Bibliographic Cite	PMID Link	Literature Type	Level of Evidence	Purpose	Population	Intervention and Outcome Measures	Results/ Recommendations	Study Limitiations
Bell KJ, White S, Hassan O, et al. Evaluation of the incremental value of a coronary artery calcium score beyond traditional cardiovascular risk assessment: A systematic review and meta-analysis. JAMA Intern Med. 2022; e221262.	35467692	Systematic review and meta-analysis	moderate	To find, assess, and synthesize all cohort studies that assessed the incremental gain from the addition of a coronary artery calcium score (CACS) to a standard cardiovascular disease (CVD) risk calculator (or CVD risk factors for a standard calculator), that is, comparing CVD risk score plus CACS with CVD risk score alone.	Eligible were cohort studies in primary prevention populations that used 1 of the CVD risk calculators recommended by national guidelines (Framingham Risk Score, QRISK, pooled cohort equation, NZ PREDICT, NORRISK, or SCORE) and assessed and reported incremental discrimination with CACS for estimating the risk of a future cardiovascular event.	Articles were screened by title and abstract independently by 2 authors. The selection process was recorded in sufficient detail to complete a PRISMA flowdiagram. A standardized form was used for data extraction of the characteristics of studies, outcomes, and risk of bias. Two review authors independently assessed the risk of bias for each included study using a modified Quality in Prognosis Studies tool. A meta-analysis was undertaken of the primary outcome: change in C statistic for the model including the CACS compared with the base model.	From 2,772 records screened, 6 eligible cohort studies were identified (with 1,043 CVD events in 17,961 unique participants). Studies varied in size from 470 to 5,185 participants (range of mean [SD] ages, 50 [10] to 75.1 [7.3] years; 38.4%-59.4%were women). The C statistic for the CVD risk models without CACS ranged from 0.693 (95%CI, 0.661 - 0.726) to 0.80. The pooled gain in C statistic from adding CACS was 0.036 (95%CI, 0.020-0.052). Among participants classified as being at low risk by the risk score and reclassified as at intermediate or high risk by CACS, 85.5%(65 of 76) to 96.4%(349 of 362) did not have a CVD event during follow-up (range, 5.1-10.0 years). Among participants classified as being at high risk by the risk score and reclassified as being at low risk by CACS, 91.4%(202 of 221) to 99.2%(502 of 506) did not have a CVD event during follow-up. The authors conclude that CACS appears to add some further discrimination to the traditional CVD risk assessment equations used in these studies, but the modest gain may often be outweighed by costs, rates of incidental findings, and radiation risks.	First, the attrition of participants from the studies included indicated unclear or high risk of bias. However, this attrition applies to measurement of both the CACS and traditional CVD risk factors and therefore may not have biased estimates of incremental value. Second, the studies only used the Framingham Risk Score and PCE CVD risk equations to evaluate potential gain from a CACS, and the incremental gainmay be smaller for other risk equations that include more risk factors, such as the QRISK and PREDICT equations.
Haase R, Schlattmann P, Gueret P, et al. Diagnosis of obstructive coronary artery disease using computed tomography angiography in patients with stable chest pain depending on clinical probability and in clinically important subgroups: Meta-analysis of individual patient data. BMJ. 2019; 365:|1945.	31189617	Meta-analysis	high	To determine whether coronary computed tomography angography (CTA) should be performed in patients with any clinical probability of coronary artery disease (CAD), and whether the diagnostic performance differs between subgroups of patients.	Prospective diagnostic accuracy studies that compared coronary CTA with coronary angiography as reference standard, using >50% diameter reduction as a cutoff value for obstructive CAD. All patients needed to have a clinical indication for coronary angiography due to suspected CAD, and both tests had to be performed in all patients. Results had to be provided using 2×2 or 3×2 cross tabulations for the comparison of CTA with coronary angiography.	Primary outcomes were the positive and negative predictive values of CTA as a function of clinical pretest probability of obstructive CAD, analysed by a generalized linear mixed model; calculations were performed including and excluding non-diagnostic CTA results. The no-treat/treat threshold model was used to determine the range of appropriate pretest probabilities for CTA. The threshold model was based on obtained post-test probabilities of < 15% in case of negative CTA and > 50% in case of positive CTA. Sex, angina pectoris type, age, and number of computed tomography detector rows were used as clinical variables to analyse the diagnostic performance in relevant subgroups.	Individual patient data from 5332 patients from 65 prospective diagnostic accuracy studies were retrieved. For pretest probability range of 7-67%, treat threshold of > 50% and no-treat threshold of < 15% post-test probability were obtained using CTA. At a pretest probability of 7%, the positive predictive value of CTA was 50.9% (95% CI 43.3% to 57.7%) and the negative predictive value of CTA was 97.8% (96.4% to 98.7%); corresponding values at a pretest probability of 67% were 82.7% (78.3% to 86.2%) and 85.0% (80.2% to 88.9%), respectively. The overall sensitivity of CTA was 95.2% (92.6% to 96.9%) and specificity was 79.2% (74.9% to 82.9%). The area under the receiver-operating-characteristic curve for CTA was 0.897 (0.889 to 0.906), and the diagnostic performance of CTA was slightly lower in women than in with men (area under the curve 0.874 (0.858 to 0.890) v 0.907 (0.897 to 0.916), P<0.001). The diagnostic performance of CTA was slightly lower in patients older than 75 (0.864 (0.834 to 0.894), P=0.018 v all other age groups). The authors conclude that the diagnosis of obstructive CAD using coronary CTA in patients with stable chest pain was most accurate when the clinical pretest probability was between 7% and 67%.	The authors list the following limitations.Even though the individual diagnostic accuracy studies were similar in terms of inclusion criteria and reference standard definitions, they varied in geographical origin and composition. Although this study was done in 22 countries and has a multicentric and multicontinental design, participation was not equally distributed across the globe, and ethnicity was not collected in data analysis. Moreover, obstructive CAD was defined by invasive coronary angiography as angiographically significant CAD in all patients, quantitative analysis of invasive angiography was used in 69% of patients, and functional definitions of CAD (eg, including invasive fractional flow reserve) were not used in the original studies. Thus, findings might not be generalisable to real world practice, although additional invasive fractional flow reserve is used in less than 10% of examinations worldwide, making the findings relevant for current clinical practice. An important limitation of the IPD analysis of the clinical performance of coronary CTA was that not all 154 studies that were identified through our search strategy could be included because the responsible corresponding authors did not provide IPD.

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Knuuti J, Ballo H, Juarez-Orozco LE, et al. The performance of non-invasive tests to rule-in and rule-out significant coronary artery stenosis in patients with stable angina: A meta-analysis focused on post-test disease probability. Eur Heart J. 2018; 39(35):3322-3330.	29850808	Meta-analysis	moderate	To determine the ranges of pre-test probability (PTP) of coronary artery disease (CAD) in which stress electrocardiogram (ECG), stress echocardiography, coronary computed tomography angiography (CCTA), single-photon emission computed tomography (SPECT), positron emission tomography (PET), and cardiac magnetic resonance (CMR) can reclassify patients into a post-test probability that defines (>85%) or excludes (<15%) anatomically (defined by visual evaluation of invasive coronary angiography [ICA]) and functionally (defined by a fractional flow reserve [FFR] ≤0.8) significant CAD.	Studies were included according to the following eligibility criteria: (i) the study aimed to investigate stable CAD (not acute coronary syndromes), (ii) either catheter-based X-ray angiography (ICA) or ICA with FFR evaluation were used as the reference standard for the diagnosis of stable CAD, (iii) the reported data was explicit or sufficient to extract numbers for true and false positive and negative results, and (iv) the study included a sample of at least 100 patients (for robustness). Selected studies were further divided according to the reference standard considered (ICA or FFR evaluation).	A broad search in electronic databases until August 2017 was performed. Studies on the aforementioned techniques in >100 patients with stable CAD that utilized either ICA or ICA with FFR measurement as reference, were included. Study-level data was pooled using a hierarchical bivariate random-effects model and likelihood ratios were obtained for each technique. The PTP ranges for each technique to rule-in or rule-out significant CAD were defined. For each included study, the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) criteria were determined by two authors. Data were recorded according to the technique and reference standard utilized. Hierarchical bivariate random-effects models were constructed to combine individual study-level data on the sensitivities and specificities across studies.	A total of 28,664 patients from 132 studies that used ICA as reference and 4131 from 23 studies using FFR, were analyzed. Stress ECG can rule-in and rule-out anatomically significant CAD only when PTP is ≥80% (76–83) and ≤19% (15– 25), respectively. Coronary computed tomography angiography is able to rule-in anatomic CAD at a PTP ≥58% (45– 70) and rule-out at a PTP ≤80% (65–94). The corresponding PTP values for functionally significant CAD were ≥75% (67–83) and ≤57% (40–72) for CCTA, and ≥71% (59–81) and ≤ 27 (24–31) for ICA, demonstrating poorer performance of anatomic imaging against FFR. In contrast, functional imaging techniques (PET, stress CMR, and SPECT) are able to rule-in functionally significant CAD when PTP is ≥46–59% and rule-out when PTP is ≤34–57%.The authors conclude that The various diagnostic modalities have different optimal performance ranges for the detection of anatomically and functionally significant CAD. Stress ECG appears to have very limited diagnostic power. The selection of a diagnostic technique for any given patient to rule-in or rule-out CAD should be based on the optimal PTP range for each test and on the assumed reference standard.	Age, gender, or participants with history of MI may effect on the estimates of diagnostic accuracy but analyses of these characteristics on a group level may lead to spurious results due to the risk of ecological fallacy bias. Authors did not have access to individual patient level data or subgroup data that are needed to validly analyse these characteristics. Another potentially important source of variation or bias is study selection based on prior test results or known CAD. Although authors excluded case-control studies, they do not know whether study selection was restricted to participants with specific prior test results. The inconsistency between studies lowers the confidence in the summary estimates and future studies should aim to dissect sources of bias and variation. Furthermore, the present study considers visual analysis alone for the determination of significant CAD through ICA.
Yang K, Yu SQ, Lu MJ et al. Comparison of diagnostic accuracy of stress myocardial perfusion imaging for detecting hemodynamically significant coronary artery disease between cardiac magnetic resonance and nuclear medical imaging: A meta-analysis. Int J Cardiol. 2019; 293:278-285.	31303392	Meta-analysis	moderate	To compare the diagnostic accuracy of stress myocardial perfusion imaging between cardiac magnetic resonance (CMR) and nuclear medical imaging, including single-photon emission computed tomography (SPECT) and positron emission tomography (PET), for the diagnosis of hemodynamically significant coronary artery disease (CAD) with fractional flow reserve (FFR) as the reference standard.	Studieswere included if:1) stressmyocardial perfusion imaging using CMR, SPECT, or PET was used as a diagnostic test for hemodynamically significant CAD; 2) FFR served as reference standard and FFR < 0.75 or 0.8 was considered hemodynamically significant CAD; 3) studies were prospective; 4) results were reported in absolute numbers of true positive, false positive, true negative, and false negative results, or sufficiently detailed data, such as sensitivity, specificity, and positive number detected by reference standard, were provided to derive these numbers.	PubMed and Embase were searched for all published studies that evaluated the diagnostic accuracy of stress myocardial perfusion imaging modalities, including CMR, SPECT, and PET, to diagnose hemodynamically significant CAD with FFR as the reference standard. The quality assessment of included studies had to conformto the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) criteria. Two investigators extracted data independently, and discrepancies were resolved by consensus.	A total of 28 articles met the inclusion criteria and were included in themeta-analysis: 14 CMR, 13 SPECT, and 5 PET articles. The results demonstrated a pooled sensitivity of 0.88 (95% confidence interval [CI]: 0.80–0.93), 0.69 (95% CI: 0.56–0.79), and 0.83 (95% CI: 0.70–0.91), and a pooled specificity of 0.89 (95% CI: 0.85–0.93), 0.85 (95% CI, 0.80–0.89), and 0.89 (95% CI, 0.86–0.91) for CMR, SPECT, and PET, respectively. The area under the curve (AUC) of CMR, PET, and SPECT was 0.94 (95% CI, 0.92–0.96), 0.92 (95% CI, 0.89–0.94), and 0.87 (95% CI, 0.83–0.89), respectively. The authors conclude that CMR and PET both have high accuracy and SPECT has moderate accuracy to detect hemodynamically significant CAD with FFR as the reference standard. Furthermore, the diagnostic accuracy of CMR at 3.0 T is superior to 1.5 T.	Several limitations should be taken into consideration for a comprehensive interpretation. Firstly, FFR measurement was not performed in all coronary arteries. Secondly, only studies using ICA with FFR as the reference standardwere eligible for inclusion. Therefore, only 5 PET studies were included in this meta-analysis. Thirdly, high degree of heterogeneity was observed in all these three imaging modalities, differences in study methodology and patient characteristics likely account for this observation, and meta regression analyses were performed to evaluate potential sources of heterogeneity, but random effects model provided an accurate summary diagnostic accuracy estimate largely unachievable by standalone studies. Fourthly, the percentage of patients with multivessel disease was different in each study, thus comparison between CMR and SPECT in a certain percentage of patients with multivessel disease (e.g. N20%) may introduce a lot of bias, so the results should be interpreted with caution. Finally, in this meta-analysis, authors note they compared a state of the art technology (CMR) versus an “archeological” one (SPECT), which may be unfair and not comparable,

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