# Calcium Scoring: Assessing Signals for Update

**Provided by:**

**Aggregate Analytics, Inc.**

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# 1. Previous Coverage Decision

A Health Technology Assessment titled: *Coronary Artery Calcium Scoring (CACS) as a Diagnostic Test for Detection of Coronary Artery Disease*, was published on September 4, 2009 by the Health Care Authority. Findings and Coverage Decision was adopted on May 14, 2010. The Committee's Coverage Decision is summarized below.

**HTCC Coverage Determination**

Cardiac Artery Calcium Scoring is a **non-covered benefit**.

**HTCC Reimbursement Determination**

Not applicable.

**Committee Decision**

Based on the deliberations of key health outcomes, the committee decided that it had the most complete information: a comprehensive and current evidence report, public comments, input from a subject matter expert, agency, and state utilization information. The committee concluded that the current evidence on Calcium Scoring demonstrates that there is insufficient evidence to cover the use of Coronary Artery Calcium Scoring (CACS). The committee considered all the evidence and gave greatest weight to the evidence it determined, based on objective factors, to be the most valid and reliable. The committee found that Calcium Scoring would be an additive test that was not supported by sufficient evidence regarding whether it is safe, cost-effective, and effectively diagnoses and prevents major cardiac events thus helping patients. Based on these findings, the committee voted 10 to 0 to not cover Calcium Scoring.

**Medicare Decision and Expert Treatment Guidelines**

CMS does not have a national coverage determination (NCD) for Coronary Artery Calcium Scoring.

- CMS Regional Coverage (Washington and Alaska) – the local regional CMS had determined that there is a lack of evidence of the medical necessity for quantitative evaluation of coronary artery calcium.

# 2. Purpose of Report

The purpose of this literature update is to determine whether or not there is sufficient evidence published after the original report to conduct a re-review of this technology based on the presence of preset signal criteria (see Figure 1). The key questions in the included original report are listed below.

# 3. Methods

## 3.1 Literature Searches

We conducted an electronic literature search for the period April 4, 2009 to April 14, 2020 using identical search terms used for the original report for key questions 1 through 4. This search included 2 main databases: PubMed and EMBASE. Additional electronic databases were searched; see Appendix A for search methodology and additional details.

## 3.2 Study selection

We sought systematic reviews (SR) of randomized controlled trials (RCTs) of efficacy and safety with meta-analysis that included articles that met inclusion and exclusion criteria similar to the original

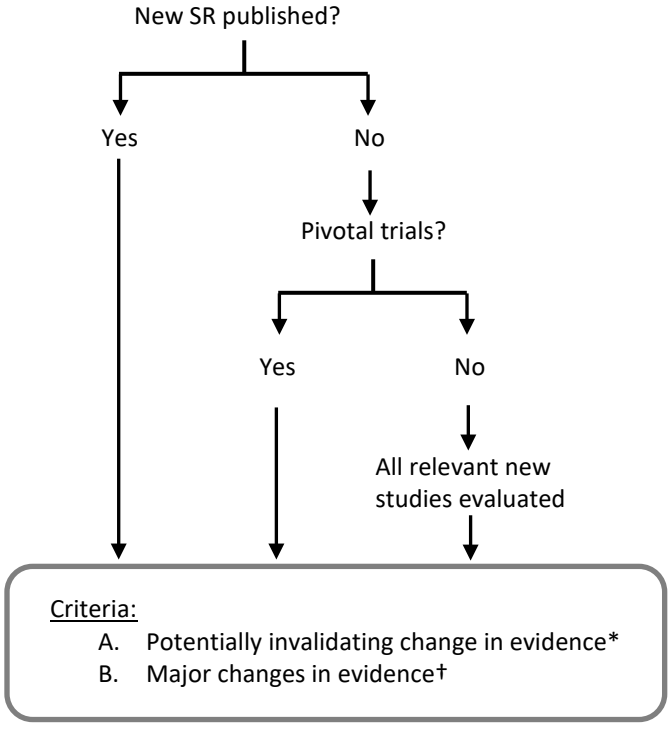
report. Consistent with the 2009 HTA, study selection focused on patients with suspected coronary artery disease (CAD) or symptoms of CAD. High quality SRs and RCTs that directly assessed the accuracy and impact of CACS as a diagnostic test and evaluated diagnostic accuracy, reliability, and clinical utility of CACS in this population were sought. A preliminary assessment of systematic review quality using AMSTAR-II was done. We attempted to focus on SRs that were the most comprehensive and of higher quality based on the following: report of search strategies (two or more databases and description of dates searched), number of included relevant studies (preferably RCTs), pre-stated inclusion and exclusion criteria, information on methodologies used for synthesis of data, inclusion of patient reported or safety outcomes and evaluation of the strength of the body of literature using GRADE or another analogous system. Given that RCTs may be less common for diagnostic tests (compared with studies of therapy), we included SRs of observational studies and attempted to identify high quality observational studies that directly addressed the key questions. For studies of test accuracy, we focused on studies that may likely be at moderately low or low risk of bias; while formal risk of bias assessment was not done, the most important components are captured in the data abstraction (e.g. independent performance and interpretation of CACS and invasive coronary angiography [ICA]; see Appendix B). A summary of the included studies is found in Appendix B. A list of citations excluded at full text is found in Appendix C.

Consistent with the 2009 HTA, the signal update did not include studies evaluating the "incremental value" of CACS in conjunction with other types of test or risk stratification strategies.

### 3.3 Compilation of Findings and Conclusions

For this assessment we constructed a summary table that included the key questions, the original conclusions, new sources of evidence, new findings, and conclusions based on available signals. To assess whether the conclusions might need updating, we used an algorithm based on a modification of the Ottawa method, Figure 1.

**Figure 1. Algorithm of the modified Ottawa Method of Identifying Signals for SR Updates**




*A-1. Opposing findings: Pivotal trial or SR including at least one new trial that characterized the treatment in terms opposite to those used earlier

A-2. Substantial harm: Pivotal trial or SR whose results called into question the use of the treatment based on evidence of harm or that did not proscribe use entirely but did potentially affect clinical decision making (e.g., the risk of harm outweighs the benefits, identification of new serious adverse events)

A-3. Superior new treatment: Pivotal trial or SR whose results identified another treatment as significantly superior to the one evaluated in the original review, based on efficacy or harm

†B-1. Important changes in effectiveness short of "opposing findings"

B-2. Clinically important expansion of treatment (e.g., to new conditions or subgroups of subjects or additional FDA indications)

B-3. Clinically important caveat

B-4. Opposing findings from discordant meta-analysis or nonpivotal trial

Additional general criterion to consider:

- Quantitative signals include a change in statistical significance in which a statistically significant result in the original report is now NOT statistically significant or vice versa which is substantial and/or a change in effect size of at least 50%.

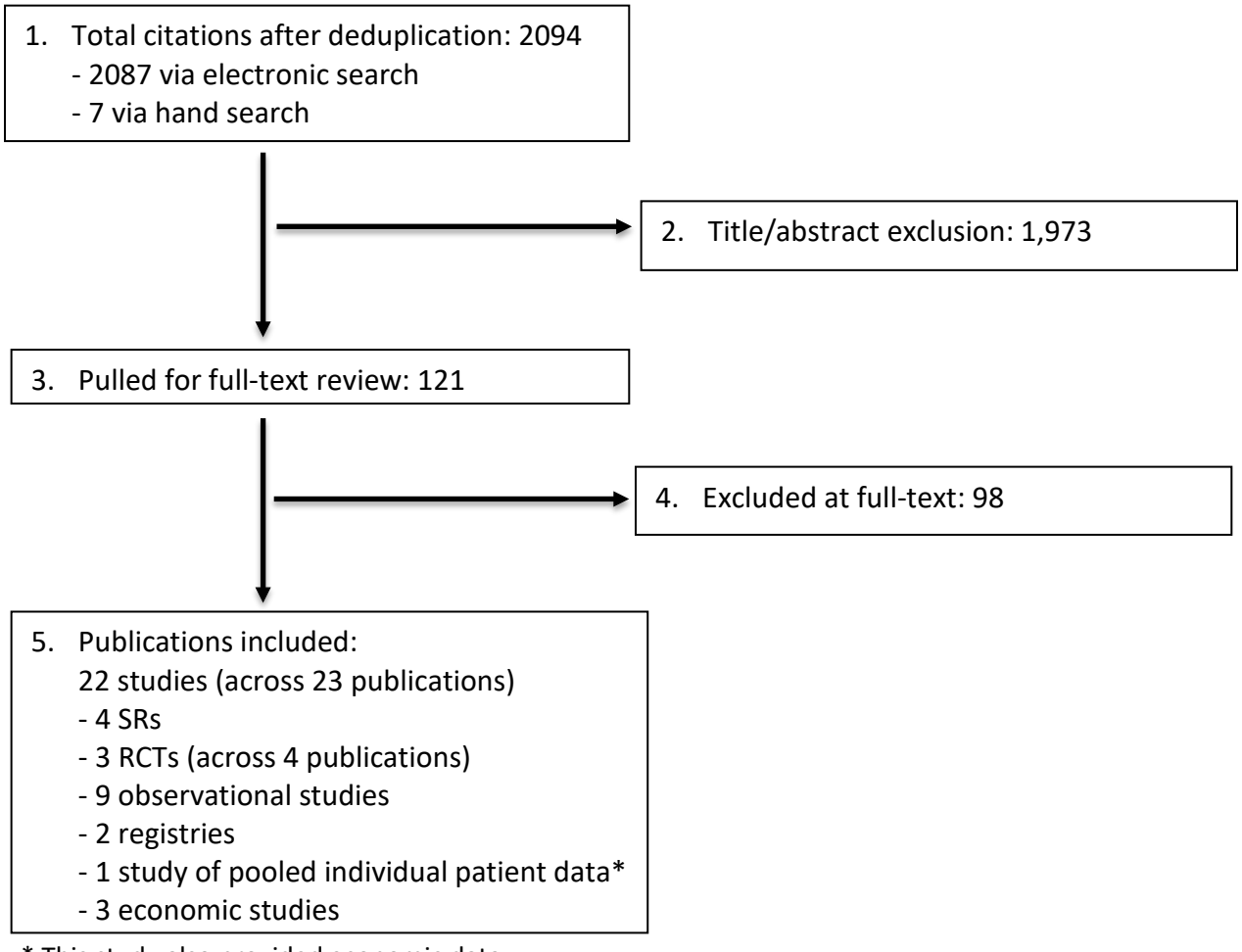
# 4. Results

## 4.1 Search

After deduplication, the signal update search and handsearching, together, identified a total of 2,094 citations. After excluding 1,973 citations at the title abstract level, 121 publications were pulled for full-text review. After full-text review, 98 publications were excluded. The remaining 22 studies (across 23 publications) were included in this signal update. In total, we identified four systematic reviews, three RCTs, nine observational studies, two registry studies, one study of pooled individual patient data (that also provided economic data), and three economic evaluations.

None of the RCTs identified randomized participants to CACS versus no CACS strategies specifically. Data from RCTs are from those that randomized participants to coronary computed tomography angiography (CCTA) or functional testing and provided analyses related to use of CACS in conjunction with CCTA. Randomization was not always preserved for these analyses. SRs[9,11,15,16] identified for inclusion were of observational studies (to include a single-arm analysis of a RCT [ROMICAT-II]). One study[4] pooled individual patient data from CCTA arms of two RCTs. Safety information from two new systematic reviews[11,15] reported incidental findings based on various cardiac computed tomography (CTs), as no reviews specific to CACS were identified. Updated information on radiation safety were obtained from a recent consensus document[13], the NICE guideline[26], an AHRQ systematic review[25] and four studies.[14,18,19,22]

**Figure 2. Flow chart showing results of literature search**




* This study also provided economic data.

### 4.2 Identifying signals for re-review

Table 1 shows the original key questions, the conclusions of the original report, the conclusions from the 2018 signal search, the new sources of evidence, the new findings, and the recommendations of Aggregate Analytics, Inc. (AAI) regarding the need for update (Figure 1).

**Table 1. Summary table of findings from the previous report and new evidence identified by the signal search**

| Outcome | Conclusions from 2009 CER Executive Summary | New Sources of Evidence | New Findings | Conclusions from AAI |
|---|---|---|---|---|
| **Key Question 1: Evidence regarding test characteristics and reliability** | | | | |
| **Validity of test** | The role of CACS as a standalone diagnostic test is not clear. There is no consensus on threshold. Based on meta-analysis of LoE I/II studies<br>• A CACS > 0 is highly sensitive (99%, CI = 98% - 99%) for identifying the presence of obstructive CAD, however 5% (range 0% to 17%) of persons (1 – negative predictive value) with a negative test would have CAD (7 studies)<br>• At thresholds of ≥ 100 (5 studies) or ≥ 400 (3 studies) the sensitivity is lower (85% and 78% respectively) but specificity is improved (77% and 83%, respectively) | Observational studies:<br>ED setting:<br>Gottlieb 2010[12], Volger, 2013[28], Matsumura 2020[20]<br><br>Outpatient Settings:<br>Budoff 2013[5], von Ziegler 2014[29], Husman 2010[14], Qian 2010[23], | The role of CACS as a standalone diagnostic test remains unclear. A threshold CACS of >0 has been suggested as a gatekeep for discharge from the ER and for considering the need for additional testing. The validity (accuracy) of CACS versus ICA from 7 newer studies which are likely at low to moderately high ROB varied across study settings and CAD prevalence (see data abstraction):<br>• **ER Setting:** A CACS > 0 in 2 studies (Gottlieb, Volger) had low sensitivity (45%, 70.1%) for identifying obstructive CAD with a range of ~ 32% of those with a negative test (1-negative predictive value) having CAD (i.e. missed cases). Reported CAD prevalence ranged from 30% to 64% across these studies; one had only 20% of patients referred from the ER. One of the studies reported 91% sensitivity and 90% NPV at a threshold of >10 (10.5% CAD prevalence, von Ziegler)<br>• One ER-based study (Matsumura) reported 80% sensitivity, and 77% specificity at a CACS threshold of 27.4 in survivors of out of hospital cardiac arrest (CAD prevalence | Data from new studies provide some additional insight into the accuracy of CACS in two settings in which it has been suggested as a gatekeeper. Findings in the outpatient setting are reasonably consistent with the prior report and included one large, high quality study (N=4137). Findings from studies in the ER setting suggest lower study accuracy versus the prior report. Integrating new studies with those in the 2009 HTA meta-analyses would the section of the report (Criterion B1, B4). |

| Outcome | Conclusions from 2009 CER Executive Summary | New Sources of Evidence | New Findings | Conclusions from AAI |
|---|---|---|---|---|
| | | | 30%). 10% of those with a negative test would have had CAD.<br>• **Non-urgent or outpatient setting**: A CACS > 0 was highly sensitive in 2 studies (99% and 98.2% Budoff, von Zigeler) for identifying the presence of obstructive CAD with only 1% to 1.4% of CAD cases missed; CAD prevalence, 24.8% (N=230) and 50.5% (N= 4137). In 1 study with CAD prevalence of 24.8% (Budoff), at thresholds of ≥ 100 or ≥ 400 the sensitivity was lower (87.7% and 59.6%) but specificity improved from 41.6% at >0 to (and 71.1% and 88.4% respectively)<br>• Two additional studies in non-emergent settings (Husman, Qian) reported low sensitivity at thresholds of 100 (70.5%) and 133 (72.7%) with CAD prevalence of 67.9% and 54.1% respectively. Specificity at CACS >100 was 36.7% and 82.1% at a threshold of >133. | |
| **Reliability of test** | • The reliability of CACS (based on Agatston method) appears to be moderate to high based on 3 small LoE II studies and descriptions in it two validation studies | 1 observational study<br>Ann 2014[3] | • Authors report that there was low intra- and interrater variability with 256 slice MDCT based on mean values of absolute and percentage differences of independent measurements taken across 104 patients by two radiologists. | Conclusions from the previous report are still valid. No update is required (Criteria A1, B1-B4). |

| Outcome | Conclusions from 2009 CER Executive Summary | New Sources of Evidence | New Findings | Conclusions from AAI |
|---|---|---|---|---|
| **Key Question 2: Evidence regarding safety** | | | | |
| **Radiation** | • While simulation and modeling of the effects of radiation exposure provide important insights into the possible changes in risks, the true attributable risk from radiation-based diagnostic tests may be difficult to determine.<br>• Radiation exposure may be reduced to the extent that CACS use avoids doing angiography. On the other hand, exposures may be increased to the extent that positive CACS results in additional testing.<br>• A typical effective dose for CACS is estimated to be 3mSV (reported range 1-12mSv). CACS results may lead to additional testing which involves radiation.<br>• In a recently published simulation based on a median effective dose of 2.3 mSv, site-specific estimates for life-time risk of radiation-induced cancer suggest that most cases would be lung cancer (6/100,000 in men, 14/100,000 in women) or breast cancer (4/100,000 in women).<br>• Decision making should include discussion of the potential for such risks. | ACC/AHA 2018 Consensus Document[13]<br><br>AHRQ 2016 Noninvasive Testing for CAD[25]<br><br>NICE Guideline 2016[26]<br><br>Information CCTA RCT data: Lubbers 2016[19], Lubbers 2018[18], Pursnani, 2015[22] | • The 2018 ACC/AHA document describes radiation exposure reduction methods across testing modalities and models of excess risk for cancer and mortality related to radiation in general which are important to consider. Risks increase with increases in accumulated dose. Authors also indicate that radiation exposure directly to the heart and surrounding sensitive structures may be higher than the overall effective dose. The true attributable risks are difficult to determine.<br>• New equipment and techniques likely reduce radiation exposure for CACS; the usual effective dose range for quoted across sources for CACS is 0.7 to 5 mSV. Ranges from CCTA are from 0.5 to 30 mSv depending on equipment parameters and contrast use. (See data abstraction)<br>• Radiation exposure may be reduced to the extent that CACS use avoids doing either CT angiography or invasive coronary angiography. On the other hand, exposures may be increased to the extent that positive CACS results in additional testing that involves radiation. Authors of the | Conclusions from the previous report are still valid (criteria A-2 or B3-B4). |

| Outcome | Conclusions from 2009 CER Executive Summary | New Sources of Evidence | New Findings | Conclusions from AAI |
|---|---|---|---|---|
| | | | CRESCENT trial postulate that if CACS had not been used as a gatekeeper to CCTA, the median exposure for the CCTA arms would have increased. | |
| **Incidental findings** | • 7%-10% of symptomatic persons will have incidental findings during a CT scan for calcium scoring that require further diagnostic testing and a small percent, 1.2%, will require therapeutic intervention based on two studies in symptomatic persons. | SRs:<br>Kay 2019[15]<br>Flor 2013[11] | • Neither SR focused on use of CT specifically or solely for CACS<br>• Incidental findings during cardiac CT are common. One SR across 49 studies reports a median prevalence of incidental findings of 45% (7% to 100%) clinically significant extracardiac findings of 17% (range 1% to 67%) across 49 studies (Kay); the other SR reported a pooled prevalence of 44% (95%CI 35% to 54%) for at least one finding but only a 0.7% (95%CI 0.55 to 1.0%) prevalence of previous unknown malignancies (Flor) | Conclusions are still valid. New evidence does not signal re-review (criteria A-2 or B3-B4). |
| **Key Question 3: Evidence regarding clinical decision making and patient outcomes** | | | | |
| **Triage in emergency department** | • Five studies suggest that a CACS = 0 may allow discharge of patients with suspected CAD. These studies, however, vary in quality. None employed a comparison group and are considered case series. | Systematic review Chaikriangkrai 2016[9] (8 observational studies; 5 new since prior HTA)<br><br>Analysis of pooled IP data Bittner 2017[4] | • Based on low rates of cardiovascular events among patients with CACS = 0, studies postulate that calcium scoring could be used to safely discharge patients without further testing, serving as a type of triage method for this specific patient population.<br>• In one SR, in patients with CACS = 0 vs. CACS >0, lower pooled rates/risks of all-cause death or MI (0.5%/year vs. 3.5%/year; RR 0.19, 95% CI 0.08 to 0.47, $I^2$=0%; 5 | • Additional data from one SR and one IP data analysis does not change the conclusions of the previous report (criteria A-1 or A3) nor provide major changes in the evidence (Criteria B1-4). They could be used to update this section if a re-review is done. |

| Outcome | Conclusions from 2009 CER Executive Summary | New Sources of Evidence | New Findings | Conclusions from AAI |
|---|---|---|---|---|
| | | (from the CCTA arms of 2 new RCTs: ACRIN-PA, ROMICAT-II) | studies, n=2,891) and MACE (0.8%/year vs. 14.6%/year; RR 0.06, 95% CI 0.04 to 0.11, $I^2$=0%; 8 studies, n=3,556) were reported over a median follow-up 10.5 months.<br>Across one pooled analysis of IP data, patients with a CACS = 0 had lower frequencies of cardiovascular events and additional testing/procedures vs. those with CACS 1-10, 11-100, 101-400, and >400: MI (0.1% vs. 0%–6% [range across CACS >0 strata]) and UA (0.4% vs. 6%–38%) at discharge; additional testing during index visit (3.9% vs. 22%–48%); subsequent ICA (1% vs. 6%–46%) and revascularization (0.4% vs. 3%–26%); and MACE at 28 days (0% vs. 1%–2%). The prevalence of obstructive CAD in this population was 13.1%. | |
| **Triage in other clinical settings** | • One study reported that referral to conventional angiography increased with increasing CACS. No comparison group was employed. | RCTs<br>Lubbers 2016 (CRESCENT trial) [19]<br>Lubbers 2018 (CRESCENT-II trial)[18] | • 2 trials randomized patients with low to intermediate risk of CAD to CT (calcium scan + CCTA [with MPI in CRESCENT-II]) vs. functional testing. In the CT arms, patients were triaged based on initial calcium scan results.<br>• In the CRESCENT trial (N=350), patients with a CACS = 0 had no further testing; CACS 1–400 went on to CCTA; and CACS >400 went on to stress testing or ICA. | • The addition of two new RCTs which specifically triage patients based on calcium scores provides new evidence that could be used to update this section if a re-review was done (Criteria B1-2). However, CACS-specified utilization is not well reported. |

| Outcome | Conclusions from 2009 CER Executive Summary | New Sources of Evidence | New Findings | Conclusions from AAI |
|---|---|---|---|---|
| | | | ○ In the 98 patients with a CACS of 0, anginal symptoms occurred less frequently (data NR) and no patient required additional downstream testing* or experienced an adverse event† over 12 months.<br>○ When compared with functional testing, patients who received the full CT strategy (calcium scan + CCTA) required less additional downstream testing* (25% [60/238] vs. 53% [57/108], p<0.0001) and experienced fewer adverse events† [3% [8/239] vs. 10% [11/108], p=0.004) over 12 months.<br>• In the CRESCENT-II trial (N=268), patients with a CACS = 0 and a low-to-intermediate pretest probability of CAD had no further testing; those with CACS >0 or CACS = 0 and high pre-test probability of CAD underwent CCTA with MPI.<br>○ In the 45 patients with a CACS = 0, no MACEs‡ were reported over 6 months of follow-up; one patient (2%) had acute chest pain and ECG changes and underwent ICA however, the biomarkers and ICA were both negative. | |

| Outcome | Conclusions from 2009 CER Executive Summary | New Sources of Evidence | New Findings | Conclusions from AAI |
|---|---|---|---|---|
| | | | ○ When compared with functional testing, more patients who underwent the full CT strategy (calcium scan + CCTA) had relief of anginal symptoms at 6 months (38% vs. 28%, p=0.12) and fewer underwent ICA without a Class I indication for revascularization (1.5% vs. 7.2%, p=0.035; overall ICA rate was similar); MACE frequency was identical between groups (3%).<br>• Both trials postulate that exclusion of CAD on the basis of a negative calcium appears safe in the intermediate-(6 months) to longer (12 months) term and that discharging patients based on a CACS = 0 may help reduce additional testing and radiation exposure. The prevalence of CAD was unclear in these populations but the authors state it was "relatively low". | |
| **Prediction of future events** | • While 3 studies§ suggest that CACS is a predictor of future cardiac events, none evaluate the role of therapeutic interventions which may influence the occurrence of such events | ***Systematic review*** Lo-Kioeng-Shioe 2020[16] (19 observational studies; 17 new since prior HTA**) | • In one SR, few patients with a CACS = 0 had a cardiovascular event (1.2%) and those with CACS >0 (vs. CACS = 0) were at a higher risk for the composite outcome of all-cause mortality or nonfatal MI (RR 3.6, 95% CI 2.7 to 4.9, $I^2$=16%; 13 studies). Additionally, increased levels of CAC (>0, ≥100 and ≥400) were associated with | • These findings do not change the conclusions of the previous report (criteria A-1 or A3) nor provide major changes in the evidence for these analyses (Criteria B1-4). They could be used to update this section if a re-review is done. |

| Outcome | Conclusions from 2009 CER Executive Summary | New Sources of Evidence | New Findings | Conclusions from AAI |
|---|---|---|---|---|
| | | ***Analysis of pooled IP data***<br>Bittner 2017[4] (from the CCTA arms of 2 RCTs: ACRIN-PA, ROMICAT-II)<br><br>***RCT***<br>Budoff 2017[6] (subanalysis of the PROMISE trial)<br><br>***Registry***<br>Villines 2011[27]; Al-Mallah 2014 (CONFIRM registry)[2] | increased risk for MACEs (see data abstraction). Pooled estimates of HR's for MACE adjusted for clinical risk factors showed a similar pattern across strata. (Proportion with obstructive CAD varied: 14%–72%).<br>• One analysis of pooled IP data, found that CACS independently predicted the risk of ACS (adj. OR 2.88, 95% CI 2.27 to 3.56), ICA (adj. OR 2.59, 95% CI 2.10 to 3.20) and downstream testing (adj. OR, 2.79 (95% CI 2.37 to 3.22). Furthermore, the risk increased with increasing CAC scores (>0–10, >10–100, >100–400, and >400) (see data abstraction). The prevalence of obstructive CAD in this population was 13.1%.<br>• One subanalysis of the PROMISE trial compared CACS to functional testing and concluded that a CACS = 0 could safely exclude future cardiovascular events whereas a normal functional scan could not (most events in this group occurred in patients who did not have inducible myocardial ischemia). Patients with a CACS = 0 had a low incidence of future cardiovascular events: cardiovascular death/MI (0.6%), cardiovascular death/MI/UA (1.0%), and all-cause death/MI/UA (1.4%). | |

| Outcome | Conclusions from 2009 CER Executive Summary | New Sources of Evidence | New Findings | Conclusions from AAI |
|---|---|---|---|---|
| | | | Furthermore, the risks of such events increased with increasing CACS (1–99, 100–400, >400) (see abstraction).<br>• One registry study reported that increasing CAC levels were independently predictive of the composite of death or nonfatal MI (N=8,627): 1–9 (adj. HR 0.8, 95% CI 0.3, 2.3), 10–99 (adj. HR 2.3, 95% CI 1.3, 3.9), 100–399 (adj. HR 3.6, 95% CI 2.1, 6.0), ≥400 (adj. HR 4.8, 95% CI 2.9, 8.7) [Al-Mallah 2014]; and the composite of all-cause mortality, nonfatal MI, late revascularization (N=8,907): 1–100 (adj. HR 2.82, 95% CI 1.83, 4.35), 101–400 (adj. HR 7.16, 95% CI 4.66, 11.0), >400 (adj. HR 9.78, 95% CI 6.29, 15.2) [Villines 2011]. The prevalence of CAD was 48%–50%, and of obstructive CAD 9%–16%, across both publications. | |
| **Key Question 4: Evidence regarding performance in special populations** | | | | |
| **Diabetes** | • Sensitivity (98-99%) and specificity (25%-39%) of CACS for the detection of any calcium is similar to that for general populations from the meta-analysis of LoE I/II studies but a higher percent (11%-25%) of persons (1 – negative predictive value) with a negative test would have CAD based on two moderate quality studies. | No SRs or new high-quality studies identified | No new evidence. | Conclusions from the previous report are still valid. No update is required (Criteria A1, B1-B4). |
| **Gender** | • Three studies evaluated CACS characteristics in women vs. men. Sensitivities were similar for both groups at CACS > 0. Specificities for women ranged for 41%-66% and those for men 24%-57%, somewhat lower. | Observational studies:<br>Von Ziegler 2014[29]<br>Budoff 2013[5] | • The largest study (N=2780 males, 1357 females; mean age 61 years, von Ziegler) reported the same sensitivity and NPVs for both sexes at CACS = 0 (99%) based on | Findings from these studies would update the prior HTA, but in and of themselves do not signal re-review (Criteria A1, B1-B4). |

| Outcome | Conclusions from 2009 CER Executive Summary | New Sources of Evidence | New Findings | Conclusions from AAI |
|---|---|---|---|---|
| | • A higher percent (4% - 11%) of men (1 – negative predictive value) with a negative test would have CAD compared with women (0%-4%)., however, the prevalence of CAD was lower in women (36%-47%) compared with men (53%-70%)<br>• Women present with CAD at an older age (~10 years) than men, which may account for the differences | | an ICA reference of ≥50% obstruction. Prevalence of CAD in males was 56.9% compared with 37.4% in females. At higher CACS thresholds, the sensitivity was lower as was 1-NPV for females compared with males. For example, at a CACS threshold >100, the sensitivity, NPV and 1-NPV in males were 73%, 70% and 30% compared with 63%, 79% and 21%respectively. At ICA threshold of ≥70% obstruction a similar pattern was noted. (see data abstraction)<br>• In the smaller study (N= 138 male, 94 females), lower sensitivity for females versus males (90% vs. 100%) but higher specificity (49.4% versus 34.4%) were seen.<br>• Differences in prevalence between men and women and the impact of age may partially explain the differences. | |
| **Age** | • Seven LoE I/II validation studies evaluated the influence of age on CACS. In general, the prevalence of coronary artery calcium increases with age.<br>• There are conflicting results regarding test performance at various ages. | No SRs or new high-quality studies identified | No new evidence. | Conclusions from the previous report are still valid. No update is required (Criteria A1, B1-B4). |
| **Key Question 5: Evidence regarding cost-effectiveness** | | | | |
| | • Two moderate quality studies suggest that at a disease prevalence of up to 70%, CACS may be more cost effective than conventional angiography, however incremental cost effectiveness is not described. | 4 Economic studies Bittner 2017[4], (US, international) | Three studies (two from the UK, one from Portugal) suggest that CACS could be cost-effective as a gatekeeper for downstream test vs. alternative strategies. | While these additional economic studies would update the prior HTA, they do not in and of themselves signal a review update. |

| Outcome | Conclusions from 2009 CER Executive Summary | New Sources of Evidence | New Findings | Conclusions from AAI |
|---|---|---|---|---|
| | • Cost-effectiveness is influenced by disease prevalence and CACS score cut-off (and corresponding sensitivity and specificity)<br>• The influence of additional testing to reflect clinical practice needs to be more fully considered.<br>• The influence of false-negative and false positive results is unclear and models did not consider follow-up of incidental findings.<br>• There is insufficient evidence for conclusions on the long-term cost utility of CACS compared with CCA alone or with regard to other non-invasive tests. | Ferreira 2014[10] (Portugal), McKavanagh 2013[21] (UK), Raman 2012[24] (UK) | • Raman: CACS prior to myocardial perfusion imaging in patients with suspected stable angina with <30% pretest probability may be cost-effective vs. stress ECG at a willingness to pay of £30,000/QALY.<br>• McKavanagh: Cost per number of significant stenoses identified was lower with CACS vs. Diamond and Forrester (DF) criteria by £93.4 and was considered better for risk stratification and targeting of clinical resources.<br>• Ferreira: In patients with PLD ranging from 10% to 90%. CACS >0 as a gatekeeper prior to CCTA was considered cost-effective and the preferred strategy at a threshold of €5,000 per additional correct diagnosis and CACS of 0 could be cost effective as a "rule out" strategy in patients with PLD of 20% to 30% across 7 modeled diagnostic strategies.<br>• Bittner: The cost to diagnose and treat 1 patient with acute coronary syndrome (MI or unstable angina was lowest in patients with CACS >400; authors conclude that increasing cost with increasing CACS were appropriate given higher prevalence of obstructive CAD | |

| Outcome | Conclusions from 2009 CER Executive Summary | New Sources of Evidence | New Findings | Conclusions from AAI |
|---|---|---|---|---|
| | | | and ACS with higher CACS and that cost-efficient testing and good diagnostic yield can be achieved even at higher CACS burden. | |

ACS = acute coronary syndrome; CACS = coronary artery calcium scoring; CAD = coronary artery disease; CCTA = coronary computed tomography angiography; CI = confidence interval; ECG = electrocardiogram; ED = emergency department; HR = hazard ratio; ICA = invasive coronary angiography; IP = individual patient; MACE = major adverse cardiovascular events; MI = myocardial infarction; MPI = myocardial perfusion imaging; OR = odds ratio; PLD = pre-test likelihood of disease; QALY = quality adjusted life years; RCT = randomized controlled trial; RR = risk ratio; SR = systematic review; UA = unstable angina; UK = United Kingdom.

*Includes noninvasive testing (13% vs. 42%), invasive angiography (9% vs. 8%), and both (3% vs. 3%).

†Includes all-cause mortality, nonfatal MI, unstable angina, nonfatal stroke, late revascularizations, and unplanned cardiac evaluations (acute chest pain at ED, palpitations at ED).

‡death, nonfatal MI, UA, urgent revascularization and stroke

§Three studies were conducted populations from non-emergency settings. In general, all report that CACS above a low threshold appears to be a predictor for hard events and that a CACS = 0 or one that is "low" was associated with few such events. The risk for future events increased with increasing CACS.

**Includes Al-Mallah 2014 (CONFIRM registry)

## 5. Summary of Results and Conclusions

There has been a substantial increase in the number of publications (2,094 citations) related to CACS subsequent to the 2009 HTA however most of the publications relate to screening of asymptomatic populations and/or use of CACS as an adjunct to CCTA or other testing that were not part of the original HTA Scope. Should a re-review be done, consideration might be given to expanding the scope to evaluate the incremental value of CACS in conjunction with other diagnostic tests.

Anecdotally, about 75% of CCTA protocols include evaluation of CACS. The negative predictive value of CCTA decreases with increasing CACS and extremely high CACS (>1000) produces artifacts that limit the value of CCTA. A CACS threshold of 0 has been suggested to triage emergency department patients for potential discharge and as a potential "gatekeeper" in various settings to obviate the need for CT angiography or other additional tests. While a 2010 NICE guideline recommended that a CACS score of 0 could be used to rule out CAD in patient with stable chest pain and low pre-test disease probability and act as a gatekeeper to CCTA, the 2016 update removes this recommendation and recommends that patients with new onset chest pain be investigated with CCTA as a first line investigation.[8,26]

New evidence on test accuracy and additional studies describing use of CACS as a gatekeeper to inform decision making regarding additional testing in the outpatient setting or discharge from the emergency department may support performance of a re-review, however, consistent with the previous report, newer publications, clinical guidelines and anecdotal information from clinical experts, CACS is not used as a "stand alone" diagnostic test for determining the presence of CAD and is generally not used in symptomatic patients.

**Key Question 1:**

- Regarding test accuracy (validity), the findings from seven new observational studies that appear to be at low to moderately high risk of bias provide some additional insight into the accuracy of CACS versus ICA (≥ 50% stenosis) in two settings in which it has been suggested as a gatekeeper (Criteria B1, B4). Studies were predominantly male (59% to 77%). Across accuracy studies in the prior report, CACS >0 was considered highly sensitive (99%) but 5% of obstructive CAD would be missed at this threshold. The prior report did not describe accuracy by setting.
    - Test accuracy reported in three new studies in an emergency department setting suggest that CACS >0 had low sensitivity for identifying obstructive CAD and ~32% of patients with a negative test (that presumably would have been discharged) would have CAD. These findings suggest lower accuracy than described in the original report.
    - In the outpatient setting, a CACS >0 was highly sensitive (98-99%) in two new studies (consistent with the prior report) with only 1% to 1.4% of those with a negative test having obstructive CAD, which is slightly lower that pooled estimates in the prior report. The larges study enrolled 4137 patients[29] and appears to be at low risk of bias.
- One new study suggests that intra- and inter-rater reliability may be high for CACS obtained via 256 slice MDCT.[3] New evidence does not signal an update review (Criteria A2, B3, B4).

**Key Question 2:**

Radiation safety:

- Changes in the past decade to equipment and refinement of techniques for image acquisition have led to potential reductions in radiation exposure during CACS and CCTA.[1,30] Radiation exposure is dependent upon the equipment used and technical parameters employed during imaging.[7,13] Reported ranges for "overall effective dose" specific for CACS across new sources tended to be similar in the original HTA (generally <1–3 mSv in newer studies). Exposure directly to the heart and surrounding sensitive structures may be higher than the overall effective dose,

however. CCTA dose ranges were higher than CACS doses and more variable, which is also consistent with the previous report.

- Radiation exposure may be reduced to the extent that CACS use avoids doing either CT angiography, myocardial perfusion imaging or invasive coronary angiography. On the other hand, exposures may be increased to the extent that positive CACS results in additional testing that involves radiation. Authors of the CRESCENT trials[17-19] postulate that if CACS had not been used as a gatekeeper to CCTA, the median exposure for the CCTA arms would have increased, however supporting data are unclear.
- New evidence does not signal an update review (Criteria A2, B3, B4)

Incidental findings:

- Incidental findings during cardiac CT (whether for CACS or other reasons) are common (44% and 45%) based on two systematic reviews; A median prevalence of clinically important findings was 17% (1% to 67%) in one SR[15] and the other reported with 0.7% prevalence of previously unknown malignancies[11]. New evidence does not signal an update review (Criteria A2, B3, B4)

**Key Question 3:**

None of the included studies evaluated the impact of specific clinical decisions for treatment or further testing based on CACS score and followed patients to final outcomes based on those decisions.

**Key Question 3: Evidence regarding clinical decision making and patient outcomes**

- One SR and one analysis of pooled individual-patient (IP) data from the CCTA arms of the ACRIN-PA and the ROMICAT-II trials were identified which evaluated the use of CACS for **triage in the emergency department (ED)**.
    - Both studies found that patients presenting to the ED who had CACS = 0 (vs. CACS >0) had lower rates/risks of adverse events, to include all-cause death or MI and MACE over a median follow-up of 10.5 months in the SR, and MI and UA at discharge and MACE at 28 days in the pooled IP data analysis; the latter also reported lower rates of additional testing during index visit, subsequent ICA, and subsequent revascularization within 28 days.
    - Both studies postulate that initial CAC testing could be used to safely discharge patients without further testing, serving as a type of triage method for this patient population presenting to the ED. Data from these two studies does not change the conclusions of the previous report (criteria A-1 or A3) nor provide major changes in the evidence (Criteria B1-4). They could be used to update this section if a re-review is done.
- Two RCTs by the same author group (CRESCENT and CRESCENT-II) were identified which evaluated the use of CACS for **triage in other clinical settings**.
    - Both trials included patients with low to intermediate risk of CAD and randomized them to a CT strategy (calcium scan followed by CCTA [with MPI in CRESCENT-II]) versus functional testing. In the CT arms, patients were triaged based on initial calcium scan results (in both trials, patients with a CACS = 0 received no further testing).
    - In both RCTs, few to no events (i.e., angina symptoms, MACE, downstream testing) occurred in patients with a CACS = 0 who received no further testing over follow-ups of 6 to 12 months. When compared with functional testing, in general, patients who received the CT strategy (calcium scan + CCTA [with MPI in CRESCENT-II]) required less additional downstream testing and experienced fewer anginal symptoms and fewer adverse events.
    - Both trials suggest an uneventful intermediate-to longer-term outcome when CAD is excluded on the basis of a negative calcium scan and indicate that calcium scanning may have a role in the triage of patients in non-ED settings.

  - The addition of two new RCTs which specifically triage patients based on calcium scores provides new evidence that could be used to update this section if a re-review was done (Criteria B1-2). However CACS-specified utilization is not well reported.
- Four studies (1 SR, 1 analysis of pooled IP data from the CCTA arms of the ACRIN-PA and the ROMICAT-II trials, 1 subanalysis of the PROMISE trial, and one registry [CONFIRM]) were identified which evaluated the use of CACS for the **prediction of future events**.
  - Across all studies, CACS was found to be a strong and often independent predictor of future cardiovascular events; furthermore, the risk of such events increased with increasing CACS categories. These findings do not change the conclusions of the previous report (criteria A-1 or A3) nor provide major changes in the evidence for these analyses (Criteria B1-4). They could be used to update this section if a re-review is done.

**Key Question 4:**

- Two studies in non-emergent outpatient settings reported diagnostic accuracy data by sex but do not explicitly test for differential test performance and the impact of age was not examined.
  - In the largest study[29] (N= 4127), with the exception of PPV, test accuracy was the same for males and females at CACS=0 using >50% obstruction on ICA. At higher CACS thresholds, the sensitivity was lower as was 1-NPV for females compared with males. Prevalence of CAD in males was 56.9% compared with 37.4% in females. (See data abstraction)
  - The smaller study[5] noted lower sensitivity for females versus males (90% vs. 100%) but higher specificity (49.4% versus 34.4%).
- Findings from these studies would update the prior HTA, but in and of themselves do not signal re-review (Criteria A1, B1-B4).

**Key Question 5:**

- Four new economic studies were identified. Two studies were performed in the UK[21,24], one in Portugal[10] the fourth used single CT arm data from an international RCT but reported results in US dollars.
- Three of the studies suggest that CACS could be cost-effective as a gatekeeper for downstream testing versus other stress EGC testing, the Diamond and Forrester criteria and as part of a "rule out" strategy prior to CCTA or other testing. Cost effectiveness appears to be primarily for patients with a pretest likelihood of CAD <30%.
- In the fourth study[4], the cost to diagnose and treat 1 patient with acute coronary syndrome (either MI or unstable angina pectoris) was lowest in patients with CACS >400. Authors report increases in diagnostic cost with increasing CACS scores but note that ACS and obstructive CAD are more prevalent with high CACS.
- While these newer economic studies would update the prior HTA, they do not in and of themselves signal a review update.

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# APPENDIX A. SEARCH STRATEGIES

**Embase Search**

Search Dates: April 4, 2009 to April 14, 2020

Total hits before deduplication: 768

| | | |
|---|---|---|
| #1 | **'coronary artery disease'**/exp OR **'angina pectoris'**/exp OR **'ischemic heart disease'**/exp | 823,760 |
| #2 | **'cardiac computed tomography'**/exp OR **'computer assisted tomography'**/exp OR **'coronary angiography'**/exp | 1,094,661 |
| #3 | **'coronary artery calcium'**/exp OR **'coronary artery calcium scanning'**/exp OR **'coronary artery calcium score'**/exp OR **'calcium score'**/exp | 5,460 |
| #4 | **'sensitivity and specificity'**/exp OR **'predictive value'**/exp | 459,855 |
| #5 | #1 AND #2 AND #3 AND #4 AND [english]/lim AND [abstracts]/lim AND [1-4-2009]/sd NOT [15-4-2020]/sd | 498 |
| #6 | **'validation study'** OR **'reproducibility'** | 320,241 |
| #7 | #1 AND #2 AND #3 AND #6 AND [english]/lim AND [abstracts]/lim AND [1-4-2009]/sd NOT [15-4-2020]/sd | 39 |
| #8 | **'cost'**/mj OR **'economic evaluation'**/exp | 314,839 |
| #9 | #1 AND #2 AND #3 AND #8 AND [english]/lim AND [abstracts]/lim AND [1-4-2009]/sd NOT [15-4-2020]/sd | 52 |
| #10 | **'clinical decision making'**/exp OR **'decision making'**/exp | 368,565 |
| #11 | #1 AND #2 AND #3 AND #10 AND [english]/lim AND [abstracts]/lim AND [1-4-2009]/sd NOT [15-4-2020]/sd | 39 |
| #12 | **'safety'**/exp OR **'device safety'**/exp OR **'incidental finding'**/exp OR **'adverse event'**/exp OR **'ionizing radiation'**/exp | 1,140,398 |
| #13 | #1 AND #2 AND #3 AND #12 AND [english]/lim AND [abstracts]/lim AND [1-4-2009]/sd NOT [15-4-2020]/sd | 140 |

**Pubmed Search**

Search Dates: February 1, 2009 to April 15, 2020

Total hits before deduplication: 1818

| | | |
|---|---|---|
| 1 | coronary artery calcium OR coronary artery calcium scor* OR CACS OR coronary calcium OR calcium scan | 27,325 |
| 2 | "Coronary Angiography"[Mesh] OR "Computed Tomography Angiography" [Mesh] OR "Tomography, X-Ray Computed"[Mesh] OR "Tomography, Spiral Computed"[Mesh] OR "Multidetector Computed Tomography"[Mesh] | 313,503 |
| 3 | "Angina Pectoris"[Mesh] OR "Coronary Artery Disease"[Mesh] OR "Coronary Disease"[Mesh] OR "Myocardial Ischemia"[Mesh] | 207,840 |
| 4 | ("Sensitivity and Specificity"[Mesh] OR "Predictive Value of Tests"[Mesh]) OR "Prospective Studies"[Mesh] | 840,548 |
| 5 | ("2009/02/01"[Date - Publication] : "1200"[Date - Publication]) | 4,949,551 |
| 6 | #1 AND #2 AND #3 AND #4 AND #5 | 910 |
| 7 | #2 AND #3 AND #5 AND "Decision Making"[Mesh] | 75 |
| 8 | #2 AND #3 AND #5 AND "Incidental Findings" [Mesh] | 89 |
| 9 | "Safety"[Mesh] OR "Equipment Safety"[Mesh] | 50,000 |
| 10 | #2 AND #3 AND #5 AND #9 | 75 |
| 11 | #10 NOT (stent) | 52 |
| 12 | validation study[Publication Type] OR "Reproducibility of Results"[Mesh] | 318,537 |
| 13 | #12 AND #1 AND #2 AND #3 | 376 |
| 14 | #1 AND #2 AND #3 AND ("Radiation, Ionizing"[Mesh] OR "Radiation, Ionizing/adverse effects"[Mesh]) | 2 |

| | | |
|---|---|---|
| 15 | ("Coronary Angiography/economics"[Mesh] OR "Tomography, X-Ray Computed/economics"[Mesh]) OR "Tomography, Spiral Computed/economics"[Mesh] | 1,348 |
| 16 | #15 AND #2 AND #3 | 209 |
| 17 | (calcium score) AND systematic[sb] | 105 |

Total hits from combined search before deduplication: 2586

**Total hits from combined search after deduplication: 2087**

## APPENDIX B. SUMMARY OF INCLUDED STUDIES

**Appendix Table B1. Data abstraction for studies included for key questions 1 (test characteristics)**

| Author (year) | Patients (sex, age, risk, etc.) | Type of CT scanner Setting | Timing of scans | Total N | CAD, n | CAD, % | ICA threshold(s) | CACS threshold(s) | Sens-itivity | Spec-ificity | PPV | NPV | 1-NPV |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Budoff (2013) | Mean age: 57 years<br>% female: 41%<br>Risk level: NR<br>All pts had chest pain and were clinically referred for ICA | 64-slice MDCT<br>Outpatient clinic; non-emergent | NR | 230 | 57 | 24.8% | ≥50% stenosis | >0 | 98.2% | 41.6% | 35.7% | 98.6% | 1.4% |
| | | | | | | | | >100 | 87.7% | 71.1% | 50.0% | 94.6% | 5.4% |
| | | | | | | | | >400 | 59.6% | 88.4% | 63.0% | 86.9% | 13.1% |
| von Ziegler (2014) | Mean age: 61 years<br>% female: 33%<br>Percent of pts w/o any cardiovascular risk factors: 16.8%<br>Mean number of cardio-vascular risk factors: 2.1<br>Chest pain: 100% | 64-slice MDCT or dual-source CT imager in thin-section mode<br>Outpatient clinic; non-emergent | 91% of patients had ICA performed within 10 days following CACS | 4137 | 2089 | 50.5% | ≥50% stenosis | 0 | 99.0% | 34.0% | 24.0% | 99.0% | 1.0% |
| | | | | | | | | >10 | 91.0% | NR | NR | 90.0% | 10.0% |
| Gottlieb (2010) | Mean age: 59 years<br>% female: 27%<br>Pre-test probability of CAD<br>-low: 5% (14/291)<br>-intermediate: 75% (218/291)<br>-high: 20% (59/291) | 64-slice MDCT<br>20% of pts referred from emergency department | Pts clinically referred for ICA were asked to undergo CACS up to 30 days before | 291 | 163 | 56.0% | ≥50% stenosis | 0 | 45.0% | 91.0% | 81.0% | 68.0% | 32.0% |

| Author (year) | Patients (sex, age, risk, etc.) | Type of CT scanner Setting | Timing of scans | Total N | CAD, n | CAD, % | ICA threshold(s) | CACS threshold(s) | Sens-itivity | Spec-ificity | PPV | NPV | 1-NPV |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Husmann (2010) | Mean age: 61 years<br>% female: 39%<br>Risk level/prob. of CAD: NR | 64-slice LightSpeed VCT XT scanner<br>Non-emergent | NR | 61 | 33 | 54.1% | ≥50% stenosis | 133 | 72.7% | 82.1% | 82.8% | 71.9% | 28.1% |
| Qian (2010) | Mean age: 66 years<br>% female: 38%<br>Risk level/prob. of CAD: NR | 32x2 MDCT<br>Non-emergent | Scans were conducted within 12 months of one another | 84 | 57 | 67.9% | ≥50% stenosis | 100 | 70.5% | 36.7% | 69.4% | 37.9% | 62.1% |
| | | | | | | | | 400 | 47.5% | 60.0% | 70.7% | 36.0% | 64.0% |
| | | | | 84 | 33 | 39.3% | ≥70% stenosis | 100 | 77.1% | 37.5% | 43.5% | 72.4% | 27.6% |
| | | | | | | | | 400 | 60.0% | 64.3% | 51.2% | 72.0% | 28.0% |
| Vogler (2013) | Mean age: 66 years<br>% female: 38%<br>Risk level for CAD: intermediate | Dual-source CT<br>Emergent (pts presented in ambulance) | ICA was performed within 4 months after CACS | 87 | 56 | 64.4% | ≥50% stenosis | >0 | 70.1% | 100.0% | 16.1% | 68.3% | 31.7% |
| | | | | | | | | ≥10 | 71.3% | 96.4% | 25.8% | 70.1% | 29.9% |
| Matsumura (2020)* | Mean age: 66 years<br>% female: 23%<br>Risk level for CAD: intermediate | 80- or 64-slice CT<br>Emergency Department | NR | 100 | 30 | 30.0% | ≥50% stenosis | 27.4 | 80% | 77.0% | 60.0% | 90.0% | 10.0% |

CACS = coronary artery calcium score; CAD = coronary artery disease; CT = computed tomography; ICA = invasive coronary angiography; MDCT = multi-detector computed tomography; NPV = negative predictive value; NR = not reported; PPV = positive predictive value.

*Authors evaluated the value of CACS to identify unstable coronary lesions in patients who were survivors of out-of-hospital cardiac arrest; Unstable lesion characteristics on ICA included irregular, irregular eccentric coronary stenosis, with or without the presence of coronary thrombus, and with a narrow neck, acute angles, or craters, which were thought to represent disrupted plaque

**Appendix Table B2. Study quality (risk of bias) assessment components for studies identified for KQ1**

| Author (year) | Do they report TP, FP, TN, FN? | CACS & ICA performed independently? | Did all patients get both tests? | Blinded CACS and ICA interpretation? |
|---|---|---|---|---|
| Budoff (2013) | N | Y | Y | Y |
| von Ziegler (2014) | Y | Y | Y | Y |
| Gottlieb (2010) | N | N | Y | Y |
| Husmann (2010) | N | Y | Y | Y |
| Qian (2010) | N | Y | Y | NR |
| Vogler (2013) | Y | Y | Y | NR |
| Matsumura (2020) | No | Unclear | Y | Unclear |

CACS = coronary artery calcium score; FN = false negative; FP = false positive; ICA = invasive coronary angiography; N = no; NR = not reported; TN = true negative; TP = true positive; Y = yes.

**Appendix Table B3. Data abstraction for the single study identified (Ann 2014) addressing the reproducibility of CACS for KQ1**

| Author, year | Study and patient characteristics | Data |
|---|---|---|
| Ann, 2014 | N=104<br><br>**Mean age**: 63 years<br><br>**% male: 57%**<br><br>**Type of scanner used**: 256-slice MDCT scans using 0.8-mm slice thickness. | **Variability between observers and MDCT scan measurements represented by the absolute difference, mean (SD)**<br>- inter-scan/interobserver: 14.45 (21.84)<br>- intra-scan/intra-observer: 1.75 (5.85)<br>- intra-scan/inter-observer: 3.3 (9.1)<br>- inter-scan/intra-observer: 13.45 (20.7)<br><br>**Variability between observers and MDCT scan measurements represented by the percentage differences, mean (SD)**<br>- inter-scan/interobserver: 12.51% (21.84%)<br>- intra-scan/intra-observer: 1.26% (3.69%)<br>- intra-scan/inter-observer: 4.8% (21.3 %)<br>- inter-scan/intra-observer 10.04% (10.46 %) |

MDCT = multidetector computed tomography

**Appendix Table B4. Additional prognostic study reporting safety data addressing KQ2***

| Author, year | Purpose | Patient population and CT characteristics | Primary Outcomes | Evidence-base Used | Primary Conclusions |
|---|---|---|---|---|---|
| **Pursnani, 2015** | To determine the value of CAC scan in patients with acute chest pain undergoing CCTA in the emergency department. | **N = 473**<br>**Mean age**: 54 years<br>**% female**: 47%<br><br>**Pre-test probability**: low to intermediate<br><br>**Discharge diagnosis during index visit**<br>• Noncardiac CP: 86% (n=407)<br>• Noncoronary cardiac CP: 1% (n=6)<br>• Coronary CP, not ACS: 5% (n=22)<br>• ACS: 8% (n=38)<br>• Unstable angina pectoris: 7% (n=32)<br>• MI: 1% (n=6)<br><br>**Type of scanner used**: 64-slice multidetector CT or newer | ACS (i.e., UA and MI during index hospitalization); MACE (i.e., death, MI, UA or urgent coronary revascularization within 28 days) | Subanalysis of the ROMICAT-II trial; includes only patients randomized to the CCTA arm, all of whom underwent CAC testing as well | **Effective Mean Radiation Dose (mSv), CAC alone vs. CCTA alone**<br>• All protocols and scanners: 1.4 ± 0.7 vs. 9.9 ± 4.9<br>• Prospectively gated CCTA (n=63): 1.5 ± 0.5 vs. 6.5 ± 3.8<br>• Retrospectively gated CCTA (n=410): 1.4 ± 0.7 vs. 10.4 ± 4.9<br>• 128-slice DSCT (n=78): 0.5 ± 0.3 vs. 5.7 ± 3.7<br>• CT scanners, excluding 128-slice DSCT (n=395): 1.6 ± 0.6 vs. 10.7 ± 4.7<br>○ the mean effective radiation dose of a CAC scan is 14% of that for CCTA<br>○ for the prospective ECG-triggered CCTA, the CAC scan represents 23% of the radiation dose of CCTA |

ACS = acute coronary syndrome; CAC = coronary artery calcium; CCTA = cardiac computed tomography angiography; CT =-computed tomography; DSCT = dual slice CT; MACE = major adverse cardiac event; MI = myocardial infarction; UA = unstable angina.

* This is data related to the prognostic value of CACS reported in this study is included in the Chaikriangkrai 2016 SR and also the Bittner 2017 analysis of pooled individual patient data. Thus, only the safety data reported by this study are included here.

**Appendix Table B5. Summary of publications reporting radiation exposure (KQ2) from CACS and CCTA, separately**

| Scan type | Author, year | Total effective dose (mSv)* Reported as mean (SD) unless otherwise stated |
|---|---|---|
| **CACS** | Skelly, 2016 (AHRQ SR) | Range from included studies: 0.69 to 0.80 |
| | Hirshfeld, 2018 (consensus document)† | Range from included studies: 1.0 to 5.0 |
| | NICE, 2016 (guideline) | Range from included studies: 1.0 to 3.0 |
| | Husmann, 2010‡ | 2.1 (0.7) |
| | Pursnani, 2015‡ | All protocols and scanners: 1.4 (0.7)§ |
| | | Prospectively gated CCTA: 1.5 (0.5) |
| | | Retrospectively gated CCTA: 1.4 (0.7) |
| | | 128-slice DSCT: 0.5 (0.3) |
| | | CT scanners, excluding 128-slice DSCT: 1.6 (0.6) |
| | Lubbers, 2016‡ | 1.3 (1.1) |
| | Lubbers, 2018‡ | 1.3 (0.7) |
| **CCTA** | Skelly, 2016 (AHRQ SR) | Range from included studies: 3.8 to 15.1 |
| | Hirshfeld, 2018 (consensus document)† | Helical, no tube current modulation: 8.0 to 30 |
| | | Helical, tube current modulation: 6.0 to 20 |
| | | Prospectively triggered axial: 0.5 to 7.0 |
| | | High-pitch helical: <0.5 to 3.0 |
| | NICE, 2016 (guideline) | 2.0 to 5.0 |
| | Carpeggiani, 2017** | 11.2 (8.1) |
| | Husmann, 2010‡ | 1.1 (0.1) |
| | Pursnani, 2015‡ | All protocols and scanners: 9.9 (4.9)§ |
| | | Prospectively gated CCTA: 6.5 (3.8) |
| | | Retrospectively gated CCTA: 10.4 (4.9) |
| | | 128-slice DSCT (n=78): 5.7 (3.7) |
| | | CT scanners, excluding 128-slice DSCT: 10.7 (4.7) |
| | Lubbers, 2016‡ | 4.1 (4.4) |
| | Lubbers, 2018‡ | 3.5 (3.0) |

CACS = coronary artery calcium score; CCTA = coronary computed tomography angiography; CT = computed tomography; DSCT = dual source computed tomography.

*Calculated whole-body quantity used to roughly compare potential stochastic risks from different partial body exposures. It is expressed as the uniform whole-body dose that would confer the stochastic risk equivalent to that caused by a regional exposure.

†The data included in this consensus document were reproduced with permission from Einstein, 2014.
Einstein AJ, Berman DS, Min JK, et al. Patient-centered imaging: shared decision making for cardiac imaging procedures with exposure to ionizing radiation. J Am Coll Cardiol. 2014 Apr 22;63(15):1480-9. PMID: 24530677.

‡For data on patient information and hypothesized reduction in exposure with use of CACS as a gatekeeper for additional testing, refer to the full data abstraction (Appendix Table B4 and B9) and results section.

§ The mean effective radiation dose of a CAC scan is 14% of that for CCTA. For the prospective ECG-triggered CCTA, the CAC scan represents 23% of the radiation dose of CCTA.

**Based on 476 exams with primary aim to detect and characterize ischemic heart disease performed as part of the RADIationdOse subproject of the EVINCI study. Doses varied substantially across 12 study centers)

**Appendix Table B6. Summary of radiation exposure reported in CRESCENT and CRESCENT II* trials for CACS + CCTA (complete CT evaluation)**

| Trial | Author, year | Radiation Exposure |
|---|---|---|
| CRESCENT trial | Lubbers (2016) | **Proportion with any radiation (mSv) exposure, % (n/N)**<br>*CT (CACS + CCTA) vs. functional testing:*<br>99.6% (241/242) vs. 42.6% (46/108)<br><br>**Mean cumulative radiation dose (mSv), mean (SD)**<br>*CT (CACS + CCTA) vs. functional testing*:<br>6.6 (8.7) vs. 6.1 (9.3), p<0.0001 |
| CRESCENT trial sub analysis | Lubbers (2017) | **Radiation dose for complete cardiac CT (CACS + CCTA)**<br>Females: median 1.7 (IQR 0.8 to 4.7); mean 3.7 (SD 4.2)<br>Males: median 2.6 (IQR 1.0 to 6.8); mean 4.6 (SD 4.8)<br><br>**Cumulative radiation dose (mSv) (appears to include downstream testing)**<br>Females:<br>- CT: median 4.7 (IQR, 0.9 to 7.9); mean 5.3 (SD 5.5)<br>- Functional testing: median 0 (IQR, 0 to 12.5); mean 6.3 (SD 10.3)<br>p=0.005<br>Males:<br>- CT: median 4.7 (IQR, 1.1 to 11.5); mean 8.2 (SD 11.2)<br>- Functional testing: median 0 (IQR, 0 to 14.0); mean 5.8 (SD 8.1)<br>p<0.001<br>Interaction p-value: 0.097<br><br>**Cumulative radiation dose in women <60 years**: Median 1.1 mSv (IQR, 0.8 to 1.5), mean 1.4 (SD 1.3) mSv |
| CRESCENT-II trial | Lubbers (2018) | **Median cumulative radiation dose (mSv)**<br>*CT (CACS + CCTA) vs. functional testing*: median 3.1 (IQR 1.6–7.8), mean 5.6 (SD 6.3) vs. median 0 (IQR 0 to 7.1), P<0.001 |

CACS = coronary artery calcium score; CCTA = coronary computed tomography angiography; CT = computed tomography; IQR = interquartile range; mSv = millisieverts; SD = standard deviation

*The CRESCENT and the CRESCENT II trials randomized patients to CT vs. functional imagining; in the CT arm all patients received a CAC scan and if patients received a CACS score of 0, they received no further testing. However, authors reported radiation exposure for the entire CT arm (i.e. combination of CACS and CCTA if done).

**Appendix Table B7. Studies of prognostic value of CACS included for KQ3**

| Author, year | Purpose | Patient population and CT characteristics | Primary Outcomes | Evidence-base Used | Primary Conclusions |
|---|---|---|---|---|---|
| **Budoff, 2017** | To evaluate how CACS compares to functional testing (FT) in estimating prognosis in symptomatic patients. | **N = 8,811**<br>**Mean age**: 61 years<br>**% female**: 52%<br><br>**Pre-test probability**: intermediate<br><br>**Framingham risk score**<br>• Low (<6%): 7%<br>• Intermediate (6-20%): 51%<br>• High (>20%): 42%<br><br>**Prevalence of CAD**: unclear<br><br>**Type of scanner used**: 64-slice multidetector CT or newer<br><br>**Setting:** Outpatient | Composite of time to MACE including death from any cause, MI, or hospitalization for unstable angina; composite of cardiovascular death, MI, or hospitalization for unstable angina; composite of cardiovascular death or MI. | Subanalysis of the PROMISE trial; includes only patients randomized to the CCTA arm who underwent CAC testing (84%; 4209/4996) and only patients randomized to the FT arm who had determinate test results (98%; 4602/4692) | ***Overall Event Rates, % (n/N), median f/u 26.1 months (IQR 18.0 to 34.4);***<br>**CACS vs. FT**<br>• All-cause death/MI/UA: 3.2% (133/4209) vs. 2.9% (132/4602, p=0.69<br>• Cardiovascular death/MI: 1.3% (53/4209) vs. 1.6% (72/4602), p=0.13<br><br>***Frequency of initial test results, % (n/N)***<br>Normal<br>• **CACS = 0**: 34.6% (1457/4209)<br>• **FT = normal**: 78.0% (3588/4602)<br>Mild<br>• **CACS = 1–99**: 31.8% (1340/4209)<br>• **FT = mild**: 9.4% (432/4602)<br>Moderate<br>• **CACS = 100–400:** 18.3% (772/4209)<br>• **FT = moderate**: 4.7% (217/4602)<br>Severe<br>• **CACS >400:** 15.2% (640/4209)<br>• **FT** = **severe**: 7.9% (365/4602)<br><br>***Outcomes stratified by CACS and FT results****; all results* are reported as % (n/N) and adjusted HR (95% CI)†*<br><br>**All-cause death/MI/UA**<br>Normal<br>• **CACS = 0**: 1.4% (21/1457)<br>• **FT = normal**: 2.1% (75/3588)<br>Mild |

| Author, year | Purpose | Patient population and CT characteristics | Primary Outcomes | Evidence-base Used | Primary Conclusions |
|---|---|---|---|---|---|
| | | | | | • **CACS = 1–99**: 2.3% (31/1340); adj. HR 1.51 (0.86, 2.65)<br>• **FT = mild:** 2.1% (9/432); adj. HR 0.94 (0.47, 1.89)<br><u>Moderate</u><br>• **CACS = 100–400**: 5.2% (40/772); adj. HR 3.14 (1.81, 5.44)<br>• **FT = moderate**: 6.0% (13/217); adj. HR 2.65 (1.46, 4.83)<br><u>Severe</u><br>• **CACS >400**: 6.4% (41/640); adj. HR 3.56 (1.99, 6.36)<br>• **FT severe**: 9.6% (35/365); adj. HR 3.88 (2.58, 5.85)<br><br>**Cardiovascular death/MI/UA**<br><u>Normal</u><br>• **CACS = 0**: 1.0% (14/1457)<br>• **FT = normal**: 1.6% (56/3588)<br><u>Mild</u><br>• **CACS = 1–99**: 1.9% (25/1340); adj. HR 1.85 (0.96, 3.58)<br>• **FT = mild:** 1.9% (8/432); adj. HR 1.11 (0.53, 2.33)<br><u>Moderate</u><br>• **CACS = 100–400**: 4.2% (32/772); adj. HR 3.85 (2.01, 7.38)<br>• **FT = moderate**: 6.0% (13/217); adj. HR 3.50 (1.89, 6.47)<br><u>Severe</u> |

| Author, year | Purpose | Patient population and CT characteristics | Primary Outcomes | Evidence-base Used | Primary Conclusions |
|---|---|---|---|---|---|
| | | | | | • **CACS >400**: 5.5% (35/640); adj. HR 4.72 (2.40, 9.28)<br>• **FT severe**: 8.5% (31/365); adj. HR 4.59 (2.93, 7.19)<br><br>**Cardiovascular death/MI**<br><u>Normal</u><br>• **CACS = 0**: 0.6% (9/1457)<br>• **FT = normal**: 1.3% (48/3588)<br><u>Mild</u><br>• **CACS = 1–99**: 1.3% (17/1340); adj. HR 1.77 (0.78, 4.02)<br>• **FT = mild:** 1.2% (5/432); adj. HR 0.81 (0.32, 2.04)<br><u>Moderate</u><br>• **CACS = 100–400**: 1.8% (14/772); adj. HR 2.16 (0.90, 5.16)<br>• **FT = moderate**: 2.3% (5/217); adj. HR 1.53 (0.60, 3.90)<br><u>Severe</u><br>• **CACS >400**: 2.0% (13/640); adj. HR 1.97 (0.78, 5.02)<br>• **FT severe**: 3.8% (14/365); adj. HR 2.13 (1.16, 3.91)<br><br>**Author conclusions**:<br>Among stable patients presenting with suspected CAD, most events occur in patients who do not have inducible myocardial ischemia, as detected by FT. Conversely, CAC=0 can safely exclude future cardiovascular events in symptomatic |

| Author, year | Purpose | Patient population and CT characteristics | Primary Outcomes | Evidence-base Used | Primary Conclusions |
|---|---|---|---|---|---|
| | | | | | patients with suspected CAD. Most events occurred in patients with positive CAC scans and the discriminatory ability of CAC suggests that it may have a role in the initial evaluation of new onset stable chest pain. However, both approaches have strengths to detect future cardiovascular events in patients with stable CAD, and a combined tiered approach may be most prudent. |
| **Villines, 2011** | To assess the prevalence and extent of CAD and clinical outcomes among a large, international registry cohort of symptomatic patients without known coronary heart disease who were referred for CCTA and found to have no measurable CAC on pre-CCTA calcium scoring. The incremental prognostic value of CAC scoring at the time of CCTA was also explored. | **N**=10,037<br>**Mean age**: 57 years<br>**% female**: 44%<br>**Follow-up:** median 2.1 (IQR 2.0) years<br><br>**Pre-test probability**: 43% (Diamond-Forrester)<br><br>**Prevalence of CAD (presence of any coronary plaque):** 48%<br><br>**Prevalence of obstructive CAD (≥50% stenosis on CCTA):** 16% (n=1603) | Composite endpoint of all-cause mortality, nonfatal MI, and coronary revascularizations performed ≥90 days after CCTA (prognosis endpoint) | CONFIRM registry (an international, multicenter, observational registry), [index publication] | ***Frequency of initial CAC test results, % (n/N)***<br>• CACS = 0: 51% (5128/10037)<br>• CACS >0: 49% (4909/10037)<br><br>**HRs (95% CI) for composite of all-cause mortality, nonfatal MI, late revascularization** (*N=8,907 with complete follow-up*)<br>• CACS = 0: referent<br>• CACS = 1–100: HR 3.08 (2.07, 4.58); adj. HR 2.82 (1.83, 4.35)§<br>• CACS = 101–400: HR 9.39 (6.42, 13.7); adj. HR 7.16 (4.66, 11.0)§<br>• CACS >400: HR 13.90 (9.52, 20.4); adj. HR 9.78 (6.29, 15.2)§<br><br>**Author conclusions**:<br>In symptomatic patients referred for CCTA, the absence of CAC reduces but does not fully eliminate the occurrence of obstructive CAD. Increasing<br>CAC scores were independently predictive of adverse events. |

| Author, year | Purpose | Patient population and CT characteristics | Primary Outcomes | Evidence-base Used | Primary Conclusions |
|---|---|---|---|---|---|
| | | **Type of scanner used**: 64-slice multidetector CT or newer<br><br>**Setting:** NR (likely outpatient) | | | |
| **Al-Mallah 2014** | To evaluate the prognostic utility of CCTA findings of CAD over CAC. | **N**=8,627<br>**Mean age**: 57 years<br>**% female**: 50%<br>**Follow-up:** median 25 (IQR 17-40) months<br><br>**Pre-test probability**: low (49%) to intermediate (42%)<br><br>**Prevalence of CAD (presence of any coronary plaque):** 49.8%<br><br>**Prevalence of obstructive CAD (≥50% stenosis on CCTA):** 8.7% (n=749)<br><br>**Type of scanner used**: 64-slice multidetector CT or newer | Composite of death or non-fatal MI | Subset of the CONFIRM registry (an international, multicenter, observational registry) | ***Frequency of initial CAC test results, % (n/N)***<br>• CACS = 0: 56% (4860/8627)<br>• CACS >0: 44% (3767/8627)<br><br>**Annual event rate**<br>• CACS = 0:<br>○ Normal: 0.21%<br>○ Nonobstructive CAD: 0.34%<br>○ Obstructive CAD: 1.29%<br>• CACS = 1–9:<br>○ Nonobstructive CAD: 0.39%<br>○ Obstructive CAD: 1.55%<br>• CACS = 10–99:<br>○ Nonobstructive CAD: 0.60%<br>○ Obstructive CAD: 4.08%<br>• CACS ≥100:<br>○ Nonobstructive CAD: 1.46%<br>○ Obstructive CAD: 3.73%<br>*In every CAC group, there was a graded increase in the annual event rate ($p<0.05$)*<br><br>**HRs (95% CI) for composite of death or nonfatal MI** |

| Author, year | Purpose | Patient population and CT characteristics | Primary Outcomes | Evidence-base Used | Primary Conclusions |
|---|---|---|---|---|---|
| | | **Setting:** NR (likely outpatient) | | | • CACS = 0: referent<br>• CACS = 1–9: HR 1.2 (0.5, 3.1); adj. HR 0.8 (0.3, 2.3)**<br>• CACS = 10–99: HR 3.9 (2.3, 6.6); adj. HR 2.3 (1.3, 3.9)**<br>• CACS = 100–399: HR 7.3 (4.5, 11.9); adj. HR 3.6 (2.1, 6.0)**<br>• CACS ≥400: HR 13.0 (8.2, 20.6); adj. HR 4.8 (2.9, 8.7)**<br>*Graded risk with increasing CACS (P<0.0001)*<br><br>Incremental to D–F pre-test likelihood, CAD risk factors, and CAC, CCTA improves discrimination of symptomatic individuals at risk of death or MI. In our cohort, only 1.36% of symptomatic patients with a zero calcium score had evidence of obstructive CAD and suggests CAC as a potentially useful 'gatekeeper' to further angiographic testing. |

ACS = acute coronary syndrome; CACS = coronary artery calcium score; CACS = coronary artery calcium; CT = computed tomography; CTA = computed tomography angiography; DSCT = dual source computed tomography; ED = emergency department; eGFR = estimated glomerular filtration rate (ml/min/1.73 m2); ICA = invasive coronary angiography; MACE = major adverse cardiac event; MI = myocardial infarction.

*Similar pattern when alternate CACS cut-offs were analyzed: CACS≤ 10, CAC >10, CACS≤ 300, CAC >300.

†Hazard ratios adjusted for age, sex, CAD risk equivalent (history of either diabetes mellitus, peripheral artery disease, or cerebrovascular disease), and the prespecification of the intended functional test (if randomly assigned to the functional testing arm).

‡Additional testing analyzed included exercise treadmill test and stress echocardiogram which were given to <5% of all CACS patients at either the index visit or the 28-day follow-up versus no patient in the >400 CACS group.

§Risk factor adjusted model: included symptoms and clinical cardiovascular risk factors.

**Adjusted for age, sex, and risk factors (hypertension, diabetes, dyslipidemia and current smoking).

**Appendix Table B8. Summary of Pooled Individual Patient Data from ACRIN-PA and ROMICAT-II trials (Bittner 2017)**

| Author, year | Purpose | Patient population and CT characteristics | Primary Outcomes | Evidence-base Used | Primary Conclusions |
|---|---|---|---|---|---|
| **Bittner, 2017** | To determine whether CACS affects efficiency of coronary CTA in patients with suspected acute coronary syndrome. | **N = 1,234**<br>**Mean age**: 51 years<br>**% female**: 50%<br><br>**Prevalence of obstructive CAD (stenosis ≥50% on CCTA):** 13.1% (n=162)<br><br>**Type of scanner used**: 64-multidetector row or newer CT scanner | Frequency of all downstream tests (beyond coronary CTA), total, and diagnostic cost across CAC strata, MACE, and Diagnostic yield of ICA. | This study is an observational cohort analysis of pooled data from the 2 largest randomized, controlled, multicenter trials ACRIN-PA and ROMICAT II using individual patient level data. | *All results are reported as % (n/N) and stratified by CACS*<br><br>**Myocardial infarction at discharge:**<br>• CACS 0: 0.1% (1/795)<br>• CACS >0 to 10: 0% (0/91)<br>• CACS >10 to 100: 0.5% (1/195)<br>• CACS >100 to 400: 3.9% (4/103)<br>• CACS >400: 6% (3/50)<br>p<0.001<br><br>**Unstable angina pectoris at discharge:**<br>• CACS 0: 0.4% (3/795)<br>• CACS >0 to 10: 5.5% (5/91)<br>• CACS >10 to 100: 9.7% (19/195)<br>• CACS >100 to 400: 12.6% (13/103)<br>• CACS >400: 38% (19/50)<br>p<0.001<br><br>**MACE at 28 day follow-up:**<br>• CACS 0: 0% (0/795)<br>• CACS >0 to 10: 1.1% (1/91)<br>• CACS >10 to 100: 0% (0/195)<br>• CACS >100 to 400: 1% (1/103)<br>• CACS >400: 2% (1/50)<br>p=0.011<br><br>**Additional testing during index visit:**<br>• CACS 0: 3.9% (31/795)<br>• CACS >0 to 10: 22% (20/91) |

| Author, year | Purpose | Patient population and CT characteristics | Primary Outcomes | Evidence-base Used | Primary Conclusions |
|---|---|---|---|---|---|
| | | | | | • CACS >10 to 100: 30.8% (60/195)<br>• CACS >100 to 400: 47.6% (49/103)<br>• CACS >400: 72% (36/50)<br>p<0.001<br><br>**Proportion of patients who went on to receive ICA:**<br>• CACS 0: 1% (8/795)<br>• CACS >0 to 10: 5.5% (5/91)<br>• CACS >10 to 100: 13.3% (26/195)<br>• CACS >100 to 400: 17.5% (18/103)<br>• CACS >400: 46% (23/50)<br>p<0.001<br><br>**Diagnostic yield of ICA, %:**<br>• CACS 0: 37.5%<br>• CACS >0 to 10: 60.0%<br>• CACS >10 to 100: 76.9%<br>• CACS >100 to 400: 66.7%<br>• CACS >400: 87.0%<br><br>**Proportion of patients receiving revascularization**:<br>• CACS 0: 0.4% (3/795)<br>• CACS >0 to 10: 3.3% (3/91)<br>• CACS >10 to 100: 7.2% (14/195)<br>• CACS >100 to 400: 7.8% (8/103)<br>• CACS >400: 26% (13/50)<br>p<0.001 |

| Author, year | Purpose | Patient population and CT characteristics | Primary Outcomes | Evidence-base Used | Primary Conclusions |
|---|---|---|---|---|---|
| | | | | | **Cost per ACS diagnosis in USD, Ratios (95% CI):**<br>• CACS 0: 464,399 (18,297 to 910,501)<br>• CACS >0 to 10: 60,186 (16,803 to 103,568)<br>• CACS >10 to 100: 44,862 (31,305 to 58,419)<br>• CACS >100 to 400: 34,465 (22,675 to 46,255)<br>• CACS >400: 19,283 (15,218 to 23,348)<br><br>**CACS independently predicted the following, adjusted* OR (95% CI):**<br>• ACS: 2.88 (2.27 to 3.56)<br>• ICA: 2.59 (2.10 to 3.20)<br>• Downstream testing: 2.79 (2.37 to 3.22)<br>*Unadjusted ORs (95% CI) by CACS category (CACS = 0 as referent)*<br>• ACS:<br>○ CAC >0–10: 10.12 (2.64 to 38.86)<br>○ CAC >10–100: 20.08 (6.63 to 60.85)<br>○ CAC >100–400: 33.61 (10.60 to 106.58)<br>○ CAC >400: 125.41 (37.17 to 423.09)<br>• ICA:<br>○ CACS >0–10: 5.02 (1.59 to 15.87)<br>○ CAC >10–100: 13.28 (5.77 to 30.59)<br>○ CAC >100–400: 17.52 (7.07 to 43.39)<br>○ CAC >400: 65.33 (24.54 to 173.94)<br>• Downstream testing:<br>○ CACS >0–10: 7.09 (3.79-13.23) |

| Author, year | Purpose | Patient population and CT characteristics | Primary Outcomes | Evidence-base Used | Primary Conclusions |
|---|---|---|---|---|---|
| | | | | | ○ CAC >10–100: 11.20 (6.84-18.33)<br>○ CAC >100–400: 23.04 (13.06-40.67)<br>○ CAC >400: 66.28 (30.39-144.56)<br><br>**Author conclusions**:<br>Downstream testing, total, and diagnostic cost increased with increasing CAC, but were found to be appropriate because obstructive coronary artery disease and ACS were more prevalent in patients with high CAC. In patients with acute chest pain undergoing coronary CTA, cost-efficient testing and excellent diagnostic yield can be achieved even with high CAC burden. |

ACS = acute coronary syndrome; CACS = coronary artery calcium score; CACS = coronary artery calcium; CT = computed tomography; CTA = computed tomography angiography; ICA = invasive coronary angiography; MACE = major adverse cardiac event.
*Adjusted for age and sex.

**Appendix Table B9. RCTs of clinical decision making included for KQ3 data abstraction**

| Study (year)<br>Study design<br>Country<br>Setting | Inclusion criteria | Intervention vs. Comparator<br>Population | Treatment algorithm incorporating calcium scan/score | Outcomes | Author conclusion/clinical decision related to calcium scoring |
|---|---|---|---|---|---|
| Lubbers (2016)<br>RCT<br>[CRESCENT trial]<br><br>The Netherlands<br><br>Outpatient clinics (4 sites) | • Stable angina, suspected obstructive CAD (known CAD excluded)<br>• Age ≥18 years<br>• No invasive angiography or stress test within past year | CT (Calcium scan + CCTA) vs. functional testing*<br><br>N=350<br>Female: 55.3%<br>Mean age: 55 years<br>F/U: 1 year<br>% F/U: 84%<br><br>low–intermediate pretest probability<br><br>**Prevalence of obstructive CAD:** unclear, authors say "relatively low" | All CT patients first underwent non-contrast-enhanced calcium scan:<br>• **0** = no further testing (40%; 98/242)<br>• **1–400** = CCTA (49%; 118/242)<br>• **>400**† = stressing testing or invasive angiography (11%; 26/242) | **Outcomes in patients (n=98) with calcium score 0 (i.e., ruled out CAD):**<br>• Anginal symptoms: less frequent vs. when CAD ruled out based on CCTA or functional testing (p=0.042; data NR)<br>• Downstream testing‡: 0% (0/98) [vs. 25% (60/238) CCTA and 53% (57/108) functional testing, p<0.0001]<br>• Adverse events§: 0% (0/98) [vs. 3% (8/239) CCTA and 10% (11/108) functional testing, p=0.004]<br><br>**Mean radiation dose (mSv) by scan type**:<br>• Calcium scan: 1.3±1.1<br>• CCTA: 4.1±4.4<br>• MPI: 14.0±2.3<br>• Invasive angiography: 14.0±14.3<br><br>**Proportion with any radiation (mSv) exposure,** *CT (calcium scan + CCTA) vs. functional testing*: 99.6% (241/242) vs. 42.6% (46/108) | • Incorporation of calcium scoring in the CT algorithm helped avoid contrast medium in 39% of patients, as well as an overall reduction in radiation exposure and costs in the CT group.<br>• Although groups are small, our results show no indication that implementation of the calcium scan in patients with a low–intermediate probability is unsafe. |

| | | | | | |
|---|---|---|---|---|---|
| | | | | **Mean cumulative radiation dose (mSv),** *CT vs. functional testing*: 6.6+8.7 vs. 6.1+9.3, P<0.0001 | |
| Lubbers (2017)<br>RCT<br>[CRESCENT trial]<br><br>*Subanalysis based on sex*<br><br>The Netherlands<br><br>Outpatient clinics (4 sites) | See above | See above | All CT patients first underwent non-contrast-enhanced calcium scan;<br>*female vs. male*:<br>• **0** = no further testing (48% [92/192] vs. 35% [55/158], p=0.036)<br>• **1–400** = CCTA (44% [85/192] vs. 51% [81/158])<br>• **>400**† = stressing testing or invasive angiography (8% [15/192] vs. 14% [22/158]) | **Symptom-free (no angina) after 1 year (CT [calcium scan + CCTA] vs. functional testing)**<br>• *Females:* 40% vs. 22%; p=0.026<br>• *Males*: 36% vs. 30%; p=0.466<br>*P-value for interaction* (females vs. males): 0.286<br><br>**Adverse events (CT [calcium scan + CCTA] vs. functional testing)**<br>*Females (n=192):*<br>• **All-cause death:** 0% (0/133) vs. 0% (0/59)<br>• **Nonfatal MI:** 0% (0/133) vs. 1.7% (1/59)<br>• **Unstable angina:** 0% (0/133) vs. 1.7% (1/59)<br>• **Nonfatal stroke:** 0% (0/133) vs. 1.7% (1/59)<br>• **Late revascularizations:** 0.8% (1/133) vs. 1.7% (1/59)<br>• **Unplanned cardiac evaluations:** 1.5% (2/133) vs. 1.7% (1/59)<br>• **ALL EVENTS:** 2.3% (3/133) vs. 8.5% (5/59)<br>*Males (n=158):*<br>• **All-cause death:** 1.8% (2/109) vs. 4.1% (2/49) | • By not performing CCTA in patients with a negative calcium scan, contrast medium and additional radiation could be avoided in 48% of women.<br>• Young women are relatively more vulnerable to radiation exposure; we observed that with the incorporation of the calcium scan, the cumulative radiation dose in this group was very low.<br>• Although it is possible that severe but noncalcified lesions may be missed if CT angiography is not performed, the clinical course of patients who did not undergo CTA was uneventful over the first 6 months. |

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| | | | | • **Nonfatal MI:** 0.9% (1/109) vs. 0% (0/49)<br>• **Unstable angina:** 0.9% (1/109) vs. 0% (0/49)<br>• **Nonfatal stroke:** 0% (0/109) vs. 0% (0/49)<br>• **Late revascularizations:** 0.9% (1/109) vs. 2.0% (1/49)<br>• **Unplanned cardiac evaluations:** 0% (0/109) vs. 6.1% (3/49)<br>• **ALL EVENTS:** 4.6% (5/109) vs. 12.2% (6/49)<br><br>**Event-free survival (CT [calcium scan + CCTA] vs. functional testing)**<br>• *Females:* 97.7% vs. 91.5%; p=0.061<br>• *Males*: 95.4% vs. 87.8%; p=0.083<br>*P-value for interaction* (females vs. males): 0.759<br><br>**Downstream Testing (CT [calcium scan + CCTA] vs. functional testing)**<br>*Females (n=189)*:<br>• **Noninvasive testing:** 6% (8/130) vs. 44% (26/59)<br>• **ICA:** 8% (10/130) vs. 10% (6/59)<br>• **Noninvasive testing and ICA:** 2% (3/130) vs. 3% (2/59)<br>• **ANY TESTING:** 16% (21/130) vs. 57% (34/59)**;** P<0.001 | |

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| | | | | *Males (n=157)*:<br>• **Noninvasive testing:** 12% (13/108) vs. 33% (16/49)<br>• **ICA:** 10% (11/108) vs. 6% (3/49)<br>• **Noninvasive testing and ICA:** 5% (5/108) vs. 2% (1/49)<br>• **ANY TESTING:** 27% (29/108) vs. 41% (20/49)**;** P=0.057<br>*P value for interaction* (by sex and randomization strategy): 0.009<br><br>**Radiation dose (mSv) for complete cardiac CT**<br>• Females: median 1.7 (IQR 0.8–4.7); mean 3.7 ± 4.2<br>• Males: median 2.6 (IQR 1.0–6.8); mean 4.6 ± 4.8<br><br>*Per authors*: "If calcium scans had not been included in the decision making, and all patients had undergone CTA instead, the estimated median radiation exposure from the CT examination might have increased to 4.7 mSv [IQR 3.7–10.7], mean 7.5 ± 8.6 mSv"<br><br>**Cumulative radiation dose (mSv)**<br>• Females:<br>○ CT (calcium scan + CCTA): median 4.7 (IQR, 0.9–7.9); mean 5.3 ± 5.5 | |

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| | | | | ○ Functional testing: median 0 (IQR, 0–12.5); mean 6.3 ± 10.3<br>○ P=0.005<br>• Males:<br>○ CT (calcium scan + CCTA): median 4.7 (IQR, 1.1–11.5); mean 8.2 ± 11.2<br>○ Functional testing: median 0 (IQR, 0–14.0); mean 5.8 ± 8.1<br>○ P<0.001<br>• Interaction p-value: 0.097<br><br>*Per authors*: "In women <60 years (59%), in whom CAD was ruled out based on a negative calcium scan in 71%, the median cumulative radiation dose was 1.1 mSv [IQR, 0.8–1.5], mean 1.4 ± 1.3 mSv." | |
| Lubbers (2018)<br>RCT<br>[CRESCENT-II trial]<br><br>The Netherlands<br><br>Outpatient clinics (4 sites) | • Chest pain symptoms suggestive of obstructive CAD (known CAD excluded)<br>• CAD probability >10%<br>• Age ≥18 years<br>• Prior MI or revascularization procedure excluded | CCTA with MPI vs. functional testing<br><br>N=268<br>Female: 49%<br>Mean age: 58 years<br>F/U: 6 months<br>% F/U: 99%<br><br>**Pre-test CAD probability**: 54 ± 30%<br><br>**Prevalence of obstructive CAD:** | All CT patients first underwent non-contrast-enhanced calcium scan:<br>• **0** *and pre-test prob low to intermediate (10% to 80%)* = no further testing (35%; 45/130)<br>• **0** *and pre-test prob high (>80%)* OR **>0** = contrast-enhanced CCTA w/ MPI (65%; 85/130) | **Outcomes in patients (n=45) with calcium score 0 (i.e., ruled out CAD):**<br>• Acute chest pain and ECG changes, underwent ICA : 2% (1/45); biomarkers and ICA were both negative<br>• MACE (death, nonfatal MI, UA, urgent revascularization and stroke): 0% (0/45)<br><br>**For CT (calcium + CCTA with MPI) vs. functional testing)**:<br>• Relief of angina symptoms: 38% (49/130) vs. 28% (38/136), p=0.12 | • Similar to CRESCENT, the present study suggests an uneventful intermediate-term outcome when CAD is excluded on the basis of a negative calcium scan.<br>• Restriction to patients with detectable calcium or a high CAD probability increased the positive yield of CCTA to more than one-third. |

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| | | unclear, authors say "typically low" | | • ICA without a Class I indication for revascularization: 1.5% (2/130) vs. 7.2% (10/136), p=0.035<br>• MACE: 3% (4/130) vs. 3% (4/136), p=1.0<br><br>**Mean radiation dose (mSv) by scan type**:<br>• Calcium scan: 1.3±0.7<br>• CCTA: 3.5±3.0<br>• CT-MPI: 10.6±6.3<br><br>**Median cumulative radiation dose (mSv),** *CT (calcium scan + CCTA) vs. functional testing*: 3.1 (IQR 1.6–7.8) [mean dose 5.6±6.3] vs. 0 (IQR 0–7.1), P<0.001 | |

*Primarily symptom-limited exercise ECG; MPI or stress echocardiography was performed in 5% of cases due to contraindications to exercise ECG or non-interpretable or equivocal results.
†Or CT contraindications or non-conclusive CT angiogram.
‡Includes noninvasive testing (13% vs. 42%), invasive angiography (9% vs. 8%), and both (3% vs. 3%).
§Includes all-cause mortality, nonfatal MI, unstable angina, nonfatal stroke, late revascularizations, and unplanned cardiac evaluations (acute chest pain at ED, palpitations at ED).

**Table B10. Data abstraction for studies addressing KQ4 (test characteristics in special populations)**

| Author (year) | Patients (sex, age, risk, etc.) Type of CT scanner Setting Timing of scans | Total N | CAD, n | CAD, % | Subgroup | ICA threshold(s) for determining CAD | CACS threshold(s) for determining CAD | Sensitivity | Specificity | PPV | NPV | 1-NPV |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| von Ziegler (2014) | Mean age: 61 years<br>% female: 33%<br>Percent of pts w/o any cardiovascular risk factors: 16.8%<br>Mean number of cardiovascular risk factors: 2.1<br>Chest pain: 100%<br><br>64-slice MDCT or dual-source CT imager in thin-section mode<br><br>Outpatient clinic; non-emergent<br><br>91% of patients had ICA performed within 10 days following CACS | 2780 | 1581 | 56.9% | Males | ≥50% stenosis | 0 | 99% | 55% | 74% | 99% | 1.0% |
| | | 1357 | 508 | 37.4% | Females | ≥50% stenosis | 0 | 99% | 56% | 58% | 99% | 1.0% |
| | | | | | | | | | | | | |
| | | | | | Males | ≥50% stenosis | >10 | 93% | 74% | 83% | 89% | 11.0% |
| | | | | | Females | ≥50% stenosis | >10 | 88% | 70% | 64% | 91% | 9.0% |
| | | | | | | | | | | | | |
| | | | | | Males | ≥50% stenosis | >100 | 73% | 84% | 86% | 70% | 30.0% |
| | | | | | Females | ≥50% stenosis | >100 | 63% | 82% | 68% | 79% | 21.0% |
| | | | | | | | | | | | | |
| | | | | | Males | ≥50% stenosis | >400 | 56% | 87% | 85% | 60% | 40.0% |
| | | | | | Females | ≥50% stenosis | >400 | 49% | 88% | 70% | 74% | 26.0% |
| | | | | | | | | | | | | |
| | | 2780 | 537 | 19.3% | Males | ≥70% stenosis | 0 | 99% | 32% | 27% | 99% | 1.0% |
| | | 1357 | 195 | 14.4% | Females | ≥70% stenosis | 0 | 98% | 47% | 24% | 99% | 1.0% |
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| | | | | | Males | ≥70% stenosis | >10 | 97% | 47% | 30% | 98% | 2.0% |
| | | | | | Females | ≥70% stenosis | >10 | 96% | 60% | 29% | 99% | 1.0% |
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| | | | | | Males | ≥70% stenosis | >100 | 92% | 71% | 43% | 97% | 3.0% |
| | | | | | Females | ≥70% stenosis | >100 | 84% | 78% | 40% | 97% | 4.0% |
| | | | | | | | | | | | | |
| | | | | | Males | ≥70% stenosis | >400 | 85% | 83% | 55% | 96% | 4.0% |
| | | | | | Females | ≥70% stenosis | >400 | 78% | 89% | 55% | 96% | 4.0% |
| Budoff (2013) | | 138 | NR | NR | Males | ≥50% stenosis | NR | 100.0% | 34.4% | NR | NR | NR |

| Author (year) | Patients (sex, age, risk, etc.) Type of CT scanner Setting Timing of scans | Total N | CAD, n | CAD, % | Subgroup | ICA threshold(s) for determining CAD | CACS threshold(s) for determining CAD | Sensitivity | Specificity | PPV | NPV | 1-NPV |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean age: 57 years<br>% female: 41%<br>Risk level: NR<br>All pts had chest pain and were clinically referred for ICA<br><br>64-slice MDCT<br><br>Outpatient clinic; non-emergent<br><br>NR | 94 | NR | NR | Females | ≥50% stenosis | NR | 90.9% | 49.4% | NR | NR | NR |

CACS = coronary artery calcium score; CAD = coronary artery disease; CT = computed tomography; ICA = invasive coronary angiography; MDCT = multidetector computed tomography; NPV = negative predictive value; NR = not reported; PPV = positive predictive value; pts = patients.

**Table B11. Summary of studies identified reporting data for KQ5 (cost-effectiveness)**

| Author, year<br>Study design<br>*Country of origin* | Patient data<br>(i.e. age, sex, risk for CAD)<br>Treatment characteristics | Economic outcomes data | Author's conclusions |
|---|---|---|---|
| Ferreira, 2014<br><br>Cost-benefit analysis<br><br>*Portugal* | Hypothetical cohorts of 100 symptomatic patients with a pre likelihood for CAD of 10% to 90%.<br><br>Seven diagnostic strategies were assessed: (1) ET followed by MPS in positive or inconclusive cases, (2) ET followed by 64-detector CCTA in positive or inconclusive cases, (3) MPS (as first option), (4) Stress Echo with dobutamine (as first option), (5) CCTA (as first option), (6) calcium scoring (CaSc) followed by CCTA (CACS-CCTA) when CACS > 0, and (7) invasive coronary angiography as the first and only test. [Only data concerning strategy 6 are abstracted here] | Incremental cost (€) per additional correct diagnosis for diagnosis strategy 6 at differing pretest likelihoods:<br>-10% pretest likelihood: €1,819<br>-20% pretest likelihood: €162 | Depending on the pretest likelihood of disease and the willingness to pay per correct diagnosis, CCTA may be used as a first-line test or reserved for patients with positive/inconclusive ergometric test results or CACS > 0. For example, for a limit of €5,000 per additional correct diagnosis, the preferred strategy would be CACS-CCTA for patients with a pre-test likelihood of disease of 10%, CCTA for those with a pretest likelihood of disease of 20% to 40%, and ICA for those with a pretest likelihood of disease of ≥50%. In high-risk patients (pre likelihood of disease ≥ 60%), immediate ICA appears to be the most cost-effective strategy. |
| McKavanagh, 2013<br><br>Cost-impact model using a subgroup of patients from one arm of an RCT<br><br>*United Kingdom* | N=246<br><br>Patients received both CACS and CCTA<br><br>% Male: 57%<br><br>Mean age: 58 years<br><br>High risk for cardiovascular disease: 35%<br><br>Hypothetical diagnosis strategy applied to this cohort: All Patients with chest pain are investigated with CACS. Of these, 126 patients had a CACS of 0 and would require no further investigation; 94 had a CACS >0 but <400 and would require a CCTA. 26 had a CACS >400 and | Cost per significant number of stenoses identified: £832.74 for CACS vs. £926.17 for DF criteria | Patients with suspected stable CAD are more accurately risk stratified by CACS compared to the traditional Diamond Forrester. CACS was more successful in the prediction of significant stenosis and appears to be more effective at targeting clinical resources to those patients that need them. |

| Author, year<br>Study design<br>*Country of origin* | Patient data<br>(i.e. age, sex, risk for CAD)<br>Treatment characteristics | Economic outcomes data | Author's conclusions |
|---|---|---|---|
| | would require an ICA. | | |
| Raman, 2012<br><br>Economic analysis using decision tree modeling<br><br>*United Kingdom* | This was a modeling study and no patient data (real or hypothetical were provided).<br><br>Six diagnostic strategies were assessed: (1) CCTA only, (2) ECG before CCTA, (3) SPECT before CCTA, (4) ECG before SPECT and CCTA, (5) CACS before CCTA, (6) CACS before SPECT and CCTA (results reported here are only those relevant to CACS) | Cost (£)/QALY at various prevalences:<br>- 10.5%: £416.86 (€500.23)/QALY<br>- 30%: £494(€593)/QALY<br>- 50%: £587(€704)/QALY | Adoption of CACS prior to MPS as the initial investigation of patients with suspected stable angina and a prior probability of CAD of less than 30%, is cost-effective to do CACS before MPS or ICA at a threshold of £30,000/QALY; for those with <30% prior probability, MPS or ICA better than CACS or Stress ECG; for prevalence of <50% more cost effective go straight to ICA. CACS had higher net monetary benefits vs. ECG-MPS-ICA as a diagnostic strategy at all CAD prevalence levels. |
| Bittner, 2017<br><br>Focused on healthcare costs during index hospitalization, assessed from reports from hospital cost-accounting systems and physician billing records. | N = 1234<br>Mean age: 61 years<br>Percent female: 50%<br>Percent of patients without detectable CAD: 64% (795/1234)<br><br>Costs were available for ROMICAT II trial patients only. A multiple linear regression model with total cost as outcome variable and detailed diagnostic test and intervention data (all from ROMICAT II) as independent variables was used to estimate cost for ACRIN patients. | Cost per ACS* diagnosis in USD for all patients stratified by CACS, Ratios (95% CI):<br>• Full cohort: 59,793 (48,632 to 70,953)<br>• CACS 0: 464,399 (18,297 to 910,501)<br>• CACS >0 to 10: 60,186 (16,803 to 103,568)<br>• CACS >10 to 100: 44,862 (31,305 to 58,419)<br>• CACS >100 to 400: 34,465 (22,675 to 46,255)<br>• CACS >400: 19,283 (15,218 to 23,348)<br><br>Cost per ACS diagnosis in USD for patients with obstructive CAD (≥50% stenosis) stratified by CACS, Ratios (95% CI):<br>• All patients with CAD: 23,643 (19792 to 27,495) | Our data confirm increasing cost with increasing extent of CAC, most likely because of an increasing burden of CAD, subsequent downstream testing, and revascularizations. Beyond that, we demonstrated that costs related to the incidence of ACS (cost per ACS) decreased across CAC strata, as the increase in the incidence of ACS was higher as compared with the increase in cost in patients with high burden of CAC. |

| Author, year<br>Study design<br>*Country of origin* | Patient data<br>(i.e. age, sex, risk for CAD)<br>Treatment characteristics | Economic outcomes data | Author's conclusions |
|---|---|---|---|
| | | • CACS ≤100: 25,746 (19,337 to 32,155)<br>• CACS >100 to 400: 26,689 (16,750 to 36,628)<br>• CACS >400: 18,664 (14,573 to 22,755) | |

ACS = acute coronary syndrome; CAD = coronary artery disease; CCTA = coronary computed tomography angiography; CI = confidence interval; ET = effective testing; ICA = invasive coronary angiography; MPS = myocardial perfusion imaging; USD = united states dollar.
*Cost per ACS was defined as sum of total cost per group divided by the number of patients with ACS in this individual group and reflects the cost to diagnose and treat 1 patient with ACS during index hospitalization. ACS was considered either myocardial infarction or unstable angina pectoris.

**Appendix table B12. Summary of systematic reviews included for KQ2 (safety)**

| Author, year *Search dates* | Purpose | Patient population and CT characteristics | Primary Outcomes | Evidence-base Used | Primary Conclusions |
|---|---|---|---|---|---|
| **Kay, 2019***<br><br>*Search dates: Inception to November 6, 2018* | Cardiac computed tomography is an established tool for evaluating cardiovascular disease, which may incidentally depict extracardiac findings. The aim of this study is to identify the spectrum and the prevalence of incidental findings detected on cardiac CT. | **N = 41,543**<br>**Median age**: 60 (range 42 to 82) years<br>**Median % female**: 41%<br><br>**Type of scanner used in studies, % (n/N) studies**<br>• Multidector CT scanners acquiring 64 simultaneous slices or more: 69% (34/49)<br><br>**Indication for CT, % (n/N) studies**<br>• Assessment of CAD: 59% (29/49)<br>• Pre-TAVI workup: 25% (12/49)<br>• Pre-PVI workup: 10% (5/49)<br>• Coronary artery bypass graft evaluation: 4% (2/49)<br>• Various indications: 2% (1/49)<br><br>**Use of contrast, % (n/N) studies**<br>• CT obtained with IV contrast: 76% (37/49)<br>• CT without IV contrast: 18% (4/49)<br>• CT with and without IV contrast: 16% (8/49) | Incidental extracardiac findings | **N = 49 studies**<br>• 15 prospective<br>• 32 retrospective<br>• 2 unclear | **Prevalence of any extracardiac findings†, Median (range):** 45% (7% to 100%)<br><br>**Prevalence of only potentially clinically significant extracardiac findings, Median (range):** 17% (1% to 67%)<br><br>**Author conclusions**: Extracardiac findings are frequently encountered on cardiac CT. Therefore, interpreting physicians should be aware of the occurrence of clinically significant findings and be familiar with the follow-up recommendations endorsed by current guidelines. |
| **Flor, 2013**<br><br>*Search dates: Inception to June 2011* | The aim of this study was to systematically review the evidence on incidental extracardiac finding in patients undergoing | **N = 15,877**<br>**Mean age**: 59 years<br>**% Female**: 55.7%<br><br>**Type of scanner used in studies, % (n/N) studies** | Incidental extracardiac findings | **N = 19 studies**<br>• 8 prospective<br>• 11 retrospective | **Pooled prevalence of patients with at least one incidental extracardiac finding, % (95% CI)**: 44% (35% to 54%), p=0.275; $I^2$ = 99% (even after removal of outliers) |

| Author, year *Search dates* | Purpose | Patient population and CT characteristics | Primary Outcomes | Evidence-base Used | Primary Conclusions |
|---|---|---|---|---|---|
| | cardiac CT and to provide a pooled estimation of the prevalence of incidental extracardiac finding, major incidental extracardiac finding, and previously unknown malignancies. | • Multidector CT scanners acquiring 64 simultaneous slices or more: 68% (13/19)<br><br>**Indication for CT, % (n/N) studies**<br>• Healthy subjects: 11% (2/19)<br>• Suspicion of CAD: 68% (13/19)<br>• Atrial fibrillation: 11% (2/19)<br>• Calcium scoring: 5% (1/19)<br>• Evaluation of pulmonary veins: 5% (1/19)<br>• Evaluation of coronary artery bypass grafts: 5% (1/19)<br>• Various indications: 5% (1/19) | | | **Pooled prevalence of patients with at least one major incidental extracardiac finding, % (95% CI)**: 16% (95% CI 14% to 20%), p<0.001; $I^2$ = 95% (even after removal of outliers)<br><br>**Pooled prevalence of previously unknown malignancies‡ (across 12 studies), % (95% CI)**: 0.7% (95% CI, 0.5% to 1.0%)<br><br>**Author conclusions**: Although the prevalence of reported incidental extracardiac finding at cardiac CT was highly variable, a homogeneous prevalence of previously unknown malignancies was reported across the studies, for a pooled estimate of 0.7%; more than 70% of these previously unknown malignancies were lung cancers. Extracardiac findings on cardiac CT require careful evaluation and reporting. |

CACS = coronary artery calcium score; CAD = Coronary artery disease; CI = confidence interval; CT = computed tomography; MACE = Major Adverse Cardiac Event; NR = not reported; TAVI = transcatheter aortic valve implantation.

**Table B13. Summary of systematic reviews included for KQ3 (influence on clinical decision making)**

| Author, year *Search dates* | Purpose | Patient population and CT characteristics | Primary Outcomes | Evidence-base Used | Primary Conclusions |
|---|---|---|---|---|---|
| **Chaikriangkrai, 2016**<br><br>*Search dates: Inception to September 5, 2015* | To evaluate the prognostic value and accuracy of a zero (normal) CACS for identifying patients at acceptable low risk for future cardiovascular events who might be safely discharged home from the ED | **N = 3,556**<br>**Mean age**: 51 years<br>**% Female**: 50%<br>**F/U:** median 10.5 months<br><br>**Pooled prevalence of CACS=0**: 60.2% (2,141/3,556) (95% CI 40% to 76%)<br><br>**Prevalence of CAD:** NR<br><br>**Type of scanner used in studies, % (n/N) studies**<br>• Multidector CT: 50% (4/8)<br>• Electron beam CT: 50% (4/8) | Cardiovascular events including the combined incidence of MACEs and the independent outcomes of all-cause death and nonfatal MI. | **N = 8 prospective, longitudinal studies§** | **Pooled MACEs rates****:<br>• Overall (n=3,556; 8 studies): 7.6%/year (0.64 events per 100 patient-months, or 237 events in 37,234 patient-months during a median follow-up of 10.5 months [IQR 1 to 29])<br>• CACS=0: 0.8%/year (0.07 events per 100 patient-months, or 13 events in 18,874 patient-months)<br>• CACS>0: 14.6%/year (1.22 events per 100 patient-months, or 224 events in 18,360 patient-months)<br><br>**Pooled all-cause death or MI rates**:<br>• Overall (n=2,891; 5 studies): 1.9%/year (0.16 events per 100 patient-months, or 39 events in 25,006 patient-months during a median follow-up of 8.6 months [IQR 1 to 29]))<br>• CACS=0: 0.5%/year (0.04 events per 100 patient-months, or 6 events in 13,656 patient-months)<br>• CACS>0: 3.5%/year (0.29 events per 100 patient-months, or 33 events in 11,350 patient-months)<br><br>**Pooled RR (95% CI) for CACS =0 vs. >0 (>0 as referent):**<br>• **MACEs (n=3,556; 8 studies)**: 0.06 (0.04 to 0.11); $I^2$=0% (RD 0.19, 95% CI 0.11 to 0.27) |

| Author, year *Search dates* | Purpose | Patient population and CT characteristics | Primary Outcomes | Evidence-base Used | Primary Conclusions |
|---|---|---|---|---|---|
| | | | | | • **All-cause death or nonfatal MI (n=2,891; 5 studies)**: 0.19 (0.08 to 0.47); $I^2$=0% (RD 0.03, 95% CI 0 to 0.05)<br><br>**Author conclusions**: Acute chest pain patients without history of coronary artery disease, ischemic ECG changes, or increased cardiac enzyme levels commonly have a CACS of zero, with a very low subsequent risk of MACEs or death or MI. This meta-analysis proffers the potential role of initial CACS testing for avoiding unnecessary hospitalization and further cardiac testing in acute chest pain patients with a CACS of zero. |
| **Lo-Kioeng-Shioe, 2020**<br><br>*Search dates: Inception to September 2017* | To assess the prognostic utility of CACS in predicting risk of MACE†† in stable patients with suspected CAD. | **N = 34,041**<br>**Mean age**: 59 years<br>**% Female, range**: 19% to 58%<br><br>**Proportion of participants with obstructive CAD (defined as ≥50% lumen stenosis), range**: 14% to 72% | MACE†† and the composite of nonfatal myocardial infarction and all-cause mortality. | **N = 19 studies** (all observational; no further details provided) | **Annual event rate per 100 patients with CACS of 0 (range across studies):** 0 to 3.64 events<br><br>**Proportion of cardiovascular events in patients with a CACS of 0, % (n/N)**: 1.18% (158 events; 1601 [4.7%] total reported cardiovascular events)<br><br>**Pooled RRs for MACE**<br>• **CACS >0 vs. 0 (n=30,057 across 18 studies)**: 5.71 (95% CI 3.98 to 8.19); $I^2$=65% (0 as referent)<br>• **CACS ≥100 vs. 0 (n=9434 across 7 studies)**: 9.57 (95% CI 6.87 to 13.33); $I^2$=23% (0 as referent) |

| Author, year *Search dates* | Purpose | Patient population and CT characteristics | Primary Outcomes | Evidence-base Used | Primary Conclusions |
|---|---|---|---|---|---|
| | | | | | • **CACS ≥400 vs. 0 (n=8577 across 9 studies)**: 8.30 (95% CI 4.95 to 13.90); $I^2$=77% (0 as referent)<br>• **CACS ≥100 vs. <100 (n=13,198 across 7 studies)**: 4.09 (95% CI 2.85 to 5.89); $I^2$=79% (<100 as referent)<br>• **CACS ≥400 vs. <100 (n=10,762 across 6 studies)**: 5.08 (95% CI 3.52 to 7.34); $I^2$=75% (<100 as referent)<br>• **CACS ≥400 vs. <400 (n=15,368 across 9 studies)**: 3.30 (95% CI 2.41 to 4.31); $I^2$=83% (<400 as referent)<br>• **Sensitivity analysis including only studies for which 100% of patients were reported to be symptomatic; CACS >0 vs. 0 (n=20,241 across 12 studies)**: 5.85 (95% CI 3.69 to 9.27); $I^2$=54%<br><br>**Pooled estimates of HRs for MACE adjusted for clinical risk factors by CACS strata (6 studies)**<br>• **CACS 1-100 vs. 0:** 1.79 (95% CI 1.14 to 2.82); $I^2$=37%<br>• **CACS 100-400 vs. 0**: 3.40 (95% CI 1.99 to 5.83); $I^2$=55%<br>• **CACS >400 vs. 0**: 4.88 (95% CI 2.44 to 9.76); $I^2$=70%<br><br>**Pooled RR for all-cause mortality or nonfatal myocardial infarction for CAC >0 vs. 0 (across 13 studies)**: 3.64 (95% CI 2.68 to 4.96); $I^2$=16% |

| Author, year *Search dates* | Purpose | Patient population and CT characteristics | Primary Outcomes | Evidence-base Used | Primary Conclusions |
|---|---|---|---|---|---|
| | | | | | **Author conclusions**: On the basis of our analyses on over 34,000 stable, symptomatic patients with suspected CAD, we conclude that increased levels of coronary artery calcium are strongly and independently associated with increased risk for MACEs. In these patients, the risk for cardiac events increased with greater CACS. The findings are clinically relevant for the large group of symptomatic patients and, although a multicenter randomized trial will be needed to assess the exact utility and incremental predictive value of calcium testing, our analyses indicate that CAC scanning should be helpful in clinical decision making in a considerable number of stable patients with chest pain. |

CACS = coronary artery calcium score; CAD = Coronary artery disease; CI = confidence interval; CT = computed tomography; MACE = Major Adverse Cardiac Event; NR = not reported; TAVI = transcatheter aortic valve implantation.

*This systematic review included studies assessing cardiac CT overall and therefore is not CACS specific.

†Across all studies, lung nodules and masses were the most common findings, followed by lung parenchymal changes (excepting emphysema), lymphadenopathy, emphysema, liver cysts or nodules, aortic dilation or aneurysm, pleural effusions or plaques, and hiatal hernia.

‡Of a total of 29 cancers, 21 (72%) were lung cancers; three, thyroid cancers; two, breast cancers; two, liver cancers; and one, mediastinal lymphoma.

§Includes Pursnani 2015, ROMICAT-II subanalysis of CT arm patients who underwent CACS

**New findings focus on all-cause death or myocardial infarction.

††Defined as the composite outcome of any of the following: late cardiac revascularization (coronary artery bypass graft or percutaneous coronary intervention), hospitalization for unstable angina pectoris or heart failure, nonfatal myocardial infarction, and cardiac death or all-cause mortality.

# APPENDIX C. ARTICLES EXCLUDED AT FULL TEXT REVIEW

**Table C1. Studies and systematic reviews excluded at full text**

| Citation | Reason for exclusion |
|---|---|
| 1. Aggarwal NR, Knickelbine T, Tande A, Stoltzfus L, Lesser JR, Schwartz RS. Noncalcified plaque: relationship between results of multislice computed tomography, risk factors, and late clinical outcome. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions 2011;78:1116-24. | Does not assess CACS as a standalone test. |
| 2. Agus AM, McKavanagh P, Lusk L, et al. The cost-effectiveness of cardiac computed tomography for patients with stable chest pain. Heart (British Cardiac Society) 2016;102:356-62. | Study evaluates comparative effectiveness of CCTA with CACS, not of CACS specifically. |
| 3. Al'Aref SJ, Maliakal G, Singh G, et al. Machine learning of clinical variables and coronary artery calcium scoring for the prediction of obstructive coronary artery disease on coronary computed tomography angiography: Analysis from the CONFIRM registry. European heart journal 2020;41:359-67. | Machine learning model. |
| 4. Almasi A, Pouraliakbar H, Sedghian A, Ali Karimi M, Firouzi A, Tehrai M. The value of coronary artery calcium score assessed by dual-source computed tomography coronary angiography for predicting presence and severity of coronary artery disease. Polish Journal of Radiology 2014;79:169-74. | No diagnostic accuracy information provided. |
| 5. Apfaltrer G, Albrecht MH, Schoepf UJ, et al. High-pitch low-voltage CT coronary artery calcium scoring with tin filtration: accuracy and radiation dose reduction. European radiology 2018;28:3097-104. | Comparison of techniques/radiation reduction protocols. |
| 6. Arbab-Zadeh A, Miller JM, Rochitte CE, et al. Diagnostic accuracy of computed tomography coronary angiography according to pre-test probability of coronary artery disease and severity of coronary arterial calcification. The CORE-64 (Coronary Artery Evaluation Using 64-Row Multidetector Computed Tomography Angiography) International Multicenter Study. Journal of the American College of Cardiology 2012;59:379-87. | Assesses the accuracy of CCTA not CACS – looks at CCTA accuracy in pts with > or < 600 CACS. |
| 7. Babaev A, Kayumov NU. Prognostic value of coronary artery calcium score in patients after myocardial infarction and diabetes mellitus. European heart journal cardiovascular Imaging 2019;20. | Included patients have symptomatic CAD and are undergoing Percutaneous Coronary Intervention. |
| 8. Bamberg F, Mayrhofer T, Ferencik M, et al. Age- and sex-based resource utilisation and costs in patients with acute chest pain undergoing cardiac CT angiography: pooled evidence from ROMICAT II and ACRIN-PA trials. European radiology 2018;28:851-60. | No info specific to calcium scoring/testing. |
| 9. Barros MV, Nunes Mdo C, Braga G, et al. Role of coronary artery calcium score for risk stratification in patients with non significant perfusion defects by myocardial perfusion single photon emission computed tomography. Cardiology journal 2015;22:330-5. | Incremental value in the prognostic evaluation of patients with myocardial perfusion imaging studies presenting non-significant perfusion deficit and suspected CAD. |

| Citation | Reason for exclusion |
|---|---|
| 10. Bauer RW, Thilo C, Chiaramida SA, Vogl TJ, Costello P, Schoepf UJ. Noncalcified atherosclerotic plaque burden at coronary CT angiography: a better predictor of ischemia at stress myocardial perfusion imaging than calcium score and stenosis severity. AJR American journal of roentgenology 2009;193:410-8. | Mixed population of patients with known or suspected CAD. |
| 11. Beigneux Y, Sablayrolles JL, Varenne O, Mas JL, Calvet D. Coronary artery calcium score improves the prediction of occult coronary artery stenosis in stroke/transient ischemic attack patients. European Stroke Journal 2016;1:27. | Abstract only. |
| 12. Bendix K, Jensen JM, Poulsen S, Mygind N, Nørgaard BL. Coronary dual source multi detector computed tomography in patients suspected of coronary artery disease: prevalence of incidental extra-cardiac findings. European journal of radiology 2011;80:109-14. | We identified and summarized two SRs on incidental findings for cardiac computed topographies; if a re-review were conducted, this would be included. |
| 13. Blaha MJ, Whelton SP, Al Rifai M, et al. Rationale and design of the coronary artery calcium consortium: A multicenter cohort study. Journal of cardiovascular computed tomography 2017;11:54-61. | Asymptomatic patients. |
| 14. Bom MJ, Van der Zee PM, Van der Zant FM, Knol RJ, Cornel JH. Independent prognostic value of coronary artery calcium score and coronary computed tomography angiography in an outpatient cohort of low to intermediate risk chest pain patients. Neth Heart J 2016;24:332-42. | Prognostic value of CACS to predict future cardiac events. |
| 15. Breuckmann F, Olligs J, Hinrichs L, et al. Coronary Artery Calcium as an Independent Surrogate Marker in the Risk Assessment of Patients With Atrial Fibrillation and an Intermediate Pretest Likelihood for Coronary Artery Disease Admitted to a German Chest Pain Unit. Clinical cardiology 2016;39:157-64. | Compares risk stratification scores. |
| 16. Budoff MJ, Kessler P, Gao YL, Qunibi W, Moustafa M, Mao SS. The interscan variation of CT coronary artery calcification score: analysis of the Calcium Acetate Renagel Comparison (CARE)-2 study. Academic radiology 2008;15:58-61. | Publication date; use of older technology. |
| 17. Carrascosa P, Leipsic JA, Deviggiano A, et al. Virtual Monochromatic Imaging in Patients with Intermediate to High Likelihood of Coronary Artery Disease: Impact of Coronary Calcification. Academic radiology 2016;23:1490-7. | Technique evaluation (monochromatic imaging). |
| 18. Chang SM, Nabi F, Xu J, et al. Value of CACS compared with ETT and myocardial perfusion imaging for predicting long-term cardiac outcome in asymptomatic and symptomatic patients at low risk for coronary disease: clinical implications in a multimodality imaging world. JACC: Cardiovascular Imaging 2015;8:134-44. | Mostly asymptomatic (>80%) population. |
| 19. Cho YK, Nam CW, Koo BK, et al. Usefulness of baseline statin therapy in non-obstructive coronary artery disease by coronary computed tomographic angiography: From the CONFIRM (COronary CT Angiography EvaluatioN For Clinical | Prognostic value of CACS to predict future cardiac events. |

| Citation | Reason for exclusion |
|---|---|
| Outcomes: An InteRnational Multicenter) study. PloS one 2018;13:e0207194. | |
| 20. Choi A, Leifer E, Shanbhag S, Bronson K, Arai A, Chen M. Coronary artery calcium scoring on 320 detector row CT demonstrates low interscan variability at standard and 70% reduced radiation dose. Journal of cardiovascular computed tomography 2015;9:S90-S1. | 320 detector row CT; reduced radiation settings; Comparison of techniques. |
| 21. Crum-Cianflone N, Stepenosky J, Medina S, Wessman D, Krause D, Boswell G. Clinically significant incidental findings among human immunodeficiency virus-infected men during computed tomography for determination of coronary artery calcium. The American journal of cardiology 2011;107:633-7. | Screening CACS; We identified and summarized two SRs on incidental findings for cardiac computed topographies; if a re-review were conducted, this would be included. |
| 22. Dedic A, Genders TS, Ferket BS, et al. Stable angina pectoris: head-to-head comparison of prognostic value of cardiac CT and exercise testing. Radiology 2011;261:428-36. | Population is a subgroup of patients with suspected CAD who ended up undergoing revascularization. |
| 23. Douglas PS, Hoffmann U, Lee KL, et al. PROspective Multicenter Imaging Study for Evaluation of chest pain: rationale and design of the PROMISE trial. American heart journal 2014;167:796-803.e1. | No info specific to calcium scoring/testing. |
| 24. Doris M, Newby DE. Coronary CT Angiography as a Diagnostic and Prognostic Tool: Perspectives from the SCOT-HEART Trial. Current cardiology reports 2016;18:1-8. | Review/editorial. |
| 25. Ferencik M, Mayrhofer T, Puchner SB, et al. Computed tomography-based high-risk coronary plaque score to predict acute coronary syndrome among patients with acute chest pain--Results from the ROMICAT II trial. Journal of cardiovascular computed tomography 2015;9:538-45. | No calcium scores/scans; only "spotty calcium" described |
| 26. Ferencik M, Liu T, Mayrhofer T, et al. hs-Troponin I Followed by CT Angiography Improves Acute Coronary Syndrome Risk Stratification Accuracy and Work-Up in Acute Chest Pain Patients: Results From ROMICAT II Trial. JACC Cardiovascular imaging 2015;8:1272-81. | No calcium scores/scans; only "spotty calcium" described |
| 27. Fujimoto S, Kondo T, Kumamaru KK, et al. Prognostic Value of Coronary Computed Tomography (CT) Angiography and Coronary Artery Calcium Score Performed Before Revascularization. Journal of the American Heart Association 2015;4:e002264. | Prognostic value of CACS to predict future cardiac events. |
| 28. Genders TSS, Coles A, Hoffmann U, et al. The External Validity of Prediction Models for the Diagnosis of Obstructive Coronary Artery Disease in Patients With Stable Chest Pain: Insights From the PROMISE Trial. JACC Cardiovascular imaging 2018;11:437-46. | Modeling study. |
| 29. Gökdeniz T, Kalaycıoğlu E, Aykan A, et al. Value of coronary artery calcium score to predict severity or complexity of coronary artery disease. Arquivos brasileiros de cardiologia 2014;102:120-7. | Assesses the incremental value of CACS. |
| 30. Goldstein JA, Chinnaiyan KM, Abidov A, et al. The CT-STAT (Coronary Computed Tomographic Angiography for Systematic Triage of Acute Chest Pain Patients to | Calcium scoring/testing not a stand-alone gatekeeper. |

| Citation | Reason for exclusion |
|---|---|
| Treatment) trial. Journal of the American College of Cardiology 2011;58:1414-22. | |
| 31. Hadamitzky M, Distler R, Meyer T, et al. Prognostic value of coronary computed tomographic angiography in comparison with calcium scoring and clinical risk scores. Circulation Cardiovascular imaging 2011;4:16-23. | Assesses the incremental value of CACS. |
| 32. Henein MY, Bengrid T, Nicoll R, Zhao Y, Johansson B, Schmermund A. Coronary calcification compromises myocardial perfusion irrespective of luminal stenosis. European heart journal cardiovascular Imaging 2016;17:i63. | Abstract only. |
| 33. Hoffmann U, Truong QA, Schoenfeld DA, et al. Coronary CT angiography versus standard evaluation in acute chest pain. New England Journal of Medicine 2012;367:299-308. | No data related to CACS |
| 34. Hong JC, Blankstein R, Shaw LJ, et al. Implications of Coronary Artery Calcium Testing for Treatment Decisions Among Statin Candidates According to the ACC/AHA Cholesterol Management Guidelines: A Cost-Effectiveness Analysis. JACC Cardiovascular imaging 2017;10:938-52. | Focus on CACS use in asymptomatic patients to inform risk stratification for statin use. |
| 35. Horiguchi J, Matsuura N, Yamamoto H, et al. Coronary artery calcium scoring on low-dose prospective electrocardiographically-triggered 64-slice CT. Academic radiology 2009;16:187-93. | Comparison of techniques. |
| 36. Horiguchi J, Matsuura N, Yamamoto H, et al. Evaluation of attenuation-based tube current control in coronary artery calcium scoring on prospective ECG-triggered 64-detector CT. Academic radiology 2009;16:1231-40. | Comparison of techniques. |
| 37. Hulten E, Bittencourt MS, Ghoshhajra B, et al. Incremental prognostic value of coronary artery calcium score versus CT angiography among symptomatic patients without known coronary artery disease. Atherosclerosis 2014;233:190-5. | Abstract only. |
| 38. Ibrahim O, Oteh M, Anwar IR, et al. Calcium score of coronary artery stratifies the risk of obstructive coronary artery diseases. La Clinica terapeutica 2013;164:391-5. | Full-text of this study was not obtainable and therefore could not be fully assessed, though it appears that it would be relevant and includable. |
| 39. Iino R, Yokoyama N, Konno K, Naito K, Isshiki T. Impact of combined assessment of coronary artery calcium score, carotid artery plaque score, and brachial-ankle pulse wave velocity for early coronary revascularization in patients with suspected coronary artery disease. International heart journal 2012;53:154-9. | Prognostic value of CACS to predict future cardiac events. |
| 40. Javadrashid R, Salehi A, Tarzamni MK, Aslanabadi N, Pak N. Diagnostic efficacy of coronary calcium score in the assessment of significant coronary artery stenosis. Kardiologia polska 2010;68:285-91. | Does not provide overall diagnostic accuracy information by more usual CACS cutoffs; provides per vessel information. |
| 41. Kim HO, Kim W, Woo JS, et al. The predictive value of aortic arch calcification on chest x-ray for cardiovascular events in comparison with the coronary artery calcium score and the framingham risk score. Journal of the American College of Cardiology 2017;69:1811. | Mixed population of asymptomatic and symptomatic patients. |

| Citation | Reason for exclusion |
|---|---|
| 42. Kunita E, Yamamoto H, Kitagawa T, et al. Prognostic value of coronary artery calcium and epicardial adipose tissue assessed by non-contrast cardiac computed tomography. Atherosclerosis 2014;233:447-53. | Prognostic value of CACS to predict future cardiac events. |
| 43. La Grutta L, Runza G, Gentile G, et al. Prognostic outcome of routine clinical noninvasive multidetector-row computed tomography coronary angiography in patients with suspected coronary artery disease: a 2-year follow-up study. La Radiologia medica 2011;116:521-31. | Prognostic value of CACS to predict future cardiac events. |
| 44. Lee JH, Park MW, Hartaigh BO, et al. Incremental utility of coronary computed tomographic angiography beyond coronary artery calcium scoring for predicting major adverse cardiac events according to impaired renal function: The confirm registry. Journal of the American College of Cardiology 2017;69:1561. | Poster presentation. |
| 45. Lee JH, Rizvi A, Hartaigh B, et al. The Predictive Value of Coronary Artery Calcium Scoring for Major Adverse Cardiac Events According to Renal Function (from the Coronary Computed Tomography Angiography Evaluation for Clinical Outcomes: An International Multicenter [CONFIRM] Registry). The American journal of cardiology 2019;123:1435-42. | CACS prediction according to renal function not of interest; incremental value of CACS beyond scope of report |
| 46. Liu YC, Sun Z, Tsay PK, et al. Significance of coronary calcification for prediction of coronary artery disease and cardiac events based on 64-slice coronary computed tomography angiography. Biomed Res Int 2013;2013:472347. | Population includes patients with both suspected and known CAD; 29% with prior myocardial infarction. |
| 47. Liu T, Maurovich-Horvat P, Mayrhofer T, et al. Quantitative coronary plaque analysis predicts high-risk plaque morphology on coronary computed tomography angiography: results from the ROMICAT II trial. The international journal of cardiovascular imaging 2018;34:311-9. | No mention of calcium scores/scans; only "spotty calcium" described. |
| 48. Lo-Kioeng-Shioe M, Vavere A, Arbab-Zadeh A, et al. Coronary calcium characteristics as predictors of major adverse cardiac events in symptomatic patients: Insights from the CORE320 multinational study. Journal of the American College of Cardiology 2017;69:1556. | Abstract only. |
| 49. Lo-Kioeng-Shioe MS, Vavere AL, Arbab-Zadeh A, et al. Coronary Calcium Characteristics as Predictors of Major Adverse Cardiac Events in Symptomatic Patients: Insights From the CORE320 Multinational Study. Journal of the American Heart Association 2019;8. | Prognostic value of CACS to predict future cardiac events. |
| 50. 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. Journal of cardiovascular computed tomography 2017;11:373-82. | No info specific to calcium scoring/testing. |

| Citation | Reason for exclusion |
|---|---|
| 51. Lu MT, Park J, Ghemigian K, et al. Epicardial and paracardial adipose tissue volume and attenuation - Association with high-risk coronary plaque on computed tomographic angiography in the ROMICAT II trial. Atherosclerosis 2016;251:47-54. | Calcium scores are not the focus. |
| 52. Machaalany J, Yam Y, Ruddy TD, et al. Potential clinical and economic consequences of noncardiac incidental findings on cardiac computed tomography. Journal of the American College of Cardiology 2009;54:1533-41. | We identified and summarized two SRs on incidental findings for cardiac computed topographies; if a re-review were conducted, this would be included. |
| 53. Maffei E, Seitun S, Palumbo A, et al. Prognostic value of Morise clinical score, calcium score and computed tomography coronary angiography in patients with suspected or known coronary artery disease. La Radiologia medica 2011;116:1188-202. | Prognostic value of CACS to predict future cardiac events. |
| 54. Mao SS, Pal RS, McKay CR, et al. Comparison of coronary artery calcium scores between electron beam computed tomography and 64-multidetector computed tomographic scanner. Journal of computer assisted tomography 2009;33:175-8. | Use of outdated technology (EBCT). |
| 55. McLenachan S, Camilleri F, Smith M, Newby DE, Williams MC. Breast arterial calcification on mammography and risk of coronary artery disease: a SCOT-HEART sub-study. Clinical radiology 2019;74:421-8. | Association of calcium score with breast arterial calcification. |
| 56. Meyer M, Henzler T, Fink C, et al. Impact of Coronary Calcium Score on the Prevalence of Coronary Artery Stenosis on Dual Source CT Coronary Angiography in Caucasian Patients with an Intermediate Risk. Academic radiology 2012;19:1316-23. | Assesses CACS for prediction of CCTA results. |
| 57. Nappi C, Nicolai E, Daniele S, et al. Long-term prognostic value of coronary artery calcium scanning, coronary computed tomographic angiography and stress myocardial perfusion imaging in patients with suspected coronary artery disease. Journal of nuclear cardiology : official publication of the American Society of Nuclear Cardiology 2018;25:833-41. | Prognostic value of CACS to predict future cardiac events. |
| 58. Naya M, Murthy VL, Foster CR, et al. Prognostic interplay of coronary artery calcification and underlying vascular dysfunction in patients with suspected coronary artery disease. Journal of the American College of Cardiology 2013;61:2098-106. | Abstract only. |
| 59. Nicoll R, Wiklund U, Zhao Y, et al. The coronary calcium score is a more accurate predictor of significant coronary stenosis than conventional risk factors in symptomatic patients: Euro-CCAD study. International journal of cardiology 2016;207:13-9. | No comparison with ICA; assessing cardiovascular risk factors, not CACS as diagnostic modality. |
| 60. Nieman K, Galema TW, Neefjes LA, et al. Comparison of the value of coronary calcium detection to computed tomographic angiography and exercise testing in patients with chest pain. The American journal of cardiology 2009;104:1499-504. | Compares CACS with CCTA and Exercise Tolerance Test. |

| Citation | Reason for exclusion |
|---|---|
| 61. Obmann VC, Klink T, Heverhagen JT, et al. Impact of Hybrid Iterative Reconstruction on Agatston Coronary Artery Calcium Scores in Comparison to Filtered Back Projection in Native Cardiac CT. RoFo : Fortschritte auf dem Gebiete der Rontgenstrahlen und der Nuklearmedizin 2015;187:372-9. | Comparison of techniques. |
| 62. Oda S, Utsunomiya D, Nakaura T, et al. The Influence of Iterative Reconstruction on Coronary Artery Calcium Scoring-Phantom and Clinical Studies. Academic radiology 2017;24:295-301. | Comparison of techniques. |
| 63. Otton JM, Lønborg JT, Boshell D, et al. A method for coronary artery calcium scoring using contrast-enhanced computed tomography. Journal of cardiovascular computed tomography 2012;6:37-44. | Comparison of techniques. |
| 64. Park MW, Lee JH, Hartaigh BO, et al. Prognostic utility of coronary computed tomographic angiography beyond coronary artery calcium score in diabetic patients with no symptoms or nontypical chest pain: The confirm registry. Journal of the American College of Cardiology 2017;69:1597. | Poster presentation. |
| 65. Parma Z, Parma R, Brzoska J, Sosnowski M. Prognostic value of coronary artery calcium score in patients with symptoms suggestive of coronary artery disease. Results from the Silesian Calcium Score (SILICAS) study. Polskie Archiwum Medycyny Wewnetrznej 2016;126:395-401. | Prognostic value of CACS to predict future cardiac events. |
| 66. Parma Z, Parma R, Syzdol M, Sosnowski M. Prediction of cardiac events based on coronary calcium score in patients with symptoms suggestive of coronary artery disease. European heart journal 2013;34:974-5. | Abstract only. |
| 67. Puchner SB, Liu T, Mayrhofer T, et al. High-risk plaque detected on coronary CT angiography predicts acute coronary syndromes independent of significant stenosis in acute chest pain: results from the ROMICAT-II trial. Journal of the American College of Cardiology 2014;64:684-92. | No mention of calcium scores/scans; only "spotty calcium" described. |
| 68. Pursnani A, Celeng C, Schlett CL, et al. Use of Coronary Computed Tomographic Angiography Findings to Modify Statin and Aspirin Prescription in Patients With Acute Chest Pain. The American journal of cardiology 2016;117:319-24. | No mention of calcium scores/scans. |
| 69. Rajani NK, Joshi FR, Babar J, Balan A, Gopalan D, Rudd JHF. Prevalence of coronary artery disease and major adverse cardiovascular events in patients with a zero calcium score: A prospective cardiac ct study. Heart (British Cardiac Society) 2014;100. | Prognostic value of CACS to predict future cardiac events. |
| 70. Rijlaarsdam-Hermsen D, Lo-Kioeng-Shioe M, van Domburg RT, Deckers JW, Kuijpers D, van Dijkman PRM. Stress-Only Adenosine CMR Improves Diagnostic Yield in Stable Symptomatic Patients With Coronary Artery Calcium. JACC Cardiovascular imaging 2020. | Prognostic value of CACS to predict future cardiac events. |

| Citation | Reason for exclusion |
|---|---|
| 71. Rijlaarsdam-Hermsen D, Lo-Kioeng-Shioe MS, Kuijpers D, van Domburg RT, Deckers JW, van Dijkman PRM. Prognostic value of the coronary artery calcium score in suspected coronary artery disease: a study of 644 symptomatic patients. Netherlands Heart Journal 2020;28:44-50. | Abstract only. |
| 72. Seneviratne SK, Truong QA, Bamberg F, et al. Incremental diagnostic value of regional left ventricular function over coronary assessment by cardiac computed tomography for the detection of acute coronary syndrome in patients with acute chest pain: from the ROMICAT trial. Circulation Cardiovascular imaging 2010;3:375-83. | No calcium scores obtained. |
| 73. Shalaeva A, Dadabaeva N, Shalaeva E. Prognostic value of coronary computed tomographic angiography in symptomatic diabetic/non-diabetic patients without history of myocardial infarction. European heart journal 2017;38:202-3. | Assesses CACS correlation with risk factors. |
| 74. Sosnowski M, Parma Z, Czekaj A, Tendera M. Traditional risk factors and coronary artery calcium in young adults. Cardiology journal 2012;19:402-7. | Prognostic value of CACS to predict future cardiac events. |
| 75. Thilo C, Gebregziabher M, Mayer FB, Zwerner PL, Costello P, Schoepf UJ. Correlation of regional distribution and morphological pattern of calcification at CT coronary artery calcium scoring with non-calcified plaque formation and stenosis. European radiology 2010;20:855-61. | Diagnostic accuracy per patient not reported. |
| 76. Ueda H, Harimoto K, Tomoyama S, et al. Relation of cardiovascular risk factors and angina status to obstructive coronary artery disease according to categorical coronary artery calcium score. Heart and vessels 2012;27:128-34. | Prognostic value of CACS to predict future cardiac events. |
| 77. Van Dijk JD, Shams MS, Ottervanger JP, Mouden M, Van Dalen JA, Jager PL. Coronary artery calcification detection with invasive coronary angiography in comparison with unenhanced computed tomography. Coronary artery disease 2017;28:246-52. | Assessed the ability of ICA to detect calcium. |
| 78. Weininger M, Ritz KS, Schoepf UJ, et al. Interplatform reproducibility of CT coronary calcium scoring software. Radiology 2012;265:70-7. | Comparison of equipment. |
| 79. Yiginer O, Bas S, Pocan S, Yildiz A, Alibek S. Incidental findings of cardiac MSCT: who might benefit from scanning the entire thorax on Ca score imaging? International journal of cardiology 2010;140:239-41. | Letter to the editor. |
| **Systematic reviews** | |
| 80. Abdulla J, Pedersen KS, Budoff M, et al. Influence of coronary calcification on the diagnostic accuracy of 64-slice computed tomography coronary angiography: a systematic review and meta-analysis. The international journal of cardiovascular imaging. 2012 Apr;28(4):943-53. PMID: 21667273. | Assesses CCTA accuracy based on CACS scores - not accuracy of CACS specifically. |

| Citation | Reason for exclusion |
|---|---|
| 81. Bavishi C, Argulian E, Chatterjee S, et al. CACS and the Frequency of Stress-Induced Myocardial Ischemia During MPI: A Meta-Analysis. JACC. Cardiovascular imaging. 2016 May;9(5):580-9. PMID: 27085440. | Association between CACS and stress induced ischemia. |
| 82. Bavishi C, Chatterjee S, Argulian E, et al. Coronary artery calcium score of <100 effectively rules out presence of significant ischemia, while >=400 rules in-insight from a meta-analysis of 14 studies. Journal of the American College of Cardiology. 2014;63(12):A1050. | Association between CACS and stress induced ischemia. |
| 83. Bunch A. Predictive value of coronary computed tomography angiography and coronary calcium scoring in detecting and evaluating acute coronary syndrome. Cardiology (Switzerland). 2013;126:458. | Conference abstract only. |
| 84. Bunch AM. A systematic review of the predictive value of a coronary computed tomography angiography as compared with coronary calcium scoring in alternative noninvasive technique in detecting coronary artery disease and evaluating acute coronary syndrome in an acute care setting. Dimensions of critical care nursing : DCCN. 2012 Mar-Apr;31(2):73-83. PMID: 22333713. | Focus is on CCTA with CACS as a reference; no new studies identified. |
| 85. Di Minno MND, Poggio P, Conte E, et al. Cardiovascular morbidity and mortality in patients with aortic valve calcification: A systematic review and meta-analysis. Journal of cardiovascular computed tomography. 2019;13(4):190-5. | Evaluation of aortic valve calcification. |
| 86. Genders TS, Steyerberg EW, Hunink MG, et al. Prediction model to estimate presence of coronary artery disease: retrospective pooled analysis of existing cohorts. BMJ (Clinical research ed.). 2012 Jun 12;344:e3485. PMID: 22692650. | Focus is on using CACS to predict future cardiac events. |
| 87. Guo SL, Guo YM, Zhai YN, et al. Diagnostic accuracy of first generation dual-source computed tomography in the assessment of coronary artery disease: a meta-analysis from 24 studies. The international journal of cardiovascular imaging. 2011 Jul;27(6):755-71. PMID: 20857200. | Focus is on CCTA. |
| 88. Harrington J, Mody P, Blankstein R, et al. Coronary Artery Calcium Testing in Patients with Chest Pain: Alive and Kicking. Current Cardiovascular Risk Reports. 2017;11(6). | Narrative review. |
| 89. Joshi PH, Blaha MJ, Blumenthal RS, et al. What is the role of calcium scoring in the age of coronary computed tomographic angiography? Journal of nuclear cardiology : official publication of the American Society of Nuclear Cardiology. 2012 Dec;19(6):1226-35. PMID: 23065416. | Narrative review. |
| 90. Kramer CK, Zinman B, Gross JL, et al. Coronary artery calcium score prediction of all cause mortality and cardiovascular events in people with type 2 diabetes: systematic review and meta-analysis. BMJ (Clinical research ed.). 2013 Mar 25;346:f1654. PMID: 23529983. | CACS used as a screening test in asymptomatic patients. |

| Citation | Reason for exclusion |
|---|---|
| 91. Malguria N, Zimmerman S, Fishman EK. Coronary Artery Calcium Scoring: Current Status and Review of Literature. Journal of computer assisted tomography. 2018 Nov/Dec;42(6):887-97. PMID: 30422915. | No summary analysis in symptomatic patients; not a true SR. |
| 92. Nasir K, Clouse M. Role of nonenhanced multidetector CT coronary artery calcium testing in asymptomatic and symptomatic individuals. Radiology. 2012 Sep;264(3):637-49. PMID: 22919038. | Narrative review. |
| 93. 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. | No discussion of how calcium scores were used. Mention of calcium scans contribution to radiation dosage. |
| 94. Pang CL, Pilkington N, Wei Y, et al. A methodology review on the incremental prognostic value of computed tomography biomarkers in addition to Framingham risk score in predicting cardiovascular disease: the use of association, discrimination and reclassification. BMC cardiovascular disorders. 2018 Feb 21;18(1):39. PMID: 29466951. | Risk assessment in asymptomatic patients. |
| 95. van Waardhuizen CN, Khanji MY, Genders TSS, et al. Comparative cost-effectiveness of non-invasive imaging tests in patients presenting with chronic stable chest pain with suspected coronary artery disease: a systematic review. European heart journal. Quality of care & clinical outcomes. 2016 Oct 1;2(4):245-60. PMID: 29474724. | CACS is not evaluated. |
| 96. Vonder M, van der Werf NR, Leiner T, et al. The impact of dose reduction on the quantification of coronary artery calcifications and risk categorization: A systematic review. Journal of cardiovascular computed tomography. 2018 Sep-Oct;12(5):352-63. PMID: 29960743. | Evaluation of technical parameters for radiation reduction. |
| 97. Westwood M, Al M, Burgers L, et al. A systematic review and economic evaluation of new-generation computed tomography scanners for imaging in coronary artery disease and congenital heart disease: Somatom Definition Flash, Aquilion ONE, Brilliance iCT and Discovery CT750 HD. Health technology assessment (Winchester, England). 2013;17(9):1-243. PMID: 23463937. | Evaluation of CCTA; CACS not mentioned. |
| 98. Xie X, Zhao Y, de Bock GH, et al. Validation and prognosis of coronary artery calcium scoring in nontriggered thoracic computed tomography: systematic review and meta-analysis. Circulation. Cardiovascular imaging. 2013 Jul;6(4):514-21. PMID: 23756678. | Evaluation of techniques for image capture. |

## APPENDIX D. REFERENCES FOR ADDITIONAL PROGNOSTIC STUDIES (KQ3)

Table D1. Summary of additionally identified prognostic studies

| Author | Year | Study design | Author's conclusions |
|---|---|---|---|
| Bom | 2016 | Prospective | Our study shows that both CCTA and higher CACS categories have independent prognostic value in chest pain patients with low to intermediate pre-test probability of obstructive CAD, in which CCTA is appropriate. Furthermore, a non-negligible number of patients with CACS = 0 have obstructive CAD at CCTA. CCTA can be used in these patients to identify those at risk for MACE. |
| Dedic | 2011 | Prospective | CT angiography findings are a strong predictor of future adverse events, showing incremental value over clinical predictors, stress testing, and coronary calcium scores. |
| Nappi | 2018 | Prospective | The results of this study suggest that patients with suspected CAD without CAC do not need further cardiac imaging investigations. Stress MPI appears to improve risk stratification over clinical variables, CAC scanning, and CCTA findings. Combined information from CCTA and MPI might allow risk stratification in patients with suspected CAD and documented coronary calcium. |
| Parma | 2016 | Prospective | In selected symptomatic patients with an intermediate probability of CAD, the CACS measurement may be used as the first-line test to assess the risk of MACEs. |
| Yerramasu | 2014 | Prospective | Patients with stable chest pain symptoms but a low likelihood of CAD can safely be diagnosed as not having obstructive CAD in the absence of detectable coronary calcification by unenhanced CT. Patients with CAC .400 Au have a high prevalence of obstructive CAD and further investigation with ICA or functional imaging may be warranted rather than CTCA. These findings support NICE guidance for the investigation of stable chest pain. |
| Rijlaarsdam | 2020a | Prospective | Stress-only adenosine CMR had high diagnostic accuracy and served as an efficient gatekeeper to CAG in stable patients with a CAC score >0. Patients with CAC scores between 0.1 and 100 could be deferred from further testing in the absence of clinical features that suggested high risk. However, in patients with CAC score ≥400, functional testing should be indicated, regardless of the type of chest pain. |
| Rijlaarsdam | 2020 | Retrospective | Risk increased with increasing CAC score. Patients with CAC >100 or ≥400 Agatston units were at increased risk of major adverse cardiac events and are eligible for preventive measures. CAC scanning provided incremental prognostic information to guide the choice of diagnostic and therapeutic options in many subjects evaluated for chest pain. |
| Hulten | 2014 | Retrospective | Among symptomatic patients with CACS zero, a 1–2% prevalence of potentially obstructive CAD occurs, although this finding was not associated with future coronary revascularization or adverse prognosis within 2 years. |

| | | | |
|---|---|---|---|
| Naya | 2013 | Retrospective | In symptomatic patients with normal MPI, global CFR but not CAC provides significant incremental risk stratification over clinical risk score for prediction of major adverse cardiac events. |
| Liu | 2013 | Retrospective | This study further confirms the significant relationship between the CACS and the prevalence of cardiac events and the presence of CAD on a vessel-based in addition to a patient-basis analysis. The prevalence of cardiac events was significantly increased with an increase of CACS. Increased CACS (>100) was also associated with an increased frequency of multivessel disease and patients with CACS > 1000 had a 100% incidence of CAD. Although our data supports calcium screening as an additional filter before coronary angiography in symptomatic patients, a zero CACS could not exclude the presence of significant CAD. |
| Breuckmann | 2016 | Retrospective | Apart from modified GRACE score, overall correlations between risk scores and calcium burden, as well as revascularization rates during index stay, were low. By contrast, the determination of CS may be used as an additional surrogate marker in risk stratification in AF patients with intermediate pretest likelihood for CAD admitted to a chest pain unit. |

# APPENDIX D. AMSTAR EVALUATION FOR INCLUDED SRs

**Appendix Table D1. AMSTAR evaluation of Lo-Kioeng-Shioe 2020 systematic review**

| | Question | Yes | Partial Yes | No | Notes |
|---|---|---|---|---|---|
| 1 | Did the research questions and inclusion criteria for the review include the components of PICO? | X | | | |
| 2 | Did the report of the review contain an explicit statement that the review methods were established prior to conduct of the review and did the report justify any significant deviations from the protocol? | | | X | |
| 3 | Did the review authors explain their selection of the study designs for inclusion in the review? | | | X | |
| 4 | Did the review authors use a comprehensive literature search strategy? | X | | | |
| 5 | Did the review authors perform study selection in duplicate? | X | | | |
| 6 | Did the review authors perform data extraction in duplicate? | | | X | Simply nothing reported re this domain |
| 7 | Did the review authors provide a list of excluded studies and justify the exclusions? | | | X | |

| | Question | Yes | Partial Yes | No | Notes |
|---|---|---|---|---|---|
| 8 | Did the review authors describe the included studies in adequate detail? | X | | | |
| 9 | Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? | X | | | Author's used Hayden's quality appraisal for prognostic studies |
| 10 | Did the review authors report on the sources of funding for the studies included in the review? | | | X | |
| 11 | If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? | X | | | |
| 12 | If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis? | | | X | |
| 13 | Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review? | | | X | |
| 14 | Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? | | | X | |
| 15 | If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? | X | | | |
| 16 | Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review? | X | | | |

**Appendix Table D2. AMSTAR evaluation of Flor 2013 systematic review**

| | Question | Yes | Partial Yes | No | Notes |
|---|---|---|---|---|---|
| 1 | Did the research questions and inclusion criteria for the review include the components of PICO? | X | | | |

| | Question | Yes | Partial Yes | No | Notes |
|---|---|---|---|---|---|
| 2 | Did the report of the review contain an explicit statement that the review methods were established prior to conduct of the review and did the report justify any significant deviations from the protocol? | | | X | |
| 3 | Did the review authors explain their selection of the study designs for inclusion in the review? | | | X | |
| 4 | Did the review authors use a comprehensive literature search strategy? | X | | | |
| 5 | Did the review authors perform study selection in duplicate? | X | | | |
| 6 | Did the review authors perform data extraction in duplicate? | | | X | |
| 7 | Did the review authors provide a list of excluded studies and justify the exclusions? | | X | | Number of studies excluded at full-text and reasons were provided, but no citations. |
| 8 | Did the review authors describe the included studies in adequate detail? | | X | | |
| 9 | Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? | | | X | |
| 10 | Did the review authors report on the sources of funding for the studies included in the review? | | | X | |
| 11 | If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? | X | | | |
| 12 | If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis? | | | X | |
| 13 | Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review? | | | X | |
| 14 | Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? | X | | | |

| | Question | Yes | Partial Yes | No | Notes |
|---|---|---|---|---|---|
| 15 | If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? | | | X | |
| 16 | Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review? | | | X | |

Appendix Table D3. AMSTAR evaluation of Kay 2019 systematic review

| | Question | Yes | Partial Yes | No | Notes |
|---|---|---|---|---|---|
| 1 | Did the research questions and inclusion criteria for the review include the components of PICO? | X | | | |
| 2 | Did the report of the review contain an explicit statement that the review methods were established prior to conduct of the review and did the report justify any significant deviations from the protocol? | | | X | |
| 3 | Did the review authors explain their selection of the study designs for inclusion in the review? | | | X | |
| 4 | Did the review authors use a comprehensive literature search strategy? | X | | | |
| 5 | Did the review authors perform study selection in duplicate? | X | | | |
| 6 | Did the review authors perform data extraction in duplicate? | X | | | |
| 7 | Did the review authors provide a list of excluded studies and justify the exclusions? | | X | | Number of studies excluded at full-text and reasons were provided, but no citations. |
| 8 | Did the review authors describe the included studies in adequate detail? | | X | | |
| 9 | Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? | | | X | |
| 10 | Did the review authors report on the sources of funding for the studies included in the review? | | | X | |
| 11 | If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? | NA | NA | NA | No meta-analysis performed |

| | Question | Yes | Partial Yes | No | Notes |
|---|---|---|---|---|---|
| 12 | If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis? | NA | NA | NA | No meta-analysis performed |
| 13 | Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review? | | | X | |
| 14 | Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? | X | | | |
| 15 | If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? | | | X | |
| 16 | Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review? | X | | | |

**Appendix Table D4. AMSTAR evaluation of Chaikriangkrai 2016 systematic review**

| | Question | Yes | Partial Yes | No | Notes |
|---|---|---|---|---|---|
| 1 | Did the research questions and inclusion criteria for the review include the components of PICO? | X | | | |
| 2 | Did the report of the review contain an explicit statement that the review methods were established prior to conduct of the review and did the report justify any significant deviations from the protocol? | | | X | |
| 3 | Did the review authors explain their selection of the study designs for inclusion in the review? | X | | | |
| 4 | Did the review authors use a comprehensive literature search strategy? | X | | | |
| 5 | Did the review authors perform study selection in duplicate? | X | | | |
| 6 | Did the review authors perform data extraction in duplicate? | X | | | |

| | Question | Yes | Partial Yes | No | Notes |
|---|---|---|---|---|---|
| 7 | Did the review authors provide a list of excluded studies and justify the exclusions? | | X | | Number of studies excluded at full-text and reasons were provided, but no citations. |
| 8 | Did the review authors describe the included studies in adequate detail? | | X | | |
| 9 | Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? | X | | | |
| 10 | Did the review authors report on the sources of funding for the studies included in the review? | | | X | |
| 11 | If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? | X | | | |
| 12 | If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis? | X | | | |
| 13 | Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review? | X | | | |
| 14 | Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? | X | | | |
| 15 | If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? | X | | | |
| 16 | Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review? | X | | | |