CATCH-2 and Yu 2020 studies was therefore not performed.

Overall, no hint of a benefit or harm from CCTA with functional evaluation vs. CCTA without functional evaluation was derived with regard to the outcome of all-cause mortality.

#### 4.3.4.2 Results on the outcome of cardiovascular mortality

For the outcome of cardiovascular mortality, data from 2 studies with a high (CATCH-2) and moderate certainty of results (Yu 2020) were available for the medium-term time of analysis (see Table 58 of the full report).

No cardiovascular deaths had occurred in either study. A meta-analytical summary of the results of the CATCH-2 and Yu 2020 studies was therefore not performed.

Overall, no hint of a benefit or harm from CCTA with functional evaluation vs. CCTA without functional evaluation was derived with regard to the outcome of cardiovascular mortality.

#### 4.3.4.3 Results on the outcome of major adverse cardiovascular events

The results for the outcome MACE were only considered if it consisted of 2 or more of the following individual components: death (all-cause or cardiovascular), myocardial infarction, stroke, unstable angina pectoris. The latter 3 outcomes did not differ considerably in their severity and in their relevance for the patients. For the outcome MACE, no usable data were available from any of the included studies.

#### 4.3.4.4 Results on the outcome of myocardial infarction

For the outcome of myocardial infarction, results from all 3 included studies with a high (CATCH-2 and FORECAST) and moderate (Yu 2020) certainty of results were available. Only results for the medium-term time of analysis were available (see Table 60 of the full report).

In the CATCH-2 (Peto OR: 0.51; 95% CI: [0.05; 4.94]; p = 0.683) and FORECAST (OR: 3.03; 95% CI: [0.82; 11.24]; p = 0.084) studies with a high certainty of results, there was no statistically significant difference. However, the FORECAST study showed a numerically striking difference to the disadvantage of CCTA with functional evaluation. In the Yu 2020 study with a moderate certainty of results, no myocardial infarctions had occurred. Therefore, a meta-analytical summary of the results of the CATCH-2 and Yu 2020 studies was not performed.

Overall, no hint of a benefit or harm from CCTA with functional evaluation vs. CCTA without functional evaluation was derived with regard to the outcome of myocardial infarction.

#### 4.3.4.5 Results on the outcome of stroke

For the outcome of stroke, data from the FORECAST study with a high certainty of results were available for the medium-term time of analysis (see Table 61 of the full report). There was no statistically significant difference in the results (OR: 0.33; 95% CI: [0.01; 8.20]; p = 0.530).

Overall, no hint of a benefit or harm from CCTA with functional evaluation vs. CCTA without functional evaluation was derived with regard to the outcome of stroke.

#### 4.3.4.6 Results on the outcome of unstable angina pectoris

For the outcome of unstable angina pectoris, data from the CATCH-2 study with a high certainty of results were available for the medium-term time of analysis (see Table 62 of the full report). The results showed no statistically significant difference (Peto OR: 1.00; 95% CI: [0.06; 16.02]; p > 0.999).

Overall, no hint of a benefit or harm from CCTA with functional evaluation vs. CCTA without functional evaluation was derived with regard to the outcome of unstable angina.

#### 4.3.4.7 Results on the outcome of angina pectoris

For the outcome of angina pectoris, data from the CATCH-2 study with a high certainty of results were available. Data were available for the medium-term time of analysis (see Table 63 of the full report). The results showed no statistically significant difference (OR: 0.73; 95% CI: [0.39; 1.38]; p = 0.530).

Overall, no hint of a benefit or harm from CCTA with functional evaluation vs. CCTA without functional evaluation was derived with regard to the outcome of angina pectoris.

#### 4.3.4.8 Results on the outcome of unnecessary invasive diagnostic tests

The outcome of unnecessary invasive diagnostic tests in this report was the proportion of patients who were not diagnosed with obstructive CHD using ICA. Since no time of analysis was reported for the majority of ICAs, this outcome was not assigned to an analysis period.

For the outcome of unnecessary invasive diagnostic tests (proportion of patients without obstructive CHD, diagnosed by ICA), results from the CATCH-2 and FORECAST studies with a high certainty of results were available (see Table 64 of the full report).

For the outcome of unnecessary invasive diagnostic tests, the CATCH-2 study showed a statistically significant difference in favour of CCTA with functional evaluation using CTP (OR: 0.34; 95% CI: [0.18; 0.66]; $p < 0.001$).

In the FORECAST study, for the comparison of CCTA with the option of functional evaluation using CT-FFR vs. standard treatment, there was a statistically significant difference (OR: 0.46; 95% CI: [0.29; 0.72]; $p < 0.001$) in favour of CCTA with the option of CT-FFR. However, in the control group (standard treatment), 27% of patients did not undergo a CCTA, but an FDT. For Question 1, there was a statistically significant result in favour of CCTA vs. FDTs for the outcome of unnecessary invasive diagnostic tests. Therefore, a sensitivity analysis was performed with the aim of excluding the possibility that the difference determined between the treatment groups of the FORECAST study was exclusively due to the patients who had been diagnosed in the control group by means of an FDT. The effects on the outcome of unnecessary invasive diagnostic tests in Question 1 (CCTA vs. FDTs) of the CATCH and PROMISE studies were taken into account - 2 RCTs with a high certainty of results that can be most easily transferred to the German health care context. The sensitivity analysis showed that the effect measured in the FORECAST study was not solely attributable to the proportion of patients in the control arm who had undergone FDTs.

Overall, for the outcome of unnecessary invasive diagnostic tests, an indication was derived of less harm from CCTA with functional evaluation vs. CCTA without functional evaluation.

#### 4.3.4.9 Results on the outcome of disease-specific quality of life (SAQ-7)

For the outcome of disease-specific quality of life, measured by the short version of the SAQ (SAQ-7), data from the FORECAST study with a moderate certainty of results were usable for the medium-term time of analysis (see Table 65 of the full report). Usable data were available for the total score of the SAQ-7.

There was no statistically significant difference for the total score (MD: -1.9; 95% CI: [-4.93; 1.13]; $p = 0.22$).

Overall, no hint of a benefit or harm from CCTA with functional evaluation vs. CCTA without functional evaluation was derived with regard to the outcome of disease-specific quality of life.

#### 4.3.4.10 Results on the outcome of adverse events

Data on AEs were not available from any of the included studies.

## 4.4 Summarized assessment of results

### Evidence map

The following Table 4 shows the evidence map for patient-relevant outcomes.

Table 4: Evidence map for patient-relevant outcomes (multi-page table)

| Comparison<br>Time of analysis | Mortality | | | Morbidity | | | | | | | | QoL | | Adverse effects |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | All-cause mortality | Cardiovascular mortality | MACE[a] | Myocardial infarction | Stroke | Unstable angina pectoris | Angina Pectoris | Health state (EQ-5D VAS) | Depressive symptoms (PHQ-9) | Health-related work productivity (SPS) | Unnecessary invasive diagnostic tests | Health-related quality of life | Disease-specific quality of life (SAQ) | Adverse events |
| **Question 1: CCTA vs. FDTs** | | | | | | | | | | | | | | |
| Periprocedural | ↔ | ↔ | – | ↔ | ↔ | ↔ | – | – | – | – | | – | – | ↔ |
| Medium term | ↔ | ↔ | – | ↗ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↑↑[b] | ↔ | ↔ | ↔ |
| Long term | ↔ | ↔ | – | ↑↑ | ↔ | ↓ | – | – | – | – | | – | – | – |
| Total periods | ⇔ | ⇔ | – | ⇑⇑ | ⇔ | ⇓ | ⇑⇓ | ⇔ | ⇔ | ⇔ | ⇑⇑ | ⇔ | ⇔ | (⇔) |
| **Question 1: CCTA vs. direct ICA** | | | | | | | | | | | | | | |
| Periprocedural | ↔ | ↔ | – | ↔ | ↔ | – | – | – | – | – | | – | – | ↑ |
| Medium term | ↔ | ↔ | – | ↔ | ↔ | ↔ | ↔ | ↔ | – | – | ↑↑[b] | ↔[c] | – | ↔ |
| Long term | – | ↔ | – | ↔ | ↑ | ↔ | ↔ | ↔ | – | – | | ↔[c] | – | – |
| Total periods | ⇔ | ⇔ | – | ⇔ | ⇑ | ⇔ | ⇔ | ⇔ | – | – | ⇑⇑ | ⇔ | – | ⇑ |
| **Question 2: CCTA with option of CT-based functional evaluation** | | | | | | | | | | | | | | |
| Periprocedural | – | – | – | – | – | – | – | – | – | – | | – | – | – |
| Medium term | ↔ | ↔ | ↔ | ↔[d] | ↔ | ↔ | ↔ | – | – | – | ↑[b] | – | ↔ | – |
| Long term | – | – | – | – | – | – | – | – | – | – | | – | – | – |
| Total periods | ⇔ | ⇔ | ⇔ | ⇔[d] | ⇔ | ⇔ | ⇔ | – | – | – | ⇑ | – | ⇔ | – |

Table 4: Evidence map for patient-relevant outcomes (multi-page table)

| Comparison<br>Time of analysis | Mortality | | | Morbidity | | | | | | | | QoL | | Adverse effects |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | All-cause mortality | Cardiovascular mortality | MACE[a] | Myocardial infarction | Stroke | Unstable angina pectoris | Angina Pectoris | Health state (EQ-5D VAS) | Depressive symptoms (PHQ-9) | Health-related work productivity (SPS) | Unnecessary invasive diagnostic tests | Health-related quality of life | Disease-specific quality of life (SAQ) | Adverse events |

↑↑: proof of an effect in favour of intervention

↑: indication of an effect in favour of intervention

↗: hint of an effect in favour of intervention

↓: indication of an effect to the disadvantage of the intervention

↔: no statistically significant difference

⇑⇑: proof of greater benefit or less harm

⇑: indication of greater benefit or less harm

⇓: indication of less benefit or greater harm

⇔: no hint, indication or proof, homogeneous result.

(⇔): no hint, indication or proof, homogeneous result; outcome based on few data, which were not collected systematically

⇑⇓: no hint, indication or proof, heterogeneous result.

-: no (usable) data reported or used.

a. The composite outcome MACE was not evaluated for Question 1 in order to avoid a multiple analysis of the same data. Statistically significant effects were already shown in this analysis at the level of the corresponding individual outcomes.
b. As no time of analysis is reported for the majority of ICAs, this outcome was not assigned to an analysis period.
c. Only the physical component of the SF-12 is presented. Since only part of the results of the SF-12 are presented, the results are assigned to the outcome category of morbidity in terms of content.
d. Striking numerical group difference to the disadvantage of the CT-FFR intervention.

Table 4: Evidence map for patient-relevant outcomes (multi-page table)

| Comparison<br>Time of analysis | Mortality | | | Morbidity | | | | | | | | QoL | | Adverse effects |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | All-cause mortality | Cardiovascular mortality | MACE[a] | Myocardial infarction | Stroke | Unstable angina pectoris | Angina Pectoris | Health state (EQ-5D VAS) | Depressive symptoms (PHQ-9) | Health-related work productivity (SPS) | Unnecessary invasive diagnostic tests | Health-related quality of life | Disease-specific quality of life (SAQ) | Adverse events |
| CCTA: coronary computed tomography angiography; CT: computed tomography; CT-FFR: computed tomography-based measurement of fractional flow reserve; EQ-5D: European Quality of Life – 5 Dimensions, 3 Level Version; QoL: quality of life; ICA: invasive coronary angiography; MACE: major adverse cardiovascular event; PHQ-9: Patient Health Questionnaire; SAQ: Seattle Angina Questionnaire; SF-12: Health Survey Short Form 12; SPS: Stanford Presenteeism Scale; VAS: Visual Analogue Scale | | | | | | | | | | | | | | |

**Assessment of the extent of unpublished data**

For Question 1, 3 studies [79-81] were identified via study registries; their status is unclear. The planned sample sizes of these 3 studies make up less than 5% of the total number of patients included in the present benefit assessment, so that biased results due to publication bias is unlikely. They therefore do not represent a limitation of the conclusion regarding Question 1.

Regarding Question 2, 1 study for which no results are available was identified via study registries and other search steps. The study with unclear status is the CTP-PRO study [82,83], in which CTP was used for functional evaluation, the estimated end of the study is reported as 1 October 2022, and 2000 patients were to be randomized as planned. The inclusion criterion is that patients must have known or suspected CHD. Since only patients with suspected CHD meet the inclusion criteria of the present report, it is unclear at this point in time whether the study would be relevant for the benefit assessment if results were available. In view of this limitation, the probability that the results of this study could have a relevant influence on the conclusion of this assessment is rated as low.

**Weighing of benefits and harms**

**Question 1: CCTA versus FDTs**

For the comparison of CCTA with the FDTs of Question 1, CCTA was shown to be superior to the FDTs with respect to the morbidity outcomes of myocardial infarction and unnecessary invasive diagnostic tests. For myocardial infarction, the proof of benefit is based on a hint of an effect for the medium-term time of analysis and proof of an effect for the long-term time of analysis in favour of CCTA. In contrast, the results for the morbidity outcome of unstable angina pectoris show an indication of an effect in the long term to the disadvantage of CCTA. Myocardial infarction is generally a life-threatening and clearly defined event, whereas unstable angina pectoris is more vaguely defined and not necessarily life-threatening. For the other usable morbidity outcomes, there was no statistically significant difference between CCTA and the FDTs. Since invasive diagnostic tests are associated with direct risks (see Section A4.3 of the full report), the proof of a reduction in unnecessary invasive diagnostic tests in favour of CCTA suggests an advantage of CCTA in comparison to FDTs. The results of the other outcomes - apart from the outcome of unstable angina pectoris - do not suggest that this reduction in diagnostic tests by means of ICA is accompanied by a deterioration elsewhere. For instance, with regard to all-cause mortality in the medium term and the outcomes of cardiovascular mortality and stroke in the medium and long term, the results show numerical trends without statistical significance in favour of CCTA. With regard to direct adverse effects in the form of AEs, there was no hint of a benefit or harm from CCTA, but only few usable data were available. CCTA is a non-invasive procedure whose direct risks can be considered as acceptable on the basis of experience with other CT-based procedures (with regard to contrast agent application and radiation exposure). Therefore, the missing or unsystematic recording

of AEs, which is to be criticized in all studies, was classified in such a way that this does not call into question the positive effects shown.

In summary, the observed benefits outweigh the potential harms of CCTA. Therefore, across all outcomes proof of a benefit in favour of CCTA was derived for Question 1 (CCTA versus FDTs).

**Question 1: CCTA versus direct ICA**

For the comparison CCTA vs. direct ICA of Question 1, CCTA was shown to be superior to direct ICA for the morbidity outcomes of stroke and unnecessary invasive diagnostic tests. For the outcome of stroke, the benefit results from an indication of an effect for the long-term time of analysis in favour of CCTA. For the other usable morbidity outcomes, there was no statistically significant difference between CCTA and FDTs. As invasive diagnostic tests are associated with direct risks (see Section A4.3 of the full report), the proof of a reduction in unnecessary invasive diagnostic tests in favour of CCTA suggests an advantage of CCTA. The results of the other outcomes do not suggest that this reduction in diagnostic tests by means of ICA is accompanied by a deterioration elsewhere. For instance, although the results on myocardial infarctions for the long-term analysis period show numerical tendencies to the disadvantage of CCTA, the results on cardiovascular mortality point numerically in the opposite direction. With regard to AEs, there was an indication of less harm from CCTA. As this result is mainly based on periprocedural events, the reduction in these AEs is probably also due to the proven reduction in unnecessary invasive diagnostic tests by CCTA.

In summary, across all outcomes proof of a benefit in favour of CCTA was derived for this question (CCTA versus direct ICA).

**Question 2**

For Question 2, CCTA with the option of CT-based functional evaluation was shown to be superior to CCTA without functional evaluation for the outcome of unnecessary invasive diagnostic tests. This advantage is based on an indication of an effect in favour of CCTA with functional evaluation using CT-FFR and CTP for the outcome of unnecessary invasive diagnostic tests. As invasive diagnostic tests are associated with direct risks (see Section A4.3 of the full report), the indication of a reduction in unnecessary invasive diagnostic tests suggests an advantage in favour of CCTA with functional evaluation.

With regard to the studies on CT-FFR, no differences can be identified for almost all outcomes that would suggest that this reduction in invasive diagnostic tests could be accompanied by a deterioration elsewhere. However, this does not apply to the outcome of myocardial infarction. For example, the FORECAST study shows a numerical trend to the disadvantage of CCTA with the option of functional evaluation through CT-FFR for the outcome of myocardial infarction at the medium-term time of analysis. Using the estimates for the proportion of

avoided unnecessary invasive diagnostic tests from the FORECAST study and for the proportion of persons with SAEs in connection with invasive diagnostic tests from the comparison of CCTA with direct ICA of the DISCHARGE study, it is possible to roughly estimate the reduction in the absolute risk of an SAE through the additional use of CT-FFR. Using the numerical group difference of the FORECAST study for the proportion of persons with myocardial infarction, the corresponding absolute risk increase for the occurrence of a myocardial infarction can be determined. Comparing the resulting values, the following picture emerges: Using CCTA with the option of functional evaluation through CT-FFR compared to CCTA without this option is estimated to save less than 1 person in 1000 from an SAE associated with invasive diagnostic tests, whereas an additional 9 people in 1000 are estimated to suffer a myocardial infarction. This comparison highlights that a strategy including CT-FFR does not sufficiently reduce the procedural risks of the overall diagnostic procedure to address the concerns raised by the non-statistically significant, but relatively large, between-group difference in myocardial infarction in the FORECAST study.

In line with the results of the FORECAST study, the PRECISE study, which was reported as supplementary information for Question 2 and investigated CCTA with the option of CT-FFR vs. FDTs, also showed a numerical tendency to the disadvantage of CCTA with the option of CT-FFR for the outcome of myocardial infarction. That this finding could be due to the addition of CT-based functional evaluation through CT-FFR in the intervention arm can be deduced on the basis of the results from Question 1. Here, a statistically significant effect in favour of CCTA alone (without the option of CT-FFR) compared to FDTs, i.e. a numerical reversal of the direction of the effect, was shown for the outcome of myocardial infarction at the mid- and long-term times of analysis. In the TARGET study, which was reported as a supplement to Question 2 and also investigated CT-FFR, no corresponding group differences occurred. However, due to the population not meeting the inclusion criteria (see Section 4.3.1), the study is unsuitable to address the concerns formulated above.

In the two studies on CT-based functional evaluation using CTP, no differences can be identified that suggest that the reduction in invasive diagnostic tests could be associated with a deterioration elsewhere. However, additional procedure-related, i.e. direct, risks are associated with diagnostic tests using CTP. For example, the administration of vasodilator medication such as adenosine for pharmacological stress simulation leads to the possibility of adverse effects. This outcome was not reported in the two included studies on CTP. Furthermore, dynamic CTP in particular is associated with an additional application of contrast agent as well as with additional radiation exposure, which, with 10-12 mSv, is markedly increased compared to CCTA with 2-4 mSv. Although static CTP can be calculated on the basis of CCTA data sets, it requires a higher radiation intensity and thus, with 5-7 mSv, also increases radiation exposure [84].

In the studies, apart from the reduction in unnecessary invasive diagnostic tests, there is no advantage of the additional application of the intervention for any other outcome. No data on adverse effects were reported in either of the two studies. Considering the absolute risks derived by means of the studies, the following picture emerges: In order to spare about 1 person in 1000 persons an intervention-related SAE (calculated from the estimate for the proportion of unnecessary invasive diagnostic tests from the CATCH-2 study and from the estimate for the proportion of persons with SAEs in connection with invasive diagnostic tests from the DISCHARGE study), all 1000 persons are exposed to the risks outlined above through injection of drugs and contrast agents. Thus, the diagnostic test to be examined (CTP) replaces the more invasive diagnostic test (replacement) for only a smaller proportion of patients, while for the majority it represents an additional diagnostic test ("add-on") associated with radiation exposure and potential drug adverse effects.

In summary, for CCTA with CT-based functional evaluation using the currently available techniques, there is no benefit and no potential in comparison to CCTA without functional evaluation.

# 5 Classification of the assessment result

## Embedding the interventions within the diagnostic strategy

As a diagnostic test for establishing the diagnosis “chronic CHD”, the test interventions CCTA and CCTA with the option of a CT-based functional evaluation have a different role within the diagnostic strategy, depending on the time of use. In the following text, the role of the test interventions within the included studies is explained in more detail, depending on the (sub-) question.

### *Question 1: CCTA versus FDTs*

In the studies identified and included for Question 1 comparing CCTA and non-invasive FDTs, the intention was usually that either CCTA or (in the control arm) non-invasive FDTs should be used as diagnostic tests.

In all studies, despite this intention, additional FDTs were used in some of the patients in the CCTA study arm. In 2 studies, this was planned a priori for unclear CCTA findings or patients with intermediate lesions in the CCTA and affected 14% (CT-STAT) and 24% (Goldstein 2007) of the included patients. In the IAEA-SPECT/CTA study, it was explicitly discouraged to perform additional tests. Only in special cases was this to be done, which ultimately applied to 16% of the patients. In the PERFECT study, 14% of patients in the CCTA study arm received additional FDTs without this being prespecified. In all other studies on the question of CCTA versus FDTs, the proportion of additional FDTs in the CCTA study arm was between 1% and 10%. Although additional FDTs were not explicitly planned in all studies, it can be noted that the FDTs were consistently used in such a way that they were applied as an additional test in the case of unclear CCTA findings. This approach of using several non-invasive procedures in sequence corresponds to the recommendations of the current ESC guideline [3]. The proportion of patients in all studies in whom supplementary FDTs were performed in addition to CCTA in the intervention arm was less than 20% (with the exception of the small Goldstein 2007 study). This means that in each of the studies, CCTA completely replaced the alternative non-invasive FDTs ("replacement") in at least 80% of the patients. In two studies, however, it is doubtful whether this is a pure replacement approach due to insufficient description. In the SCOT-HEART study, it is unclear to what extent the data on the ASSIGN score were also taken into account in the intervention arm. In the CATCH study, it cannot be assessed whether the exercise ECG data were also taken into account in the intervention arm for further clinical decision-making. In both cases, it therefore cannot be excluded that CCTA was at least partially used as an additional subsequent diagnostic option ("add-on").

The subsequent use of ICA – planned and reported in all studies – was performed in case of unclear and positive results from non-invasive diagnostic tests. Therefore, CCTA or pure FDTs in the control arm had the function of supporting the decision to use invasive diagnostic tests.

In summary, the studies investigated the question of how well CCTA can largely replace other non-invasive FDTs as an alternative diagnostic test ("replacement") and for deciding whether to use invasive diagnostic tests ("triage").

***Question 1: CCTA versus direct ICA***

In the 4 studies included for the comparison of CCTA and ICA, a CCTA in the intervention arm was preceded by an ICA in order to decide on the use of this invasive procedure in the intervention arm, while ICA was always used in the control arm. The studies in this sub-question thus examine the question of how well the use of a CCTA in the sense of a "triage" is suitable for reducing the use of ICA.

***Question 2: CCTA with functional evaluation***

In the studies identified for Question 2, CCTA with functional evaluation was used in different roles within the diagnostic strategy.

In 2 of the studies, CT-based functional evaluation was performed in addition to CCTA in all patients in the intervention arm, while in the control arm only CCTA was used. In the CATCH-2 study, the functional evaluation (static CTP) was used after the CCTA, while in the Yu 2020 study it was used before the CCTA (dynamic CTP). Thus, in both studies, it is an "add-on" use of CTP in a study population fully examined with CCTA compared to CCTA alone.

In the FORECAST study included for Question 2, CCTA was performed almost universally in the intervention group (96%), followed by optional FDT (CT-FFR). The latter was performed in 31% of the patients. In the control arm, on the other hand, the standard treatment was according to the NICE guideline [7]. This standard treatment could include CCTA, which 63% of patients received. This study thus investigated the effect of a CT-based functional evaluation as an as-needed "add-on" to CCTA as a standard compared to a diagnostic strategy with a high proportion of CCTA. With the help of a sensitivity analysis, it could be shown in this analysis that the existing effect (reduction in unnecessary invasive diagnostic tests) would also have been shown under certain assumptions if CCTA had been used primarily (rather than only in 63% of cases) in the control arm (see Section 4.3.4.8).

In the PRECISE study, the PROMISE Minimal Risk Tool was initially used in the intervention group to defer further diagnostic tests in patients with low risk. In 16%, no test was subsequently performed. In the control arm, only 7% did not undergo further diagnostic tests. Thus, the PRECISE study is not only testing CCTA, but also the use of an improved risk score. The majority received CCTA (79%) followed by optional FDT (CT-FFR; 31%). The control arm used a standard treatment that included non-invasive tests such as exercise ECG, stress echocardiography, SPECT, PET and stress MRI, as well as ICA, but was not allowed to include CCTA. Thus, in this study, the use of CCTA followed by optional CT-FFR was a "replacement" strategy compared to a diagnostic strategy without CCTA. As no reliable conclusion on the

benefit of CT-FFR compared to a strategy without this option is possible on the basis of the comparison of the study (see Section 4.3.1), this study is only reported as supplementary information in this report.

In the TARGET study, CCTA was performed before randomization and CT-FFR was used in 100% of patients in the intervention arm. In the control arm of the TARGET study, 94% of patients underwent a non-invasive FDT (exercise ECG, stress echo or SPECT). This is therefore a "replacement" strategy of confirming results of CCTA using CT-FFR versus confirming results of CCTA using other FDTs that are not CT-based. As the study does not sufficiently meet the inclusion criteria of this assessment (see Section 4.3.1), this study is only reported as supplementary information.

**Value of a diagnosis of non-obstructive CHD**

The outcome of unnecessary invasive diagnostic tests, i.e. the proportion of ICAs with the result that no obstructive CHD is present, was assessed as patient-relevant in this benefit assessment. The proportion of patients who underwent an unnecessary ICA consists of patients who do not have CHD and those who have non-obstructive CHD (< 50% stenosis). The diagnosis of non-obstructive CHD could provide prognostic information and thus prompt further drug therapy to slow down progression. The DISCHARGE and Rice 2022 studies showed that a greater proportion of non-obstructive CHD was diagnosed by CCTA compared with direct ICA (36% vs. 22% DISCHARGE; 35% vs. 13% Rice 2022). CCTA, in contrast to direct ICA, thus allows a better differentiation between cases in which obstructive CHD is present and those in which CHD can be excluded. The thesis put forward in the commenting procedure on the preliminary report that the diagnosis of non-obstructive CHD by means of CCTA could be advantageous was discussed in the oral debate on the preliminary report. There is a higher risk of complications for patients with chest pain and non-obstructive CHD compared to the general population [3]. However, no RCTs are available that examine the impact of the diagnosis of non-obstructive CHD by CCTA (and subsequent adjustment or initiation of treatment) on patient-relevant outcomes. In the debate, it also remained unclear whether this thesis potentially only applies to people with a certain degree of hypercholesterolaemia. In the DISCHARGE study, the reason for the reduction in strokes and AEs in the CCTA arm compared to the control arm (direct ICA) could be an improved diagnosis of non-obstructive CHD, but this connection remains speculative without corresponding studies.

**Calcium scoring**

In the majority of the included studies, CCTA was preceded by calcium scoring, which is currently not part of the scope of services provided by SHI. Calcium scoring was primarily used to calculate the required radiation dose or (in the case of a CHD diagnosis) to estimate the prognosis. This was not considered a reason for exclusion in the present benefit assessment as long as CCTA (or its combination with subsequent CT-based functional evaluation)

represented the central intervention in the corresponding study arm. If, on the other hand, calcium scoring was used as a triage test upstream in studies and CCTA (or its combination with subsequent CT-based functional evaluation) was only used selectively, this did not cover the inclusion criteria of the question in the present report. In the CRESCENT study [85], for example, only just under half of the patients in the corresponding study arm received CCTA after calcium scoring, so that this comparison cannot contribute to answering the questions of the present report. Likewise, studies in which calcium scoring was used in other areas of application, such as prognosis and patient adherence, were irrelevant for this assessment.

# 6 Conclusion

## Question 1

Depending on the control intervention, the conclusion for Question 1 is divided into:

### CCTA versus FDTs

To answer the question about the comparison of CCTA vs. FDTs, a total of 11 studies were analysed.

For the outcome of myocardial infarction, a diagnostic strategy using CCTA was shown to be superior to a diagnostic strategy using FDTs in the medium and long term (proof of benefit). For the outcome of unnecessary invasive diagnostic tests, it was shown that after CCTA, patients in the intervention group were less likely to have undergone invasive diagnostic tests with the result "no obstructive CHD" than patients who had undergone FDTs (proof of less harm).

In contrast, the analysis for the outcome of unstable angina pectoris provided an indication of less benefit of CCTA compared to FDTs in the long term.

For all other outcomes, there were no relevant differences between the diagnostic tests or no usable data were available. There were hardly any usable data on AEs.

Since the role of unstable angina pectoris and potential adverse effects in the form of AEs is considered to be less important than that of myocardial infarctions and unnecessary invasive diagnostic tests, across all outcomes there is proof of a greater benefit of a diagnostic strategy using CCTA vs. a diagnostic strategy using FDTs in patients who are suspected of having chronic CHD after basic diagnostic tests.

### CCTA versus direct ICA

To answer Question 1, the comparison between CCTA and invasive coronary angiography (ICA), a total of 4 studies were analysed.

For the outcome of stroke, the analysis showed that in the long term, fewer events occurred in the CCTA group than in the direct ICA group (indication of a benefit). In addition, for the outcome of unnecessary invasive diagnostic tests, it was shown that a lower proportion of patients in the CCTA group underwent invasive diagnostic tests with the result of "no obstructive CHD" than in the direct ICA group (proof of less harm). For the outcome of AEs, the CCTA group was also shown to have fewer periprocedural AEs (indication of less harm).

For all other outcomes, there were no relevant differences between the comparisons or no usable data were available.

Overall, based on the outcomes of stroke, unnecessary invasive diagnostic tests and AEs, there is proof across outcomes of a greater benefit of the diagnostic strategy using CCTA compared with direct ICA in patients suspected of having chronic CHD after basic diagnostic tests.

**Question 2: CCTA with the option of CT-based functional evaluation versus strategies without the option of CT-based functional evaluation**

A total of 3 studies were analysed for this question. These studies investigated 2 different functional evaluation methods as a possible adjunct to CCTA: CT-based measurement of fractional flow reserve (CT-FFR) and CT-based measurement of myocardial perfusion (CTP).

The study results show that both CT-FFR and CTP, as optional add-ons to CCTA, help to avoid unnecessary invasive diagnostic tests (indication of less harm). With the exception of the case described below, for all other outcomes there were either no relevant differences between the comparisons or no usable data were available. No data were available on AEs.

The reduction in unnecessary invasive diagnostic tests is contrasted by conspicuous numerical trends in the CT-FFR from the included study (as well as from another study reported as supplementary information) for the outcome of myocardial infarction, to the disadvantage of the intervention. Because of these numerical group differences, there is concern that harm could be associated with a reduction in invasive diagnostic tests.

In the two studies on CTP, there were no numerically conspicuous group differences, but there was also no effect in favour of the intervention for any other outcome. As CTP is associated with additional procedural risks due to the injection of drugs and contrast agents, there is no advantage of the option of CT-based functional evaluation using CTP.

Overall, there is no benefit or potential of CCTA with CT-based functional evaluation compared with CCTA without CT-based functional evaluation in patients with suspected chronic CHD after basic diagnostic tests, because of concerns about potential harm (CT-FFR), or because no advantage is apparent after weighing the potential benefits and harms (CTP).

**References for English extract**

Please see full final report for full reference list.

1. Bundesärztekammer, Kassenärztliche Bundesvereinigung, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften. Nationale VersorgungsLeitlinie: Chronische KHK; Langfassung; Version 6.0 [online]. 2022 [Accessed: 02.11.2022]. URL: https://www.leitlinien.de/themen/khk/pdf/khk-vers6-0-lang.pdf.

2. Statistisches Bundesamt (Destatis), Wissenschaftszentrum Berlin für Sozialforschung (WZB), Bundesinstitut für Bevölkerungsforschung (BiB). Datenreport 2021; ein Sozialbericht für die Bundesrepublik Deutschland, Gesamtausgabe [online]. 2021 [Accessed: 25.02.2022]. URL: https://www.destatis.de/DE/Service/Statistik-Campus/Datenreport/Downloads/datenreport-2021.pdf?__blob=publicationFile.

3. Knuuti J, Wijns W, Saraste A et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J 2020; 41(3): 407-477. https://dx.doi.org/10.1093/eurheartj/ehz425.

4. Peper J, Sucha D, Swaans M et al. Functional cardiac CT-Going beyond Anatomical Evaluation of Coronary Artery Disease with Cine CT, CT-FFR, CT Perfusion and Machine Learning. Br J Radiol 2020; 93(1113): 20200349. https://dx.doi.org/10.1259/bjr.20200349.

5. Baumann S, Overhoff D, Tesche C et al. Morphologische und funktionelle Diagnostik der koronaren Herzkrankheit mittels Computertomographie. Herz 2022. https://dx.doi.org/10.1007/s00059-022-05098-7.

6. Gorenoi V, Schonermark MP, Hagen A. CT coronary angiography vs. invasive coronary angiography in CHD. GMS Health Technol Assess 2012; 8: Doc02. https://dx.doi.org/10.3205/hta000100.

7. National Guideline Centre. Recent-onset chest pain of suspected cardiac origin: assessment and diagnosis; NICE guideline CG95; methods, evidence and recommendations [online]. 2016 [Accessed: 01.03.2022]. URL: https://www.nice.org.uk/guidance/cg95/evidence/full-guideline-pdf-245282221.

8. Institut für Qualitätssicherung und Transparenz im Gesundheitswesen. Qualitätsreport [online]. 2020 [Accessed: 17.01.2022]. URL: https://iqtig.org/downloads/berichte/2019/IQTIG_Qualitaetsreport-2020_2021-02-11.pdf.

9. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. CT- oder MRT-Diagnostik bei Verdacht auf chronische koronare Herzkrankheit; eine Evidenzkartierung; Arbeitspapier [online]. 2020 [Accessed: 25.10.2022]. URL: https://www.iqwig.de/download/GA20-01_Herz-CT-oder-MRT-bei-Verdacht-auf-KHK_Arbeitspapier_V1-0.pdf.

10. Agus AM, McKavanagh P, Lusk L et al. The cost-effectiveness of cardiac computed tomography for patients with stable chest pain. Heart 2016; 102(5): 356-362. https://dx.doi.org/10.1136/heartjnl-2015-308247.

11. McKavanagh P, Lusk L, Ball PA et al. A comparison of cardiac computerized tomography and exercise stress electrocardiogram test for the investigation of stable chest pain: the clinical results of the CAPP randomized prospective trial. Eur Heart J Cardiovasc Imaging 2015; 16(4): 441-448. https://dx.doi.org/10.1093/ehjci/jeu284.

12. Ulster Hospital. Cardiac computed tomography (CT) for the Assessment of chest Pain and Plaque: a randomised controlled trial [online]. [Accessed: 30.08.2022]. URL: https://trialsearch.who.int/Trial2.aspx?TrialID=ISRCTN52480460.

13. Lee SP, Seo JK, Hwang IC et al. Coronary computed tomography angiography vs. myocardial single photon emission computed tomography in patients with intermediate risk chest pain: a randomized clinical trial for cost-effectiveness comparison based on real-world cost. Eur Heart J Cardiovasc Imaging 2019; 20(4): 417-425. https://dx.doi.org/10.1093/ehjci/jey099.

14. Seoul National University Hospital. Comparison of the Cost-Effectiveness of Coronary CT Angiography Versus Myocardial SPECT in Patients With Intermediate Risk of Coronary Heart Disease (CARE-CCTA) [online]. 2012 [Accessed: 30.08.2022]. URL: https://ClinicalTrials.gov/show/NCT01542086.

15. Linde JJ, Hove JD, Sorgaard M et al. Long-Term Clinical Impact of Coronary CT Angiography in Patients With Recent Acute-Onset Chest Pain: The Randomized Controlled CATCH Trial. JACC Cardiovasc Imaging 2015; 8(12): 1404-1413. https://dx.doi.org/10.1016/j.jcmg.2015.07.015.

16. Linde JJ, Kofoed KF, Sorgaard M et al. Cardiac computed tomography guided treatment strategy in patients with recent acute-onset chest pain: results from the randomised, controlled trial: CArdiac cT in the treatment of acute CHest pain (CATCH). Int J Cardiol 2013; 168(6): 5257-5262. https://dx.doi.org/10.1016/j.ijcard.2013.08.020.

17. Hvidovre University Hospital. Cardiac-CT in the Treatment of Acute Chest Pain (CATCH) [online]. 2014 [Accessed: 30.08.2022]. URL: https://ClinicalTrials.gov/show/NCT01534000.

18. Goldstein JA, Chinnaiyan KM, Abidov A et al. The CT-STAT (Coronary Computed Tomographic Angiography for Systematic Triage of Acute Chest Pain Patients to Treatment) trial. J Am Coll Cardiol 2011; 58(14): 1414-1422. https://dx.doi.org/10.1016/j.jacc.2011.03.068.

19. William Beaumont Hospitals. Coronary Computed Tomography for Systematic Triage of Acute Chest Pain Patients to Treatment (CT-STAT) (CTSTAT) [online]. 2009 [Accessed: 20.09.2022]. URL: https://ClinicalTrials.gov/show/NCT00468325.

20. Goldstein JA, Gallagher MJ, O'Neill WW et al. A randomized controlled trial of multi-slice coronary computed tomography for evaluation of acute chest pain. J Am Coll Cardiol 2007; 49(8): 863-871. https://dx.doi.org/10.1016/j.jacc.2006.08.064.

21. William Beaumont Hospitals. Study of Coronary Artery Computed Tomography to Diagnose Emergency Chest Pain [online]. 2006 [Accessed: 30.08.2022]. URL: https://ClinicalTrials.gov/show/NCT00273832.

22. Karthikeyan G, Guzic Salobir B, Jug B et al. Functional compared to anatomical imaging in the initial evaluation of patients with suspected coronary artery disease: An international, multi-center, randomized controlled trial (IAEA-SPECT/CTA study). J Nucl Cardiol 2017; 24(2): 507-517. https://dx.doi.org/10.1007/s12350-016-0664-3.

23. All India Institute of Medical Sciences. Stress Testing Compared to Coronary Computed Tomographic Angiography in Patients With Suspected Coronary Artery Disease [online]. 2015 [Accessed: 30.08.2022]. URL: https://clinicaltrials.gov/ct2/show/NCT01368770.

24. International Atomic Energy Agency Iaea. Stress-rest MIBI-SPECT compared to Coronary CT Angiography as the initial test in the evaluation of patients at intermediate risk of coronary events - A Pilot Randomized Controlled Trial (IAEA SPECT/CT CAD) [online]. [Accessed: 30.08.2022]. URL: https://trialsearch.who.int/Trial2.aspx?TrialID=CTRI/2010/091/001384.

25. Min JK, Koduru S, Dunning AM et al. Coronary CT angiography versus myocardial perfusion imaging for near-term quality of life, cost and radiation exposure: a prospective multicenter randomized pilot trial. J Cardiovasc Comput Tomogr 2012; 6(4): 274-283. https://dx.doi.org/10.1016/j.jcct.2012.06.002.

26. Nabi F, Kassi M, Muhyieddeen K et al. Optimizing evaluation of patients with low-to-intermediate-risk acute chest pain: A randomized study comparing stress myocardial perfusion tomography incorporating stress-only imaging versus cardiac CT. J Nucl Med 2016; 57(3): 378-384. https://dx.doi.org/10.2967/jnumed.115.166595.

27. Uretsky S, Argulian E, Supariwala A et al. Comparative effectiveness of coronary CT angiography vs stress cardiac imaging in patients following hospital admission for chest pain work-up: The Prospective First Evaluation in Chest Pain (PERFECT) Trial. J Nucl Cardiol 2017; 24(4): 1267-1278. https://dx.doi.org/10.1007/s12350-015-0354-6.

28. St. Luke's-Roosevelt Hospital Center. ProspEctive First Evaluation in Chest Pain Trial [online]. 2016 [Accessed: 30.08.2022]. URL: https://clinicaltrials.gov/ct2/show/NCT01604655.

29. Litwin SE, Coles A, Pagidipati N et al. Effects of obesity on noninvasive test results in patients with suspected cardiac ischemia: Insights from the PROMISE trial. J Cardiovasc Comput Tomogr 2019; 13(4): 211-218. https://dx.doi.org/10.1016/j.jcct.2019.03.010.

30. Sharma A, Sekaran NK, Coles A et al. Impact of Diabetes Mellitus on the Evaluation of Stable Chest Pain Patients: Insights From the PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) Trial. Journal of the American Heart Association 2017; 6(11). https://dx.doi.org/10.1161/jaha.117.007019.

31. Hoffmann U, Ferencik M, Udelson JE et al. Prognostic Value of Noninvasive Cardiovascular Testing in Patients With Stable Chest Pain: Insights From the PROMISE Trial (Prospective Multicenter Imaging Study for Evaluation of Chest Pain). Circulation 2017; 135(24): 2320-2332. https://dx.doi.org/10.1161/circulationaha.116.024360.

32. Lowenstern A, Alexander KP, Hill CL et al. Age-Related Differences in the Noninvasive Evaluation for Possible Coronary Artery Disease: Insights From the Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) Trial. JAMA Cardiology 2020; 5(2): 193-201. https://dx.doi.org/10.1001/jamacardio.2019.4973.

33. Lu MT, Douglas PS, Udelson JE et al. Safety of coronary CT angiography and functional testing for stable chest pain in the PROMISE trial: A randomized comparison of test complications, incidental findings, and radiation dose. J Cardiovasc Comput Tomogr 2017; 11(5): 373-382. https://dx.doi.org/10.1016/j.jcct.2017.08.005.

34. Mark DB, Anstrom KJ, Sheng S et al. Quality-of-Life Outcomes With Anatomic Versus Functional Diagnostic Testing Strategies in Symptomatic Patients With Suspected Coronary Artery Disease: Results From the PROMISE Randomized Trial. Circulation 2016; 133(21): 1995-2007. https://dx.doi.org/10.1161/circulationaha.115.020259.

35. Pagidipati NJ, Coles A, Hemal K et al. Sex differences in management and outcomes of patients with stable symptoms suggestive of coronary artery disease: Insights from the PROMISE trial. Am Heart J 2019; 208: 28-36. https://dx.doi.org/10.1016/j.ahj.2018.11.002.

36. Pagidipati NJ, Hemal K, Coles A et al. Sex Differences in Functional and CT Angiography Testing in Patients With Suspected Coronary Artery Disease. J Am Coll Cardiol 2016; 67(22): 2607-2616. https://dx.doi.org/10.1016/j.jacc.2016.03.523.

37. Sharma A, Coles A, Sekaran NK et al. Stress Testing Versus CT Angiography in Patients With Diabetes and Suspected Coronary Artery Disease. J Am Coll Cardiol 2019; 73(8): 893-902. https://dx.doi.org/10.1016/j.jacc.2018.11.056.

38. Douglas PS, Hoffmann U, Patel MR et al. Outcomes of anatomical versus functional testing for coronary artery disease. N Engl J Med 2015; 372(14): 1291-1300. https://dx.doi.org/10.1056/NEJMoa1415516.

39. Douglas PS, Hoffmann U, Lee KL et al. PROspective Multicenter Imaging Study for Evaluation of chest pain: rationale and design of the PROMISE trial. Am Heart J 2014; 167(6): 796-803.e1. https://dx.doi.org/10.1016/j.ahj.2014.03.003.

40. Duke University. PROspective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) [online]. 2016 [Accessed: 30.08.2022]. URL: https://ClinicalTrials.gov/show/NCT01174550.

41. Adamson PD, Hunter A, Williams MC et al. Diagnostic and prognostic benefits of computed tomography coronary angiography using the 2016 National Institute for Health and Care Excellence guidance within a randomised trial. Heart 2018; 104(3): 207-214. https://dx.doi.org/10.1136/heartjnl-2017-311508.

42. Adamson PD, Williams MC, Dweck MR et al. Guiding Therapy by Coronary CT Angiography Improves Outcomes in Patients With Stable Chest Pain. J Am Coll Cardiol 2019; 74(16): 2058-2070. https://dx.doi.org/10.1016/j.jacc.2019.07.085.

43. Mangion K, Adamson PD, Williams MC et al. Sex associations and computed tomography coronary angiography-guided management in patients with stable chest pain. Eur Heart J 2020; 41(13): 1337-1345. https://dx.doi.org/10.1093/eurheartj/ehz903.

44. Williams MC, Hunter A, Shah A et al. Symptoms and quality of life in patients with suspected angina undergoing CT coronary angiography: a randomised controlled trial. Heart 2017; 103(13): 995-1001. https://dx.doi.org/10.1136/heartjnl-2016-310129.

45. CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open-label, parallel-group, multicentre trial. Lancet 2015; 385(9985): 2383-2391. https://dx.doi.org/10.1016/s0140-6736(15)60291-4.

46. Williams MC, Hunter A, Shah ASV et al. Use of Coronary Computed Tomographic Angiography to Guide Management of Patients With Coronary Disease. J Am Coll Cardiol 2016; 67(15): 1759-1768. https://dx.doi.org/10.1016/j.jacc.2016.02.026.

47. Newby DE, Williams MC, Flapan AD et al. Role of multidetector computed tomography in the diagnosis and management of patients attending the rapid access chest pain clinic, The Scottish computed tomography of the heart (SCOT-HEART) trial: study protocol for randomized controlled trial. Trials 2012; 13: 184. https://dx.doi.org/10.1186/1745-6215-13-184.

48. Newby DE, Adamson PD, Berry C et al. Coronary CT angiography and 5-year risk of myocardial infarction. N Engl J Med 2018; 379(10): 924-933. https://dx.doi.org/10.1056/NEJMoa1805971.

49. University of Edinburgh. Scottish COmputed Tomography of the HEART Trial (SCOT-HEART) [online]. 2017 [Accessed: 30.08.2022]. URL: https://ClinicalTrials.gov/show/NCT01149590.

50. Bosserdt M, Feger S, Rief M et al. Performing Computed Tomography Instead of Invasive Coronary Angiography: Sex Effects in Patients With Suspected CAD. JACC Cardiovasc Imaging 2020; 13(3): 888-889. https://dx.doi.org/10.1016/j.jcmg.2019.10.014.

51. Dewey M, Rief M, Martus P et al. Evaluation of computed tomography in patients with atypical angina or chest pain clinically referred for invasive coronary angiography: randomised controlled trial. BMJ 2016; 355: i5441. https://dx.doi.org/10.1136/bmj.i5441.

52. Charite University. Coronary Artery Disease Management Using Multislice Computed Tomography and Magnetic Resonance Imaging (CAD-Man) [online]. 2021 [Accessed: 30.08.2022]. URL: https://ClinicalTrials.gov/show/NCT00844220.

53. Chang HJ, Lin FY, Gebow D et al. Selective Referral Using CCTA Versus Direct Referral for Individuals Referred to Invasive Coronary Angiography for Suspected CAD: A Randomized, Controlled, Open-Label Trial. JACC Cardiovasc Imaging 2019; 12(7 Pt 2): 1303-1312. https://dx.doi.org/10.1016/j.jcmg.2018.09.018.

54. Lee SE, Lin FY, Lu Y et al. Rationale and design of the Coronary Computed Tomographic Angiography for Selective Cardiac Catheterization: Relation to Cardiovascular Outcomes, Cost Effectiveness and Quality of Life (CONSERVE) trial. Am Heart J 2017; 186: 48-55. https://dx.doi.org/10.1016/j.ahj.2016.12.007.

55. MDDX LLC. Coronary Computed Tomographic Angiography for Selective Cardiac Catheterization (CONSERVE) [online]. 2017 [Accessed: 30.08.2022]. URL: https://ClinicalTrials.gov/show/NCT01810198.

56. Napp AE, Haase R, Laule M et al. Computed tomography versus invasive coronary angiography: design and methods of the pragmatic randomised multicentre DISCHARGE trial. Eur Radiol 2017; 27(7): 2957-2968. https://dx.doi.org/10.1007/s00330-016-4620-z.

57. Group DT, Maurovich-Horvat P, Bosserdt M et al. CT or Invasive Coronary Angiography in Stable Chest Pain. N Engl J Med 2022; 386(17): 1591-1602. https://dx.doi.org/10.1056/NEJMoa2200963.

58. Charite University. Diagnostic Imaging Strategies for Patients With Stable Chest Pain and Intermediate Risk of Coronary Artery Disease (DISCHARGE) [online]. 2021 [Accessed: 30.08.2022]. URL: https://clinicaltrials.gov/ct2/show/NCT02400229.

59. Reis JF, Ramos RB, Marques H et al. Cardiac computed tomographic angiography after abnormal ischemia test as a gatekeeper to invasive coronary angiography. Int J Cardiovasc Imaging 2022. https://dx.doi.org/10.1007/s10554-021-02426-6.

60. Sorgaard M, Linde JJ, Hove JD et al. Myocardial perfusion 320-row multidetector computed tomography-guided treatment strategy for the clinical management of patients with recent acute-onset chest pain: Design of the CArdiac cT in the treatment of acute CHest pain (CATCH)-2 randomized controlled trial. Am Heart J 2016; 179: 127-135. https://dx.doi.org/10.1016/j.ahj.2016.05.016.

61. Sorgaard MH, Linde JJ, Kuhl JT et al. Value of Myocardial Perfusion Assessment With Coronary Computed Tomography Angiography in Patients With Recent Acute-Onset Chest Pain. JACC Cardiovasc Imaging 2018; 11(11): 1611-1621. https://dx.doi.org/10.1016/j.jcmg.2017.09.022.

62. Rigshospitalet Denmark. CArdiac cT in the Treatment of Acute CHest Pain 2 - Myocardial CT Perfusion (CATCH2) [online]. 2021 [Accessed: 07.10.2022]. URL: https://clinicaltrials.gov/ct2/show/NCT02014311.

63. Curzen N, Nicholas Z, Stuart B et al. Fractional flow reserve derived from computed tomography coronary angiography in the assessment and management of stable chest pain: the FORECAST randomized trial. Eur Heart J 2021; 42(37): 3844-3852. https://dx.doi.org/10.1093/eurheartj/ehab444.

64. Mahmoudi M, Nicholas Z, Nuttall J et al. Fractional Flow Reserve Derived from Computed Tomography Coronary Angiography in the Assessment and Management of Stable Chest Pain: Rationale and Design of the FORECAST Trial. Cardiovasc Revasc Med 2020; 21(7): 890-896. https://dx.doi.org/10.1016/j.carrev.2019.12.009.

65. University Hospital Southampton NHS Foundation Trust. Fractional Flow Reserve Derived From Computed Tomography Coronary Angiography in the Assessment and Management of Stable Chest Pain (FORECAST) [online]. 2020 [Accessed: 29.06.2022]. URL: https://clinicaltrials.gov/ct2/show/NCT03187639.

66. Nanna MG, Vemulapalli S, Fordyce CB et al. The prospective randomized trial of the optimal evaluation of cardiac symptoms and revascularization: Rationale and design of the PRECISE trial. Am Heart J 2022; 245: 136-148. https://dx.doi.org/10.1016/j.ahj.2021.12.004.

67. HeartFlow. The PRECISE Protocol: Prospective Randomized Trial of the Optimal Evaluation of Cardiac Symptoms and Revascularization [online]. 2022 [Accessed: 29.06.2022]. URL: https://clinicaltrials.gov/ct2/show/NCT03702244.

68. Douglas P. The PRECISE protocol - prospective randomized trial of the optimal evaluation of cardiac symptoms and revascularization - v1.5 [unpublished]. 2019.

69. Douglas P, Nanna M, Kelsey M et al. PRECISE - Comparision of a precision care strategy with usual testing to guide management of stable patients with suspected coronary artery disease (unveröffentlicht). 2022.

70. Douglas P, Nanna M, Kelsey M et al. Comparison of an Initial Risk-Based Testing Strategy vs Usual Testing in Stable Symptomatic Patients With Suspected Coronary Artery Disease: The PRECISE Randomized Trial; Risk-Based Strategy vs Usual Testing for Suspected Coronary Artery Disease [unpublished]. 2023.

71. Yang J, Shan D, Wang X et al. On-Site Computed Tomography-Derived Fractional Flow Reserve to Guide the Management of Patients with Stable Coronary Artery Disease: the TARGET Randomized Trial. Circulation 2023; 147(18): 1369-1381. https://dx.doi.org/10.1161/CIRCULATIONAHA.123.063996.

72. Yang J, Shan D, Dong M et al. The effect of on-site CT-derived fractional flow reserve on the management of decision making for patients with stable chest pain (TARGET trial): objective, rationale, and design. Trials [Electronic Resource] 2020; 21(1): 728. https://dx.doi.org/10.1186/s13063-020-04649-9.

73. Chinese PLA General Hospital. Role of On-site CT-derived FFR in the Management of Suspect CAD Patients (TARGET) [online]. 2019 [Accessed: 15.02.2023]. URL: https://ClinicalTrials.gov/show/NCT03901326.

74. Yu M, Shen C, Dai X et al. Clinical Outcomes of Dynamic Computed Tomography Myocardial Perfusion Imaging Combined With Coronary Computed Tomography Angiography Versus Coronary Computed Tomography Angiography-Guided Strategy. Circ Cardiovasc Imaging 2020; 13(1): e009775. https://dx.doi.org/10.1161/circimaging.119.009775.

75. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden; Version 6.1 [online]. 2022 [Accessed: 24.01.2022]. URL: https://www.iqwig.de/methoden/allgemeine-methoden-v6-1.pdf.

76. Nanna MG, Vemulapalli S, Fordyce CB et al. The prospective randomized trial of the optimal evaluation of cardiac symptoms and revascularization: Rationale and design of the PRECISE trial. Am Heart J 2022; 245: 136-148. https://dx.doi.org/10.1016/j.ahj.2021.12.004.

77. Gutberlet M, Krieghoff C, Gohmann R. [Is FFR(CT) a game changer in coronary CT angiography?]. Herz 2020; 45(5): 431-440. https://dx.doi.org/10.1007/s00059-020-04944-w.

78. Fordyce CB, Douglas PS, Roberts RS et al. Identification of Patients With Stable Chest Pain Deriving Minimal Value From Noninvasive Testing: The PROMISE Minimal-Risk Tool, A Secondary Analysis of a Randomized Clinical Trial. JAMA Cardiology 2017; 2(4): 400-408. https://dx.doi.org/10.1001/jamacardio.2016.5501.

79. Walter Reed Army Medical Center. CT-FIRST: Cardiac Computed Tomography Versus Stress Imaging For Initial Risk STratification (CT-FIRST) [online]. 2012 [Accessed: 15.02.2023]. URL: https://clinicaltrials.gov/ct2/show/NCT01061398.

80. Women's College Hospital. Risk Evaluation and Stratification of Low Risk for Cardiovascular Disease in Women (RESOLVE) [online]. 2019 [Accessed: 15.02.2023]. URL: https://ClinicalTrials.gov/show/NCT03929341.

81. The Queen Elizabeth Hospital. In patient groups with an intermediate probability of coronary artery disease is there a difference between computer tomography coronary angiography and myocardial perfusion imaging in ruling out significant coronary artery disease [online]. [Accessed: 15.02.2023]. URL: https://anzctr.org.au/ACTRN12608000386336.aspx.

82. Centro Cardiologico Monzino. Impact of Stress CT Myocardial Perfusion on Downstream Resources and Prognosis [online]. 2019 [Accessed: 15.02.2023]. URL: https://clinicaltrials.gov/ct2/show/NCT03976921.

83. Pontone G, De Cecco C, Baggiano A et al. Design of CTP-PRO study (impact of stress Cardiac computed Tomography myocardial Perfusion on downstream resources and PROgnosis in patients with suspected or known coronary artery disease: A multicenter international study). Int J Cardiol 2019; 292: 253-257. https://dx.doi.org/10.1016/j.ijcard.2019.06.012.

84. Tesche C, Ebersberger U, Hoffmann E et al. Aktueller Stellenwert der kardialen Computertomographie in der Diagnostik der koronaren Herzerkrankung. Der Kardiologe 2018; 12(3): 217-230. https://dx.doi.org/10.1007/s12181-018-0251-8.

85. Lubbers M, Dedic A, Coenen A et al. Calcium imaging and selective computed tomography angiography in comparison to functional testing for suspected coronary artery disease: the multicentre, randomized CRESCENT trial. Eur Heart J 2016; 37(15): 1232-1243. https://dx.doi.org/10.1093/eurheartj/ehv700.

86. Wong SS, Wilczynski NL, Haynes RB. Comparison of top-performing search strategies for detecting clinically sound treatment studies and systematic reviews in MEDLINE and EMBASE. J Med Libr Assoc 2006; 94(4): 451-455.

87. Lefebvre C, Glanville J, Briscoe S et al. Cochrane Handbook for Systematic Reviews of Interventions; Version 6.2; Technical Supplement to Chapter 4: Searching for and selecting studies [online]. 2021 [Accessed: 27.05.2021]. URL: https://training.cochrane.org/handbook/version-6.1/chapter-4-tech-suppl.

The full report (German version) is published under

https://www.iqwig.de/en/projects/d22-01.html

# Appendix A Search strategies

## A.1 Searches in bibliographic databases

### A1.1.1 Search for systematic reviews

***1. MEDLINE***

*Search interface: Ovid*

- Ovid MEDLINE(R) ALL 1946 to April 28, 2022

The following filter was adopted:

- Systematic review: Wong [86] – High specificity strategy

| # | Searches |
|---|---|
| 1 | Coronary Artery Disease/ |
| 2 | Angina Stable/ |
| 3 | (coronary* adj1 artery* adj1 disease*).ti,ab. |
| 4 | (angina* adj1 (stable* or pectoris*)).ti,ab. |
| 5 | (angina* adj3 (coronary* adj1 heart* adj1 disease*)).ti,ab. |
| 6 | or/1-5 |
| 7 | Computed Tomography Angiography/ |
| 8 | Coronary Angiography/ |
| 9 | ((coronary* or CT) adj3 angiography*).ti,ab. |
| 10 | or/7-9 |
| 11 | and/6,10 |
| 12 | ..l/ 11 yr=2020-Current |
| 13 | Fractional Flow Reserve, Myocardial/ |
| 14 | fractional flow reserve*.ti,ab. |
| 15 | or/13-14 |
| 16 | and/6,15 |
| 17 | Myocardial Perfusion Imaging/ |
| 18 | perfusion*.ti,ab. |
| 19 | or/17-18 |
| 20 | and/6,19 |
| 21 | or/16,20 |
| 22 | ..l/ 21 yr=2017-Current |
| 23 | or/12,22 |
| 24 | Cochrane database of systematic reviews.jn. |
| 25 | (search or MEDLINE or systematic review).tw. |
| 26 | meta analysis.pt. |
| 27 | or/24-26 |

| # | Searches |
|---|---|
| 28 | 27 not (exp animals/ not humans.sh.) |
| 29 | and/23,28 |
| 30 | 29 and (english or german or multilingual or undetermined).lg. |

***2. International HTA Database***

*Search interface: INAHTA*

| # | Searches |
|---|---|
| 1 | coronary disease |

### A1.1.2 Search for primary studies

**Question 1 (diagnostic strategies using CCTA)**

***1. MEDLINE***

*Search interface: Ovid*

- Ovid MEDLINE(R) 1946 to June 02, 2022

The following filter was adopted:

- Cochrane HSSS: sensitivity-maximizing version (2008 revision) Lefebvre [87] – Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision)

| # | Searches |
|---|---|
| 1 | exp Coronary Stenosis/ |
| 2 | Coronary Artery Disease/ |
| 3 | Angina, Stable/ |
| 4 | (coronary* adj1 artery* adj1 disease*).ti,ab. |
| 5 | (coronary* adj3 stenos*).ti,ab. |
| 6 | (angina* adj1 (stable* or pectoris*)).ti,ab. |
| 7 | (angina* adj3 (coronary* adj1 heart* adj1 disease*)).ti,ab. |
| 8 | or/1-7 |
| 9 | Computed Tomography Angiography/ |
| 10 | Coronary Angiography/ |
| 11 | ((coronary* or CT* or (computed adj1 tomograph*)) adj3 angiography*).ti,ab. |
| 12 | or/9-11 |
| 13 | and/8,12 |
| 14 | Randomized Controlled Trial.pt. |
| 15 | Controlled Clinical Trial.pt. |

| # | Searches |
|---|---|
| 16 | (randomized or placebo or randomly or trial or groups).ab. |
| 17 | drug therapy.fs. |
| 18 | or/14-17 |
| 19 | exp animals/ not humans/ |
| 20 | 18 not 19 |
| 21 | and/13,20 |
| 22 | (animals/ not humans/) or comment/ or editorial/ or exp review/ or meta analysis/ or consensus/ or exp guideline/ |
| 23 | hi.fs. or case report.mp. |
| 24 | or/22-23 |
| 25 | 21 not 24 |
| 26 | 25 and (english or german or multilingual or undetermined).lg. |
| 27 | 26 and 201511:3000.(dt). |

*Search interface: Ovid*

- Ovid MEDLINE(R) Epub Ahead of Print and In-Process, In-Data-Review & Other Non-Indexed Citations June 02, 2022

| # | Searches |
|---|---|
| 1 | (coronary* adj3 artery* adj3 disease*).ti,ab. |
| 2 | (coronary* adj5 stenos*).ti,ab. |
| 3 | (angina* adj3 (stable* or pectoris*)).ti,ab. |
| 4 | (angina* and (coronary* adj3 heart* adj3 disease*)).ti,ab. |
| 5 | or/1-4 |
| 6 | ((coronary* or CT* or (computed adj3 tomograph*)) and angiography*).ti,ab. |
| 7 | and/5-6 |
| 8 | (clinical trial* or random* or placebo).ti,ab. |
| 9 | trial.ti. |
| 10 | or/8-9 |
| 11 | (animals/ not humans/) or comment/ or editorial/ or exp review/ or meta analysis/ or consensus/ or exp guideline/ |
| 12 | hi.fs. or case report.mp. |
| 13 | or/11-12 |
| 14 | 10 not 13 |
| 15 | and/7,14 |
| 16 | 15 and (english or german or multilingual or undetermined).lg. |
| 17 | 16 and 201511:3000.(dt). |

### *2. Embase*

*Search interface: Ovid*

- Embase 1974 to 2022 June 02

The following filter was adopted:

- RCT: Wong [86] – Strategy minimizing difference between sensitivity and specificity

| # | Searches |
|---|---|
| 1 | exp Coronary artery disease/ |
| 2 | angina pectoris/ |
| 3 | stable angina pectoris/ |
| 4 | *ischemic heart disease/ |
| 5 | (coronary* adj1 artery* adj1 disease*).ti,ab. |
| 6 | (coronary* adj3 stenos*).ti,ab. |
| 7 | (angina* adj1 (stable* or pectoris*)).ti,ab. |
| 8 | (angina* adj3 (coronary* adj1 heart* adj1 disease*)).ti,ab. |
| 9 | or/1-8 |
| 10 | computed tomographic angiography/ |
| 11 | coronary angiography/ |
| 12 | *computer assisted tomography/ |
| 13 | ((coronary* or CT* or (computed adj1 tomograph*)) adj3 angiography*).ti,ab. |
| 14 | or/10-13 |
| 15 | and/9,14 |
| 16 | (random* or double-blind*).tw. |
| 17 | placebo*.mp. |
| 18 | or/16-17 |
| 19 | and/15,18 |
| 20 | 19 not medline.cr. |
| 21 | 20 not (exp animal/ not exp human/) |
| 22 | 21 not (Conference Abstract or Conference Review or Editorial).pt. |
| 23 | 22 not ((afrikaans or albanian or arabic or armenian or azerbaijani or basque or belorussian or bosnian or bulgarian or catalan or chinese or croatian or czech or danish or dutch or english or esperanto or estonian or finnish or french or gallegan or georgian or german or greek or hebrew or hindi or hungarian or icelandic or indonesian or irish gaelic or italian or japanese or korean or latvian or lithuanian or macedonian or malay or norwegian or persian or polish or polyglot or portuguese or pushto or romanian or russian or scottish gaelic or serbian or slovak or slovene or spanish or swedish or thai or turkish or ukrainian or urdu or uzbek or vietnamese) not (english or german)).lg. |
| 24 | 23 and 201511:3000.(dc). |

### *3. The Cochrane Library*

*Search interface: Wiley*

4) Cochrane Central Registry of Controlled Trials, Issue 5 of 12, May 2022

| # | Searches |
|---|---|
| 1 | [mh "Coronary Stenosis"] |
| 2 | [mh ^"Coronary Artery Disease"] |
| 3 | [mh ^"Angina, Stable"] |
| 4 | (coronary* NEAR/1 artery* NEAR/1 disease*):ti,ab |
| 5 | (coronary* NEAR/3 stenos*):ti,ab |
| 6 | (angina* NEAR/1 (stable* or pectoris*)):ti,ab |
| 7 | (angina* NEAR/3 (coronary* NEAR/1 heart* NEAR/1 disease*)):ti,ab |
| 8 | #1 or #2 or #3 or #4 or #5 or #6 or #7 |
| 9 | [mh ^"Computed Tomography Angiography"] |
| 10 | [mh ^"Coronary Angiography"] |
| 11 | ((coronary* or CT* or (computed NEAR/1 tomograph*)) NEAR/3 angiography*):ti,ab |
| 12 | #9 or #10 or #11 |
| 13 | #8 and #12 |
| 14 | #13 not (*clinicaltrial*gov* or *trialsearch*who* or *clinicaltrialsregistry*eu* or *anzctr*org*au* or *trialregistry*nl* or *irct*ir* or *isrctn* or *controlled*trials*com* or *drks*de*):so |
| 15 | #14 not ((language next (afr or ara or aze or bos or bul or car or cat or chi or cze or dan or dut or es or est or fin or fre or gre or heb or hrv or hun or ice or ira or ita or jpn or ko or kor or lit or nor or peo or per or pol or por or pt or rom or rum or rus or slo or slv or spa or srp or swe or tha or tur or ukr or urd or uzb)) not (language near/2 (en or eng or english or ger or german or mul or unknown))) |
| 16 | #15 with Cochrane Library publication date Between Nov 2015 and Dec 2022, in Trials |

**Question 2 (diagnostic strategies using CCTA with functional evaluation)**

***1. MEDLINE***

*Search interface: Ovid*

- Ovid MEDLINE(R) 1946 to June 24, 2022

The following filter was adopted:

- Cochrane HSSS: sensitivity-maximizing version (2008 revision) Lefebvre [87] – Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision)

| # | Searches |
|---|---|
| 1 | exp Coronary Stenosis/ |
| 2 | Coronary Artery Disease/ |
| 3 | Angina, Stable/ |
| 4 | (coronary* adj1 artery* adj1 disease*).ti,ab. |
| 5 | (coronary* adj3 stenos*).ti,ab. |
| 6 | (angina* adj1 (stable* or pectoris*)).ti,ab. |
| 7 | (angina* adj3 (coronary* adj1 heart* adj1 disease*)).ti,ab. |
| 8 | or/1-7 |
| 9 | Computed Tomography Angiography/ |
| 10 | Coronary Angiography/ |
| 11 | ((coronary* or CT* or (computed adj1 tomograph*)) adj3 angiography*).ti,ab. |
| 12 | or/9-11 |
| 13 | exp Perfusion Imaging/ |
| 14 | ((myocardial* or tomograph*) adj3 perfusion*).ti,ab. |
| 15 | or/13-14 |
| 16 | and/8,12,15 |
| 17 | Fractional Flow Reserve, Myocardial/ |
| 18 | fractional flow reserve*.ti,ab. |
| 19 | FFR*.ti,ab. |
| 20 | or/17-19 |
| 21 | and/12,20 |
| 22 | or/16,21 |
| 23 | Randomized Controlled Trial.pt. |
| 24 | Controlled Clinical Trial.pt. |
| 25 | (randomized or placebo or randomly or trial or groups).ab. |
| 26 | drug therapy.fs. |
| 27 | or/23-26 |

| # | Searches |
|---|---|
| 28 | (animals/ not humans/) or comment/ or editorial/ or exp review/ or meta analysis/ or consensus/ or exp guideline/ |
| 29 | hi.fs. or case report.mp. |
| 30 | or/28-29 |
| 31 | 27 not 30 |
| 32 | and/22,31 |
| 33 | 32 and (english or german or multilingual or undetermined).lg. |

*Search interface: Ovid*

- Ovid MEDLINE(R) Epub Ahead of Print and In-Process, In-Data-Review & Other Non-Indexed Citations June 24, 2022

| # | Searches |
|---|---|
| 1 | (coronary* adj3 artery* adj3 disease*).ti,ab. |
| 2 | (coronary* adj5 stenos*).ti,ab. |
| 3 | (angina* adj3 (stable* or pectoris*)).ti,ab. |
| 4 | (angina* and (coronary* adj3 heart* adj3 disease*)).ti,ab. |
| 5 | or/1-4 |
| 6 | ((coronary* or CT* or (computed adj3 tomograph*)) and angiography*).ti,ab. |
| 7 | ((myocardial* or tomograph*) and perfusion*).ti,ab. |
| 8 | and/5-7 |
| 9 | fractional flow reserve*.ti,ab. |
| 10 | FFR*.ti,ab. |
| 11 | or/9-10 |
| 12 | and/6,11 |
| 13 | or/8,12 |
| 14 | (clinical trial* or random* or placebo).ti,ab. |
| 15 | trial.ti. |
| 16 | or/14-15 |
| 17 | and/13,16 |
| 18 | (animals/ not humans/) or comment/ or editorial/ or exp review/ or meta analysis/ or consensus/ or exp guideline/ |
| 19 | hi.fs. or case report.mp. |
| 20 | or/18-19 |
| 21 | 17 not 20 |
| 22 | 21 and (english or german or multilingual or undetermined).lg. |

### *2. Embase*

*Search interface: Ovid*

- Embase 1974 to 2022 June 24

The following filter was adopted:

- RCT: Wong [86] – Strategy minimizing difference between sensitivity and specificity

| # | Searches |
|---|---|
| 1 | exp Coronary artery disease/ |
| 2 | angina pectoris/ |
| 3 | stable angina pectoris/ |
| 4 | *ischemic heart disease/ |
| 5 | (coronary* adj1 artery* adj1 disease*).ti,ab. |
| 6 | (coronary* adj3 stenos*).ti,ab. |
| 7 | (angina* adj1 (stable* or pectoris*)).ti,ab. |
| 8 | (angina* adj3 (coronary* adj1 heart* adj1 disease*)).ti,ab. |
| 9 | or/1-8 |
| 10 | computed tomographic angiography/ |
| 11 | coronary angiography/ |
| 12 | *computer assisted tomography/ |
| 13 | ((coronary* or CT* or (computed adj1 tomograph*)) adj3 angiography*).ti,ab. |
| 14 | or/10-13 |
| 15 | Myocardial Perfusion Imaging/ |
| 16 | heart muscle perfusion/ |
| 17 | ((myocardial* or tomograph*) adj3 perfusion*).ti,ab. |
| 18 | or/15-17 |
| 19 | and/9,14,18 |
| 20 | fractional flow reserve/ |
| 21 | fractional flow reserve*.ti,ab. |
| 22 | FFR*.ti,ab. |
| 23 | or/20-22 |
| 24 | and/14,23 |
| 25 | or/19,24 |
| 26 | (random* or double-blind*).tw. |
| 27 | placebo*.mp. |
| 28 | or/26-27 |
| 29 | and/25,28 |
| 30 | 29 not medline.cr. |
| 31 | 30 not (exp animal/ not exp human/) |

| # | Searches |
|---|---|
| 32 | 31 not (Conference Abstract or Conference Review or Editorial).pt. |
| 33 | 32 not ((afrikaans or albanian or arabic or armenian or azerbaijani or basque or belorussian or bosnian or bulgarian or catalan or chinese or croatian or czech or danish or dutch or english or esperanto or estonian or finnish or french or gallegan or georgian or german or greek or hebrew or hindi or hungarian or icelandic or indonesian or irish gaelic or italian or japanese or korean or latvian or lithuanian or macedonian or malay or norwegian or persian or polish or polyglot or portuguese or pushto or romanian or russian or scottish gaelic or serbian or slovak or slovene or spanish or swedish or thai or turkish or ukrainian or urdu or uzbek or vietnamese) not (english or german)).lg. |

### *3. The Cochrane Library*

*Search interface: Wiley*

- Cochrane Central Registry of Controlled Trials Issue 6 of 12, June 2022

| # | Searches |
|---|---|
| #1 | [mh "Coronary Stenosis"] |
| #2 | [mh ^"Coronary Artery Disease"] |
| #3 | [mh ^"Angina, Stable"] |
| #4 | (coronary* NEAR/1 artery* NEAR/1 disease*):ti,ab |
| #5 | (coronary* NEAR/3 stenos*):ti,ab |
| #6 | (angina* NEAR/1 (stable* or pectoris*)):ti,ab |
| #7 | (angina* NEAR/3 (coronary* NEAR/1 heart* NEAR/1 disease*)):ti,ab |
| #8 | #1 or #2 or #3 or #4 or #5 or #6 or #7 |
| #9 | [mh ^"Computed Tomography Angiography"] |
| #10 | [mh ^"Coronary Angiography"] |
| #11 | ((coronary* or CT* or (computed NEAR/1 tomograph*)) NEAR/3 angiography*):ti,ab |
| #12 | #9 or #10 or #11 |
| #13 | [mh "Perfusion Imaging"] |
| #14 | ((myocardial* or tomograph*) NEAR/3 perfusion*):ti,ab |
| #15 | #13 or #14 |
| #16 | #8 and #12 and #15 |
| #17 | [mh ^"Fractional Flow Reserve, Myocardial"] |
| #18 | fractional flow reserve*:ti,ab |
| #19 | FFR*:ti,ab |
| #20 | #17 or #18 or #19 |
| #21 | #12 and #20 |
| #22 | #16 or #21 |
| #23 | #22 not (*clinicaltrial*gov* or *trialsearch*who* or *clinicaltrialsregistry*eu* or *anzctr*org*au* or *trialregistry*nl* or *irct*ir* or *isrctn* or *controlled*trials*com* or *drks*de*):so |

| # | Searches |
|---|---|
| #24 | #23 not ((language next (afr or ara or aze or bos or bul or car or cat or chi or cze or dan or dut or es or est or fin or fre or gre or heb or hrv or hun or ice or ira or ita or jpn or ko or kor or lit or nor or peo or per or pol or por or pt or rom or rum or rus or slo or slv or spa or srp or swe or tha or tur or ukr or urd or uzb)) not (language near/2 (en or eng or english or ger or german or mul or unknown))) |
| #25 | #24 in Trials |

## A.2 Searches in study registries

### Question 1 (diagnostic strategies using CCTA)

#### *1. ClinicalTrials.gov*

*Provider: U.S. National Institutes of Health*

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

| Search strategy |
|---|
| AREA[ConditionSearch] ( coronary artery disease OR angina stable OR angina pectoris OR coronary stenosis ) AND AREA[InterventionSearch] (coronary angiography OR cardiac computed tomography) |

#### *2. International Clinical Trials Registry Platform Search Portal*

*Provider: World Health Organization*

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

| Search strategy |
|---|
| (coronary artery disease OR angina stable OR angina pectoris OR coronary stenosis) AND (coronary angiography OR CT angiography OR cardiac CT OR cardiac computed tomography) |

### Question 2 (diagnostic strategies using CCTA with functional evaluation)

### *1. ClinicalTrials.gov*

*Provider: U.S. National Institutes of Health*

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

| **Search strategy** |
| --- |
| (AREA[ConditionSearch] ( coronary artery disease OR angina stable OR angina pectoris OR coronary stenosis ) AND AREA[InterventionSearch] ( perfusion OR CTP )) OR ((( computed tomography OR CT ) AND ( FFR OR fractional flow reserve )) OR FFRCT) |

### *2. International Clinical Trials Registry Platform Search Portal*

*Provider: World Health Organization*

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

| **Search strategy** |
| --- |
| ((coronary artery disease OR angina stable OR angina pectoris OR coronary stenosis) AND (perfusion OR CTP)) OR ((( computed tomography OR CT ) AND ( FFR OR fractional flow reserve )) OR FFRCT) |