Aus dem Institut für Radiologie
der Medizinischen Fakultät Charité – Universitätsmedizin Berlin

DISSERTATION

Nicht-invasive kardiale Diagnostik bei Verdacht auf eine koronare Herzkrankheit: Metaanalyse individueller Patientendaten zur diagnostischen Genauigkeit der computertomographischen Koronarangiographie unter Einfluss der Prätestwahrscheinlichkeit

zur Erlangung des akademischen Grades
Doctor medicinae (Dr. med.)

vorgelegt der Medizinischen Fakultät
Charité – Universitätsmedizin Berlin

von

Robert Haase

aus Templin

Datum der Promotion: 25.11.2022

In dieser Arbeit wird aus Gründen der besseren Lesbarkeit das generische Maskulinum verwendet. Weibliche und anderweitige Geschlechteridentitäten sind dabei ausdrücklich mitgemeint, soweit es für die Aussage erforderlich ist.

Inhalt

Abkürzungsverzeichnis

CAD	Coronary artery disease
COME-CCT	Collaborative Meta-Analysis of Cardiac Computed Tomography
CT	Computed tomography / Computertomographie
CCTA	Coronary computed tomography angiography / koronare computertomographische Angiographie
EKG	Elektrokardiogramm
ESC	European Society of Cardiology / Europäische Gesellschaft für Kardiologie
FFR	Fraktionelle Flussreserve
IPD	Individual participant data / Individuelle Patientendaten
KHK	Koronare Herzkrankheit
95% CI	95% confidence interval / 95% Konfidenzintervall
MRT	Magnetresonanztomographie
NICE	National Institute for Health and Care Excellence
NPV	Negative predictive value / Negativ prädiktiver Wert
PET	Positronen-Emissions-Tomographie
PPV	Positive predictive value / Positiv prädiktiver Wert
PTP	Pretest probability / Prätestwahrscheinlichkeit
ROC	Receiver operating characteristic
SPECT	Single Photon Emission Computed Tomography / Einzelphotonen-Emissionscomputertomographie
vs	Versus

Abstrakt

Abstract (English)

Objectives. To analyse the association between individual patient characteristics, their pretest probability (PTP) and the diagnostic performance of coronary computed tomography angiography (CCTA) in patients with suspected coronary artery disease (CAD).

Methods. The Collaborative Meta-Analysis of Cardiac Computed Tomography (COME-CCT) was formed to pool patient-level data from diagnostic accuracy studies of CCTA enrolling patients with a clinical indication for invasive coronary angiography as the reference standard for obstructive CAD. A systematic search identified eligible primary studies from which individual participant data (IPD) were sought. The positive and negative predictive values (PPV and NPV) of CCTA as a function of PTP of CAD were analysed by a generalised linear mixed model. In defining the thresholds of PTP when other causes for symptoms (PTP too low) or other diagnostic methods should be applied (PTP too high), the no-treat/treat threshold model determined the range of appropriate PTP for CCTA based on obtained posttest probabilities of below 15% in case of negative CCTA and above 50% in case of positive CCTA. Gender, angina pectoris type, and age were used as clinical variables to evaluate the diagnostic performance in relevant subgroups. Further outcomes were the diagnostic performance of CCTA using ≤64 versus (vs) >64 detector rows.

Results. Individual data of 5332 patients from 65 eligible diagnostic accuracy studies were included. Applying a no-treat/treat threshold model, the highest diagnostic performance of CCTA was achieved in the range of 7 to 67% PTP with a NPV of 97.8% (95% confidence interval [95% CI] 96.4 to 98.7%) at 7% PTP and 85.0% (95% CI 80.2 to 88.9%) at 67% PTP and a PPV of 50.9% (95% CI 43.3 to 57.7%) and 82.7% (95% CI 78.3 to 86.2) accordingly. CCTA with >64 detector rows improved diagnostic performance of CCTA in sensitivity and specificity in comparison to CCTA using up to 64 detector rows. CCTA showed slightly higher diagnostic performance in men compared with women. While the diagnostic performance of CCTA in patients with different types of angina pectoris was similar, it was lower in patients older than 75.

Conclusions. In patients with a PTP ranging from 7 to 67% CCTA reliably ruled out obstructive CAD while also achieving a good positive predictive value. Female patients and patients older than 75 had slightly lower diagnostic performance of CCTA. CT using >64 detector rows should be used if possible. The type of angina pectoris had no influence on diagnostic performance.

Abstrakt (Deutsch)

Zielsetzung. Ziel der Arbeit ist die Untersuchung des Zusammenhangs zwischen Patientencharakteristiken, der Prätestwahrscheinlichkeit (PTP) und der diagnostischen Genauigkeit der koronaren computertomographischen Angiographie (CCTA) in Patienten und Patientensubgruppen mit Verdacht auf eine koronare Herzkrankheit (KHK).

Methoden. Das COME-CCT Projekt trägt individuelle Patientendaten (IPD) aus diagnostischen Genauigkeitsstudien zur CCTA zusammen, die Patienten mit einer klinischen Indikation zum Herzkatheter als Goldstandard zur Diagnose der obstruktiven KHK eingeschlossen haben. Diese wurden über eine systematische Suche identifiziert und die zugrundeliegenden IPD erhoben. Die positiven und negativen prädiktiven Werte (PPV und NPV) der CCTA wurden als Funktion der PTP der KHK über ein generalisiertes lineares gemischtes Regressionsmodell berechnet. Das Behandeln/Nicht-Behandeln-Schwellenwertmodell wurde zur Bestimmung des geeigneten PTP-Bereiches für die Durchführung der CCTA verwendet, indem die PTP definiert wird, ab der andere Gründe für Beschwerden in Betracht gezogen (PTP zu niedrig) oder andere diagnostische Verfahren angewendet werden sollten (PTP zu hoch). Die Schwellenwerte wurden durch die resultierenden Posttestwahrscheinlichkeiten von weniger als 15% im Falle einer negativen und über 50% im Falle einer positiven CCTA definiert. Zur Analyse der diagnostischen Genauigkeit in den relevanten Patientensubgruppen wurden die klinischen Variablen Alter, Geschlecht und die Art der Angina pectoris verwendet. Zudem wurde die diagnostische Genauigkeit zwischen Computertomographie(CT)-Scannern mit ≤64 und >64 Detektorzeilen verglichen.

Resultate. Die individuellen Daten von 5332 Patienten aus 65 Studien wurden in die Metaanalyse eingeschlossen. In dem Behandeln/Nicht-Behandeln-Schwellenwertmodell erreichte die CCTA die höchste diagnostische Genauigkeit in dem Bereich von 7 bis 67% PTP mit einem NPV von 97.8% (95% Konfidenzintervall [95% CI] 96.4-98.7%) bei 7% PTP und 85.0% (95% CI 80.2-88.9%) bei 67% PTP und einem entsprechenden PPV von 50.9% (95% CI 43.3-57.7%) und 82.7% (95% CI 78.3-86.2%). Im Vergleich zu CT mit bis zu 64 Detektorzeilen zeigten CT mit mehr als 64 Detektorzeilen eine höhere Sensitivität und Spezifität. Die diagnostische Genauigkeit der CCTA erzielte ähnliche Ergebnisse bei den verschiedenen Typen der Angina pectoris und zeigte eine leicht geringere diagnostische Genauigkeit bei Frauen im Vergleich zu Männern und bei Patienten älter als 75 Jahre.

Schlussfolgerung. Die CCTA hat eine KHK zuverlässig bei Patienten ausgeschlossen, deren Wahrscheinlichkeit für das Vorliegen einer KHK vor der Untersuchung zwischen 7 und 67% liegt. CT mit mehr als 64 Detektorzeilen sollten vornehmlich verwendet werden. In Frauen und bei Patienten älter als 75 Jahre zeigte die CCTA eine leicht geringere diagnostische Leistung. Die Art der Angina pectoris hatte keinen Einfluss auf die diagnostische Genauigkeit der CCTA.

Manteltext

1. Einleitung

Koronare Herzkrankheit

Die KHK ist die Manifestation der Arteriosklerose in den Koronararterien.[1] Sie ist aufgrund ihrer Folgen und Komplikationen wie einem Herzinfarkt die häufigste Todesursache in industrialisierten Ländern und soll laut Schätzungen bis 2030 auch weltweit die häufigste Todesursache sein.[2] Symptome können durch die Patienten typischerweise als Brustschmerzen (Angina pectoris) wahrgenommen werden. Anhand der Klassifikation durch Diamond und Forrester werden diese in typische und atypische Angina pectoris, nicht anginöse Brustschmerzen sowie andere Brustbeschwerden eingeteilt.[3] Ausgelöst werden die Beschwerden durch eine limitierte Koronarperfusion, die aus einer durch die Arteriosklerose bedingten Stenosierung der Koronargefäße resultiert. Diese Stenosen können sowohl anhand ihres anatomischen Diameters als auch anhand ihrer gemessenen Flusslimitierung (Fraktionelle Flussreserve, FFR) in signifikante und nichtsignifikante Stenosen klassifiziert werden.

Diagnostik der KHK

Goldstandard in der Diagnostik der stenosierenden KHK ist der Linksherzkatheter mit Angiographie der Koronararterien.[1] Stenosen können hierbei sowohl anatomisch als auch funktionell beurteilt werden. Die Verwendung der FFR zur funktionellen Klassifizierung der Stenosen wird jedoch in der klinischen Praxis selten angewandt.[4] Eine Angiographie der Koronararterien mittels Linksherzkatheter bietet den Vorteil der möglichen Therapie in Form einer perkutanen koronaren Angioplastie zur interventionellen Revaskularisierung in derselben Sitzung. Gleichzeitig gehen aufgrund der Invasivität des Katheters aber auch Risiken mit dieser Art der Untersuchung einher, wozu als seltene aber schwere Komplikationen auch ein Herzinfarkt und Schlaganfall zählen. Sowohl die europäische als auch die amerikanische Leitlinie sehen bei Patienten mit stabilen Brustschmerzen und Verdacht auf eine KHK daher zunächst eine nichtinvasive Diagnostik vor. Diese kann als funktioneller Test mit dem Nachweis oder Ausschluss einer Ischämie des Myokards, oder als anatomischer Test mit dem Nachweis oder Ausschluss relevanter Koronarstenosen erfolgen.[1]

Herausforderungen im diagnostischen Management der KHK

Obwohl der Herzkatheter die Möglichkeit der gleichzeitigen Therapie einer KHK bietet, liegt die Erkrankung bei etwa zwei Drittel der Patienten, die einen Herzkatheter erhalten, nicht vor.[5, 6] Jährlich werden in Europa etwa zwei Millionen Herzkatheter in Patienten ohne relevante KHK durchgeführt. Hauptsächlich wird das durch die niedrigen prädiktiven Werte der funktionellen Tests verursacht.[6] Eine Optimierung der Patientenselektion vor der Herzbildgebung und –intervention könnte daher helfen, das Management der Patienten mit Verdacht auf eine KHK effizienter zu gestalten.[5] Dies könnte auf der einen Seite helfen, Kosten für das Gesundheitssystem zu

senken.[7] Auf der anderen Seite könnten Risiken für die Patienten minimiert und das diagnostische Management verbessert werden.

Die nicht-invasive kardiale computertomographische Angiographie

Die CCTA ist das nicht-invasive diagnostische Verfahren mit der höchsten diagnostischen Genauigkeit und erlaubt es, die KHK mit sehr hoher Wahrscheinlichkeit auszuschließen. Metaanalysen berichten von einer mittleren Sensitivität auf Patientenebene von 97.2% (95% CI 96.2-98.0%) und einer Spezifität von 87.4% (95% CI 84.5-89.8%).[8] Darüber hinaus benötigt eine moderne CCTA weniger Strahlendosis als ein Herzkatheter[9] und verbessert die Patienten-akzeptanz der Untersuchung.[10]

Wenig ist jedoch darüber bekannt, welche Patienten bzw. Patientensubgruppen am meisten von einer CCTA profitieren. Hingegen ist bekannt, dass die Genauigkeit diagnostischer Tests, in erster Linie die positiv und negativ prädiktiven Werte, durch die Prävalenz und damit einhergehend durch die PTP für das Vorliegen der zu untersuchenden Erkrankungen beeinflusst wird.[11] In den aktuellen Leitlinien wird daher empfohlen, die PTP der Patienten vor der Zuführung zu einem diagnostischen Test zu bestimmen. In der neuesten Version der europäischen Leitlinie wird dabei auch erstmals anhand der PTP zwischen der Zuführung der Patienten zu einer CCTA bei niedriger bis mittlerer PTP einerseits und zu einem funktionellen Test bei mittlerer bis hoher PTP andererseits unterschieden.[1]

Collaborative Meta-Analysis of Cardiac CT (COME-CCT)

Nach unserem Kenntnisstand existiert bislang noch keine Metaanalyse individueller Patienten-daten, die die diagnostische Genauigkeit der CCTA in Abhängigkeit der PTP untersucht. Unsere Arbeitsgruppe hat das COME-CCT Projekt gegründet, um diese Fragestellung für die CCTA zu beantworten. Da eine solche Fragestellung nicht mit aggregierten Studiendaten beantwortet werden kann, wurden IPD erhoben, um die PTP der einzelnen Patienten errechnen zu können und so die diagnostische Genauigkeit der CCTA als eine Funktion der PTP bei Patienten mit Verdacht auf eine KHK zu ermitteln. Darüber hinaus ermöglichen die IPD eine weitergehende Analyse verschiedener Patientensubgruppen, Untersuchungsprotokolle und CT-Eigenschaften.

Zielsetzung der Arbeit

Die primäre Zielsetzung der Arbeit ist es, den Einfluss der Prätestwahrscheinlichkeit für eine KHK auf die diagnostische Genauigkeit der CCTA zu bestimmen und verschiedene Patienten-subgruppen zu untersuchen und festzustellen, ab welcher CT-Detektorzeilenzahl die CCTA die besten Ergebnisse aufweist. Die dadurch gewonnenen Daten sollen helfen, die Patienten adäquat für diese nicht-invasive diagnostische Herzbildgebung zu selektieren. Diese werden dadurch definiert, dass für sie die CCTA den größten klinischen Nutzen hat, weil sie nicht von einem Herz-katheter oder einer anderen kardialen Diagnostik profitieren würden. Vice versa werden auch so die Patientengruppen identifiziert, die nicht von einer CCTA profitieren würden, da für sie die

prädiktiven Werte zu niedrig sind. Dieser „diagnostische“ Bereich der CCTA wird in unserem Projekt durch die sogenannten Behandeln/Nicht-Behandeln-Schwellenwerte definiert.

Das Behandeln/Nicht-Behandeln-Schwellenwertmodell

Hunink et al. gehen davon aus, dass es einen Schwellenwert der Krankheitswahrscheinlichkeit gibt, an dem der zu erwartende Nutzen einer Intervention und einer Nicht-Intervention exakt gleich und keine der beiden Optionen zu bevorzugen ist.[12] Dieser Schwellenwert (threshold) wird als Grenze des PTP-Bereichs angenommen, in dem eine CCTA empfohlen wird. Dabei wird als untere Grenze der Punkt angenommen, an dem der zu erwartende Nutzen einer CCTA und der Nutzen keiner kardialen Diagnostik exakt gleich sind. Das heißt Patienten mit einer geringeren Krankheitswahrscheinlichkeit als dieser „Nicht-Behandeln-Schwellenwert“ sollte keine kardiale Diagnostik empfohlen und nach einer anderen Ursache für die Beschwerden gesucht werden. Als obere Grenze wird der Punkt angenommen, an dem der zu erwartende Nutzen einer CCTA und der Nutzen funktioneller Tests beziehungsweise eines Herzkatheters exakt gleich sind. Patienten mit einer höheren Krankheitswahrscheinlichkeit als dieser „Behandeln-Schwellenwert“ würden demnach nicht von einer CCTA profitieren, da die Wahrscheinlichkeit eines folgenden Herzkatheters zu hoch ist. Nach der European Society of Cardiology (ESC) werden bei Patienten mit Verdacht auf eine KHK nicht-invasive kardiale diagnostische Tests in einem Prätest-wahrscheinlichkeitsbereich von 15 bis 50% empfohlen. Bei einer Prätestwahrscheinlichkeit <15% sollte nach einer anderen Ursache der Beschwerden gesucht werden, wohingegen bei einer höheren Prätestwahrscheinlichkeit (>50%) primär ein funktioneller nicht-invasiver kardialer Test durchgeführt werden sollte.[1]

2. Methoden

COME-CCT

Das COME-CCT Projekt ist eine kollaborative Metaanalyse, die es möglich machte, individuelle Daten von Patienten, in denen sowohl eine CCTA als auch invasive Koronarangiographie angewendet wurden, von Studienzentren bzw. Forschern weltweit zusammenzutragen und gebündelt unter Berücksichtigung der IPD auszuwerten. Das von der AG Dewey initiierte Projekt wurde durch die Deutsche Forschungsgemeinschaft und das Bundesministerium für Bildung und Forschung gefördert (01KG1110).

COME-CCT ist als weltweite Multicenter-Studie konzipiert, die bei PROSPERO registriert (CRD42012002780) und deren Protokoll veröffentlicht wurde.[13] Die PRISMA-Kriterien für systematische Übersichtsarbeiten wurden berücksichtigt und im Appendix der zugrunde liegenden Publikation veröffentlicht.[14]

Suchstrategie und Verwendbarkeit der Primärstudien

In den Datenbanken Medline (via PubMed), Embase (via Ovid) und Web of Science wurden Primärstudien gesucht. Es wurde eine sensitive Suchstrategie verwendet, die zuvor publiziert wurde.[8] Die Studienauswahl erfolgte durch zwei voneinander unabhängige Untersucher. Unterschiede wurden im Konsens gelöst.

Die Einschlusskriterien für die Primärstudien waren:

- Prospektive diagnostische Genauigkeitsstudien,
- CCTA wurde mit dem Herzkatheter als Goldstandard verglichen,
- ≥50% Diameterstenose als Grenzwert für eine relevante KHK,
- Patienten haben einen Sinusrhythmus und eine klinische Indikation zur Untersuchung mit dem Herzkatheter,
- CCTA und Herzkatheter mussten in allen Studienpatienten durchgeführt worden sein,
- Resultate werden in Vier- oder Sechsfeldertafeln angegeben.[15]

Sammlung der individuellen Patientendaten

Nach Abschluss der Studiensuche und –selektion wurden alle studienrelevanten aggregierten Daten der veröffentlichten Studien durch drei unabhängige Untersucher extrahiert. Unterschiede wurden im Konsens gelöst. Parallel dazu wurden die Korrespondenzautoren jeder Studie kontaktiert. In Form eines Anschreibens wurden die Korrespondenzautoren über die Metaanalyse informiert und gebeten, die IPD der relevanten Studien im Rahmen einer Kollaboration zur Verfügung zu stellen. Bei Mitarbeit übersandten die Autoren die IPD in einer Excel-Tabelle, die zuvor standardisiert erstellt und im Online-Appendix der Publikation veröffentlicht wurde.[14] Darüber hinaus wurden bei allen Autoren auch unpublizierte, geeignete Studien angefragt, deren IPD in die Metaanalyse einfließen sollten. Wenn der Kontakt zum Korrespondenzautor nicht erfolgreich hergestellt werden konnte, wurden weitere Autoren der jeweiligen Studie kontaktiert. Erst wenn die Kontaktaufnahme zu allen Autoren einer Studie nicht erfolgreich war oder keine Antwort erhalten wurde, wurde diese Studie als Studie gewertet, zu der keine IPD erhalten wurden.

Nach Erhalt der IPD über die zurückgesandte Excel-Tabelle überprüften die drei unabhängigen Untersucher die Datenqualität und –plausibilität, auch im Vergleich zu den publizierten Daten einer Studie. Geprüft wurden jeder einzelne Datensatz u.a. hinsichtlich der Datenbereiche, der Mittel- und Medianwerte sowie Minimal- und Maximalwerte im Vergleich zu den veröffentlichten Daten. Weiterhin wurde nach Falscheinträgen und unlogischen Werten gesucht. Unstimmigkeiten zwischen den Untersuchern wurden im Konsens gelöst. Bei weiterhin bestehenden nicht plausiblen Daten wurden diese in einer weiteren Excel-Tabelle aufbereitet, welche per Email an den jeweiligen Korrespondenzautor mit der Bitte auf Datenabgleich gesendet wurde. Dieses Procedere wurde so oft durchgeführt, bis der Datensatz als vollständig galt. Nach Vervollständigung wurden die einzelnen Datensätze in einer Haupttabelle im Excel-Format für die statistische Analyse zusammengeführt.

Studienendpunkte

Primäre Endpunkte der Studie waren die PPV und NPV der CCTA als Funktion der PTP für das Vorliegen einer KHK. Dabei wurden die PPV und NPV sowohl unter Ausschluss als auch unter Verwendung der nicht-diagnostischen CT-Untersuchungen errechnet. Nach dem Intention-to-Diagnose-Prinzip, bei dem nicht-beurteilbare Untersuchungsergebnisse belassen werden, wurde ein „Worst-Case-Szenario" implementiert (**Tabelle 1**). Nicht-diagnostische CCTA-Untersuchungen wurden als falsch positiv kodiert, wenn das Ergebnis des Herzkatheters als Referenztest negativ war, sowie als falsch negativ, wenn das Ergebnis des Referenztests positiv war, um die Sensitivität und Spezifität der CCTA nicht zu überschätzen (**Tabelle 1 bis 4**).[15] Nicht-diagnostische CT-Untersuchungen wurden definiert als Untersuchungen, bei denen mindestens ein Koronarsegment mit einem Durchmesser von ≥1,5 mm nicht auswertbar bzw. nicht beurteilbar war.

Sekundäre Endpunkte waren Maße der diagnostischen Performance der CCTA in verschiedenen Patientensubgruppen. Dazu wurden die Kovariaten Alter, Geschlecht und klinische Präsentation in Form der Angina-pectoris-Klassifikation in receiver operating characteristic (ROC)-Kurven untersucht, sowohl unter Einschluss als auch unter Ausschluss der nicht-diagnostischen CT-Untersuchungen. Der Unterschied zwischen CT-Scannern mit ≤64 Detektorzeilen und >64 Detektorzeilen erfolgte über einen Vergleich der empirischen Sensitivität und Spezifität.

Einschluss nicht-beurteilbarer Ergebnisse mit ‚Intention-To-Diagnose'		**Referenzstandard**	
		+	**–**
Index-Test	**+**	Richtig Positiv	Falsch Positiv ↑
	Nicht-beurteilbar	Nicht-beurteilbar	Nicht-beurteilbar ↑
	–	Falsch Negativ ↓	Richtig Negativ
	Sensitivität↓, Spezifität↓		

Tabelle 1. Einschluss nicht-beurteilbarer Ergebnisse mit ‚Intention-to-Diagnose'. Übersetzt aus Schuetz 2012.[15] Hierbei werden nicht-beurteilbare Testergebnisse als falsch positiv gewertet, wenn der Referenztest negativ war und als falsch negativ, wenn der Referenztest positiv war. Dadurch sinken sowohl Sensitivität als auch Spezifität.

Ausschluss nicht-beurteilbarer Ergebnisse		**Referenzstandard**	
		+	**–**
Index-Test	**+**	Richtig Positiv	Falsch Positiv
	Nicht-beurteilbar	~~Nicht-beurteilbar~~	~~Nicht-beurteilbar~~
	–	Falsch Negativ	Richtig Negativ
	Sensitivität↑, Spezifität↑		

Tabelle 2. Ausschluss nicht-beurteilbarer Testergebnisse. Übersetzt aus Schuetz 2012.[15] Der Ausschluss nicht-beurteilbarer Testergebnisse resultiert in einer Erhöhung der Sensitivität und Spezifität.

Einschluss nicht-beurteilbarer Ergebnisse als Test positiv		**Referenzstandard**	
		+	**–**
Index-Test	**+**	Richtig Positiv ↑	Falsch Positiv ↑
	Nicht-beurteilbar	Nicht-beurteilbar	Nicht-beurteilbar
	–	Falsch Negativ	Richtig Negativ
	Sensitivität↑, Spezifität↓		

Tabelle 3. Einschluss nicht-beurteilbarer Testergebnisse als Test positiv. Übersetzt aus Schuetz 2012.[15] Der Einschluss nicht-beurteilbarer Testergebnisse als Test positiv erhöht sowohl die richtig Positiven als auch falsch Positiven, sodass die Sensitivität steigt und die Spezifität sinkt.

Einschluss nicht-beurteilbarer Ergebnisse als Test negativ		**Referenzstandard**	
		+	–
Index-Test	**+**	Richtig Positiv	Falsch Positiv
	Nicht-beurteilbar	Nicht-beurteilbar ↓	Nicht-beurteilbar ↓
	–	Falsch Negativ	Richtig Negativ
	Sensitivität↓, Spezifität↑		

Tabelle 4. Einschluss nicht-beurteilbarer Ergebnisse als Test negativ. Übersetzt aus Schuetz 2012.[15] Der Einschluss nicht-beurteilbarer Testergebnisse als Test negativ erhöht sowohl die richtig Negativen als auch die falsch Negativen, sodass die Sensitivität sinkt aber die Spezifität steigt.

Prätestwahrscheinlichkeit

Die PTP wurde in einem validierten Vorhersagetool (CAD Consortium Predictiontool) berechnet, welches sich der aktualisierten Version des Diamond und Forrester Modells bedient.[16, 17] In das Tool wurden die demografischen Patientenmerkmale Alter und Geschlecht und die klinische Symptomatik in Form der Angina-pectoris-Klassifikation nach Diamond und Forrester als Faktoren eingebracht.[3] Letztere basiert auf drei anamnestisch zu erhebenden Fragen:

(1) Sind die Beschwerden retrosternal lokalisiert?
(2) Werden sie durch körperliche Belastung ausgelöst?
(3) Bessern sich die Beschwerden durch Ruhe oder Nitroglycerin innerhalb von 30 Sekunden bis zehn Minuten?

Eine typische Angina pectoris liegt demnach dann vor, wenn alle Fragen mit „ja“ und eine atypische Angina pectoris, wenn zwei Fragen mit „ja“ beantwortet wurden. Bei der ursprünglichen Angina-pectoris-Klassifikation durch Diamond und Forrester wurden sowohl bei Vorliegen einer mit „ja“ beantworteten Frage als auch bei allen mit „nein“ beantworteten Fragen die Beschwerden als

nicht-anginöse Beschwerden klassifiziert. Im COME-CCT-Projekt teilten wir diese Gruppe weiter auf, sodass auch in dieser Arbeit alle Patienten, die eine Frage mit „ja“ beantworteten mit nicht-anginösen Beschwerden und alle Patienten, die keine Frage mit „ja“ beantworteten mit anderen Beschwerden klassifiziert wurden.

(1) Drei Fragen mit „ja“ beantwortet = typische Angina pectoris
(2) Zwei Fragen mit „ja“ beantwortet = atypische Angina pectoris
(3) Eine Frage mit „ja“ beantwortet = nicht-anginöse Beschwerden
(4) Keine Frage mit „ja“ beantwortet = andere Beschwerden

Statistische Analyse

Auf Basis der erhobenen IPD und der errechneten PTP erfolgte die Ermittlung der mittleren logarithmischen PPV und NPV, sowie deren Standardfehler und 95% CI. Die logarithmischen Werte wurden anschließend zurücktransformiert, um die mittleren PPV und NPV zu erhalten. Abweichend vom Studienprotokoll wurde dazu eine univariate logistische Regressionsanalyse verwendet. Die Analyse wurde durch zufällige Studieneffekte (random effects) und eine Regressionssteigung (random slope) für CCTA bzw. Katheteranwendung erweitert. Nach der Idee von Skrondal und Rabe-Hasketh[18, 19] konnte mit diesen Daten und dem eingesetzten Modell eine neue Kohorte statistisch vorhergesagt werden.

Basierend auf dem generalisierten linearen gemischten Modell erfolgte auch die Ermittlung der sekundären Endpunkte. Mit dem Testergebnis als abhängige Variable wurde die durchschnittliche logarithmische Sensitivität und Spezifität bestimmt, deren Variabilität zwischen den verschiedenen Studien sowie die Kovarianz und der Einfluss der Kovariaten. Flächen unter den ROC-Kurven wurden anhand der empirischen Daten und des Modells errechnet. Die Signifikanztestung der Kovariaten erfolgte über den Likelihood-Quotienten-Test. Der DeLongs’ Test wurde angewendet, um die Flächen unter den ROC-Kurven zu vergleichen, sowohl unter Inklusion als auch unter Exklusion der nicht-diagnostischen CCTA.[20]

Die aggregierten Studiendaten der Studien für die IPD vorlagen, wurden mit den aggregierten Studiendaten der Studien verglichen für die keine IPD eingebracht wurden, um einen Selektionsbias auszuschließen. Unterschiede wurden in einem bivariaten generalisierten gemischten Modell mit IPD als Kovariate berechnet. Der Likelihood-Quotienten-Test wurde mit und ohne IPD als Variable durchgeführt. Das Modell resultierte in einer aggregierten Vierfeldertafel nach einer Methode von Chu und Cole.[21]

Als statistische Programme kamen für die Analyse STATA 14 und die Pakete GLLAMM und gllapred für die Voraussagen zum Einsatz, sowie MIDAS für die diagnostische Vierfelder-Metaanalyse. Weiterführende statistische Auswertungen erfolgten über SAS Version 9.4. und R 3.4, sowie die Pakete lme4, meta and pROC.

Schwellenwerte des diagnostischen Bereichs der CCTA

Zur Erhebung der Schwellenwerte des diagnostischen Bereichs der CCTA gingen wir von dem oben genannten und von der ESC empfohlenen idealen Prätestwahrscheinlichkeitsbereich von 15-50% aus. Aus den durch die Metaregression gewonnenen prädiktiven Werten der CCTA errechneten wir die Prätestwahrscheinlichkeiten des hier verwendeten Kalkulators, die eine Posttestwahrscheinlichkeit nach CCTA von <15% im Falle eines negativen Testergebnisses (Nicht-Behandeln-Schwellenwert) und eine Postwahrscheinlichkeit von >50% nach positivem Testergebnis erzielten (Behandeln-Schwellenwert).

3. Ergebnisse

Studienselektion und -analyse

154 geeignete Studien wurden über die systematische Suche und den direkten Kontakt mit Autoren identifiziert. Die Autoren aller Studien wurden angeschrieben und die Kollaboration im COME-CCT Projekt mit Übersenden der IPD angefragt, sowie auch um das Übersenden der IPD unveröffentlichter Studien gebeten. Von 76 Studien (davon 74 veröffentlichte und zwei nicht publizierte) wurden die IPD für 7813 Patienten übermittelt. In einem umfangreichen Prozess erfolgte die intensive Aufarbeitung der individuellen Patientendaten durch die drei unabhängigen Untersucher und nach Konsens auch mit den kooperierenden Autoren in mehreren Revisions-runden. Von den 78 Studien für die keine IPD vorlagen, war der Hauptgrund hierfür, dass 56 (71,8%) der Korrespondenzautoren nicht geantwortet haben und auch der Kontakt zu weiteren Autoren der Studie nicht erfolgreich hergestellt werden konnte. Sieben Autoren gaben an, dass sie keinen Zugang mehr zu den originalen Daten haben. Jeweils zwei Autoren äußerten, nicht die Möglichkeit zur Partizipation zu haben, antworteten nach der Deadline oder wollten nicht teilnehmen. Jeweils ein Autor gab gesundheitliche Probleme, veränderte Forschungs-schwerpunkte, keine vollständigen Daten, technische Probleme, eine fehlende Eignung der Originaldaten oder Zeitmangel als Ursache an, nicht teilnehmen zu können. Zu insgesamt drei Studien waren die in der Publikation angegebenen Korrespondenz-Emailadressen nicht existent und es konnten auch keine weiteren funktionierenden Emailadressen von Autoren der Studien gefunden werden. Das Flussdiagramm zur Studiensuche und –selektion ist in **Abbildung 1** illustriert.

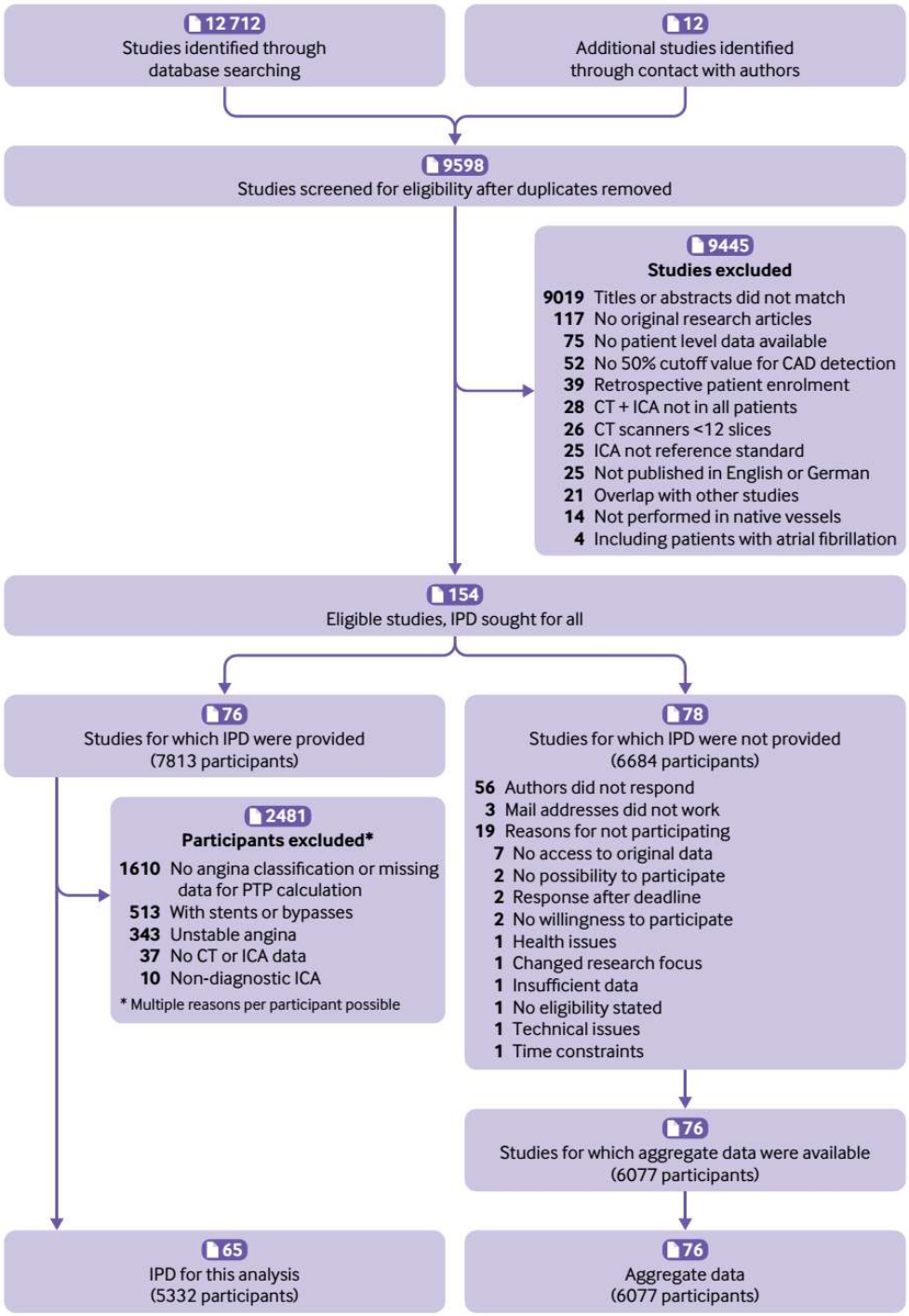


Abbildung 1. Flussdiagramm zur Studiensuche und -selektion.[22]

Im Vergleich der aggregierten Studiendaten zeigten die Studien von denen IPD erhalten wurden keinen Unterschied zu den Studien, von denen keine IPD erhalten wurden (p=0.73) (**Abbildung 2**).

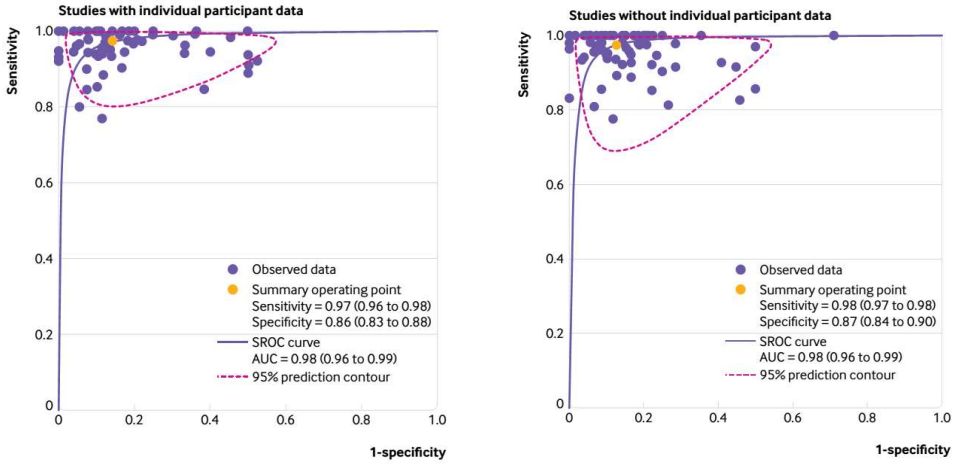


Abbildung 2. Vergleich der aggregierten Studiendaten zwischen den Studien, zu denen IPD erhalten und den Studien, zu denen keine IPD erhalten wurden.[22]

Im Funnelplot zeigte sich kein Hinweis auf einen Publikationsbias (**Abbildung 3**). Das Risiko für Bias in den Items des QUADAS-2-Tools war in der Mehrheit der Studien gering.[22]

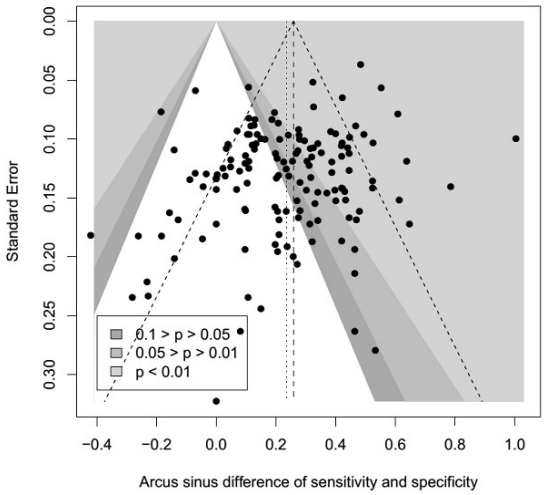


Abbildung 3. Contour-enhanced Funnelplot.[22] Auf der X-Achse sind die Arcussinusdifferenz von Sensitivität und Spezifität als Studienergebnisse gegen den Standard-Fehler auf der Y-Achse als Maß der Präzision aufgetragen. Die symmetrische Verteilung der Studien (als schwarze Punkte) um den errechneten Mittelwert ergibt keinen Hinweis auf einen Publikationsbias. Auch im Rangkorrelationstest nach Rücker zeigte sich keine Korrelation zwischen Studienergebnissen und Studienpräzision (p=0,2585).

Aus dem IPD-Pool konnten 2491 Patienten aus insgesamt elf Studien nicht in dieser primären Analyse berücksichtigt werden, da nicht die erforderlichen Daten zur Klassifizierung der Angina pectoris vorlagen, Patienten mit instabiler Angina pectoris eingeschlossen wurden oder die Patienten bereits Koronarstents oder Bypässe hatten. Letztlich konnten in die Analyse die individuellen Daten von 5332 Patienten aus 65 Studien einfließen. Für 554 Patienten waren dabei die Ergebnisse der CCTA nicht-diagnostisch.

Patientencharakteristiken und deskriptive Analyse

Die eingeschlossenen Patienten waren im Mittel 61 Jahre alt. Der Anteil der Frauen betrug 35% (1859 von 5332). Die Patientencharakteristiken sind als mittlere Werte und für Prätestwahrscheinlichkeitskategorien in 10%-Schritten in **Tabelle 5** angegeben. Der Anteil der Frauen nahm mit steigender Prätestwahrscheinlichkeit ab, von 100% der Patienten mit einer Prätestwahrscheinlichkeit von 0 bis 10% bis zu 0% ab einer Prätestwahrscheinlichkeit von 80%.

4666 Patienten wurden mit CT-Scannern untersucht, die ≤64 Detektorzeilen einsetzen, und 558 Patienten mit CT-Scannern mit >64 Detektorzeilen. Von den 4666 Untersuchungen mit CT-Scannern ≤ 64 Detektorzeilen waren 538 (11.5%) nicht-diagnostisch. Hingegen waren nur 16 (2.9%) der Untersuchungen mit CT-Scannern >64 Detektorzeilen nicht-diagnostisch. Die empirische Sensitivität und Spezifität der CCTA mit ≤64 Detektorzeilen waren 86.5% und 72.6%, die der CCTA mit >64 Detektorzeilen hingegen signifikant höher; 93.4% ($p=0.002$) und 84.4% ($p<0.001$).

Bis zu einer PTP von 40% überschätzten die PTP-Vorhersagen des verwendeten Modells/Prediction Tools die reale Prävalenz der KHK um ca. 10 Prozentpunkte, während die Prävalenz um ca. 10 Prozentpunkte unterschätzt wurde, wenn die PTP über 50% lag.

Table 1 | Baseline patient characteristics and empirical diagnostic performance of computed tomography angiography to diagnose coronary artery disease, stratified by pretest probability category and scanner detector rows

		Pretest probability categories									
	Overall (n=5332)	0 to <10% (n=86)	10 to <20% (n=530)	20 to <30% (n=601)	30 to <40% (n=727)	40 to <50% (n=745)	50 to <60% (n=752)	60 to <70% (n=590)	70 to <80% (n=535)	80 to <90% (n=698)	90 to 100% (n=68)
Demographic characteristics (median (range) or No (%))											
Median age (years)	61 (18-96)	47 (18-50)	56 (23-70)	59 (24-82)	57 (37-89)	55 (27-87)	63 (30-91)	70 (36-88)	55 (47-92)	66 (59-77)	80 (78-89)
Men	3473 (65)	0	29 (5)	211 (35)	509 (70)	576 (77)	507 (67)	391 (66)	484 (90)	698 (100)	68 (100)
Women	1859 (35)	86 (100)	501 (95)	390 (65)	218 (30)	169 (23)	245 (33)	199 (34)	51 (10)	0	0
Median body mass index	26.3 (14.3-57.1)	25.6 (17.9-39.3)	26.2 (14.3-47.3)	25.9 (16.1-44.8)	26.2 (16.9-41.8)	26.4 (17.5-45.2)	26.5 (17.2-57.1)	26.4 (15.5-56.2)	27.0 (17.5-42.5)	26.9 (16.9-56.7)	25.9 (16.8-35.2)
Clinical presentation (No)											
Typical angina	1967	0	0	4	43	137	247	306	464	698	68
Atypical angina	1592	1	138	269	235	280	339	260	70	0	0
Non-anginal chest pain	796	38	162	157	188	158	80	12	1	0	0
Other chest discomfort	977	47	230	171	261	170	86	12	0	0	0
Diagnostic performance (No or %)											
CAD prevalence (%)*	48.3	17.4	24.0	32.1	40.9	46.8	46.8	53.7	68.6	71.6	82.4
TP	2251	14	120	176	272	321	310	256	317	420	45
TN	2031	52	313	312	334	287	294	194	103	134	8
FP	728	19	90	96	96	109	106	79	65	64	4
FN	322	1	7	17	25	28	42	61	50	80	11
NDX†	554	13	58	50	54	67	76	79	60	85	12
NDX rate (%)†	10.4	15.1	10.9	8.3	7.4	9.0	10.1	13.4	11.2	12.2	17.6
PPV (%)	75.6	42.4	57.1	64.7	73.9	74.7	74.5	76.4	83.0	86.8	91.8
NPV (%)	86.3	98.1	97.8	94.8	93.0	91.1	87.5	76.1	67.3	62.6	42.1
Sensitivity (%)	87.5	93.3	94.5	91.2	91.6	92.0	88.1	80.8	86.4	84.0	80.4
Specificity (%)	73.6	73.2	77.7	76.5	77.7	72.5	73.5	71.1	61.3	67.7	66.7
Diagnostic accuracy (%)	80.3	76.7	81.7	81.2	83.4	81.6	80.3	76.3	78.5	79.4	77.9
LR+	3.32	3.49	4.23	3.88	4.10	3.34	3.32	2.79	2.23	2.60	2.41
LR−	0.17	0.09	0.07	0.12	0.11	0.11	0.16	0.27	0.22	0.24	0.29
CT scanners with ≤64 detector rows (No or %)											
No of patients	4666	80	452	529	651	634	637	530	472	619	62
CAD prevalence (%)	48.2	17.5	24.1	31.2	41.8	45.5	46.0	54.0	67.4	72.5	85.5
TP	1943	13	102	150	248	264	256	226	270	372	42
TN	1757	47	265	273	295	247	246	170	95	114	5
FP	662	19	78	91	84	99	98	74	59	56	4
FN	304	1	7	15	24	24	37	60	48	77	11
NDX†	538	13	54	50	50	65	75	77	58	84	12
NDX rate (%)†	11.5	16.3	11.9	9.5	7.7	10.3	11.8	14.5	12.3	13.6	19.4
PPV (%)	74.6	40.6	56.7	62.2	74.7	72.7	72.3	75.3	82.1	86.9	91.3
NPV (%)	85.2	97.9	97.4	94.8	92.5	91.1	86.9	79.9	66.4	59.7	31.3
Sensitivity (%)	86.5	92.9	93.6	90.9	91.2	91.7	87.4	79.0	84.9	82.9	79.2
Specificity (%)	72.6	71.2	77.3	75.0	77.8	71.4	71.5	69.7	61.7	67.1	55.6
Diagnostic accuracy (%)	79.3	75.0	81.2	80.0	83.4	80.6	78.8	74.7	77.3	78.5	75.8
LR+	3.16	3.23	4.12	3.64	4.11	3.20	3.07	2.61	2.22	2.52	1.78
LR−	0.19	0.10	0.08	0.12	0.11	0.12	0.18	0.30	0.24	0.26	0.37
CT scanners with >64 detector rows (No or %)											
No of patients	558	6	73	62	66	87	103	55	41	59	6
CAD prevalence (%)*	46.1	16.7	21.9	37.1	30.3	54.0	49.5	50.9	75.6	62.7	50.0
TP	240	1	16	21	19	44	46	27	29	34	3
TN	254	5	46	36	39	33	47	22	6	17	3
FP	47	0	11	3	7	7	5	5	4	5	0
FN	17	0	0	2	1	3	5	1	2	3	0
NDX†	16	0	4	0	4	2	1	2	2	1	0
NDX rate (%)†	2.9	0.0	5.5	0.0	6.1	2.3	1.0	3.6	4.9	1.7	0.0
PPV (%)	83.6	100	59.3	87.5	73.1	86.3	90.2	84.4	87.9	87.2	100
NPV (%)	93.7	100	100	94.7	97.5	91.7	90.4	95.7	75.0	85.0	100
Sensitivity (%)	93.4	100	100	91.3	95.0	93.6	90.2	96.4	93.5	91.9	100
Specificity (%)	84.4	100	80.7	92.3	84.8	82.5	90.4	81.5	60.0	77.3	100
Diagnostic accuracy (%)	88.5	100	84.9	91.9	87.9	88.5	90.3	89.1	85.4	86.4	100
LR+	5.98	∞	5.18	11.87	6.24	5.35	9.38	5.21	2.34	4.04	∞
LR−	0.08	0	0	0.09	0.06	0.08	0.11	0.04	0.11	0.10	0

TP=true positives; TN=true negatives; FP=false positives; FN=false negatives; PPV=positive predictive value; NPV=negative predictive value; LR+=positive likelihood ratio; LR−=negative likelihood ratio; NDX=non-diagnostic results.
The empirical results were derived from raw data and thus differ from the results of the statistical model.
*CAD prevalence was defined by coronary angiography.
†Non-diagnostic results were included in the estimation of diagnostic accuracy as false positives if the reference standard was negative, and as false negative if the reference standard was positive.

Tabelle 5. Patientencharakteristiken und empirische diagnostische Genauigkeit der CCTA stratifiziert nach Prätestwahrscheinlichkeit in Kategorien und CT-Detektorzeilenzahl.[22]

Diagnostische Performance der CCTA in Abhängigkeit der Prätestwahrscheinlichkeit

In der Regressionsanalyse zeigte der PPV mit steigender PTP einen leicht degressiven Verlauf, während 1-NPV mit steigender PTP einen leicht progressiven Verlauf aufwies. In dem Bereich von 7 bis 67% PTP erreichte die CCTA, unter Einschluss der nicht-diagnostischen Untersuchungen nach dem Intention-to-Diagnose-Prinzip, die höchste diagnostische Leistung, sodass Posttestwahrscheinlichkeiten von 15 bis 50% erzielt wurden (**Abbildung 4**).

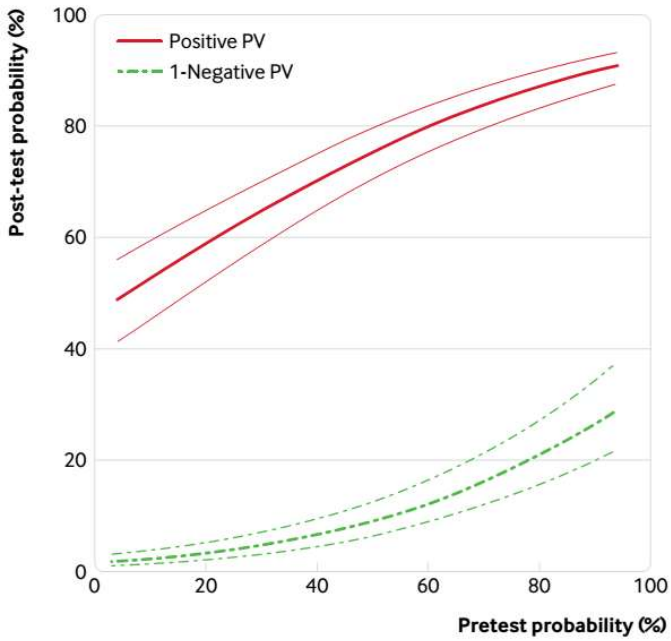


Abbildung 4. Die prädiktiven Werte der CCTA in Abhängigkeit von der Prätestwahrscheinlichkeit.[22] Die X-Achse stellt die Prätestwahrscheinlichkeit in Prozent dar, die Y-Achse die Posttestwahrscheinlichkeit anhand der prädiktiven Werte (PPV und 1-NPV). Die prädiktiven Werte sind mit ihrem 95% CI anhand des generalisierten linearen gemischten Modells mit Einschluss der nicht-diagnostischen Untersuchungen in rot (PPV) und grün (1-NPV) dargestellt.

Bei einer PTP von 7% war der PPV 50.9% (95% CI 43.3-57.7%) und der NPV 97.8% (95% CI 96.4-98.7%). Bei einer PTP von 67% war der PPV 82.7% (95% CI 78.3-86.2%) und der NPV 85.0% (95% CI 80.2-88.9%). Unter Anwendung der ESC-Schwellenwerte als PTP ergaben sich für eine PTP von 15% ein NPV von 97.1% (95% CI 95.4-98.2%) und ein PPV von 55.8% (95% CI 48.6-62.3%), während bei einer PTP von 50% ein NPV von 90.9% (95% CI 87.5-93.4%) und ein PPV von 75.4% (95% CI 70.5-79.5%) resultierten.

Die durchschnittliche Sensitivität betrug für alle Patienten 95.2% (92.6-96.9%) und die Spezifität 79.2% (74.9-82.9%). In einer ROC-Analyse resultierten CCTA inklusive nicht-diagnostischer Untersuchungen in einer Fläche unter der ROC-Kurve von 0.897 (0.889-0.906). Im Vergleich lag die Fläche unter der ROC-Kurve für CCTA unter Ausschluss der nicht-diagnostischen Untersuchungen signifikant höher (0.949, 0.943-0.954, p<0.001) (**Abbildung 5**).

Da der Einschluss nicht-diagnostischer CCTA näher an der klinischen Realität liegt, werden alle weiteren Ergebnisse inklusive der Daten nicht-diagnostischer CCTA als oben beschriebenes Worst-Case-Szenario angegeben.

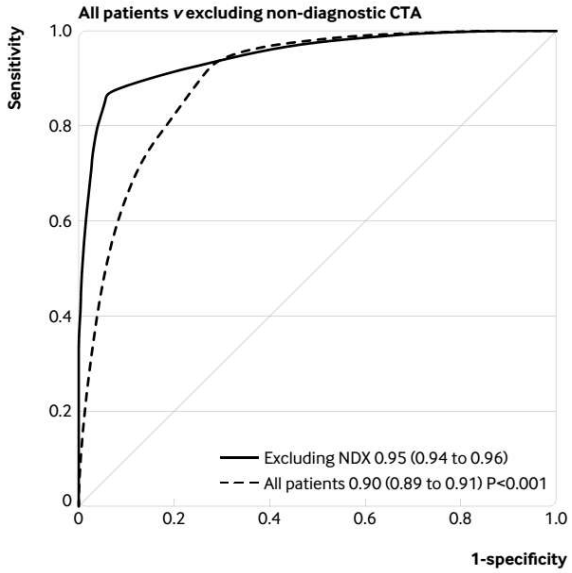


Abbildung 5. Diagnostische Genauigkeit der CCTA unter Ein- und Ausschluss der nicht-diagnostischen Untersuchungen.[22] In der ROC-Kurve sind 1-Spezifität auf der X-Achse und Sensitivität auf der Y-Achse aufgetragen. Der Einschluss der nicht-diagnostischen Untersuchungen mit ‚Intention-to-Diagnose' (gestrichelte Linie) resultiert in einer signifikant kleineren Fläche unter der Kurve gegenüber dem Ausschluss nicht-diagnostischer Untersuchungen (NDX, durchgezogene Linie), p<0,001.

Diagnostische Performance der CCTA bei verschiedenen Patientensubgruppen

Für Frauen ergab sich eine Sensitivität der CCTA von 93.5% (89.6-96.0%) und für Männer von 95.8% (93.4-97.4%), die Spezifität war bei Frauen 80.6% (75.9-84.6%) und Männern 77.4% (72.4-81.8%, P<0.001). In der ROC-Analyse war die Leistung der CCTA bei Männern höher im Vergleich zu Frauen (Fläche unter der ROC-Kurve 0.907 [0.897-0.916] vs 0.874 [0.858-0.890], p<0.001) (**Abbildung 6**).

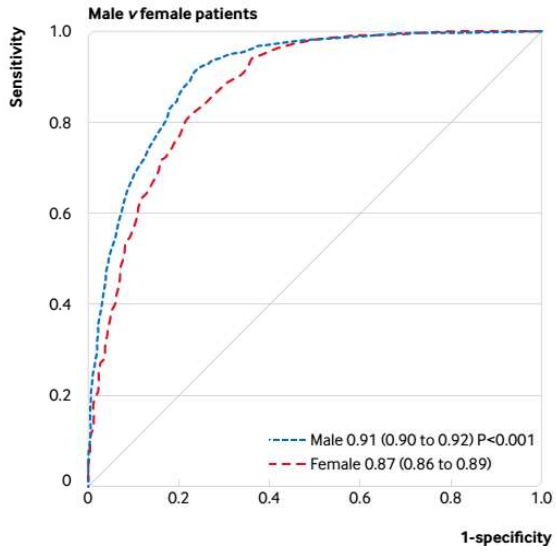


Abbildung 6. Diagnostische Genauigkeit der CCTA bei Frauen und Männern.[22] In der ROC-Kurve sind 1-Spezifität auf der X-Achse und Sensitivität auf der Y-Achse aufgetragen. Männer (blau) weisen eine etwas größere Fläche unter der Kurve auf als Frauen (rot).

Eine deskriptive Auswertung zeigte, dass die Herzfrequenz während der CCTA bei Frauen höher war als bei Männern (**Abbildung 7**). Die Herzfrequenz wurde als einziger signifikanter Faktor für nicht-diagnostische CCTA identifiziert. Unter Ausschluss der nicht-diagnostischen CCTA-Untersuchungen war der Unterschied in der diagnostischen Genauigkeit nicht mehr signifikant (0.942 in Frauen [0.930-0.953] und 0.952 in Männern [0.945-0.959], p=0.11).

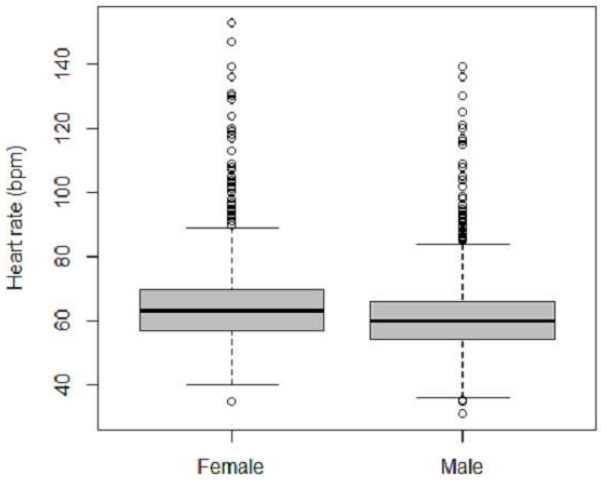


Abbildung 7. Herzfrequenz während der CCTA bei Frauen und Männern.[22] Die Boxplots zeigen die Herzfrequenz in Schlägen pro Minute (Y-Achse) für Frauen und Männer (X-Achse). Der Median der Herzfrequenz bei Frauen ist 63 (Interquartilsabstand 57-70), bei Männern 60 (Interquartilsabstand 54-66). Der Unterschied ist im Mann-Whitney-Test signifikant (p<0.001).

Die Fläche unter der Kurve ist bei Patienten >75 kleiner als in allen anderen Altersgruppen, (0.864 [0.834-0.894], p=0.018 vs alle weiteren Altersgruppen). Für Patienten älter als 75 Jahre betrug die Sensitivität der CCTA 93.2% (88.6-96.0%) und die Spezifität 73.6% (65.7-80.2%). Die diagnostische Genauigkeit der CCTA war damit in dieser Altersgruppe signifikant niedriger als in allen anderen Altersgruppen (**Abbildung 8**).

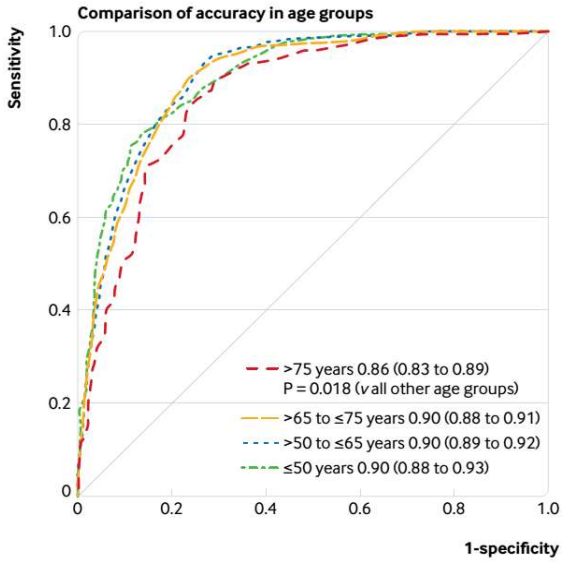


Abbildung 8. Vergleich der diagnostischen Genauigkeit der CCTA bei verschiedenen Altersgruppen.[22] In der ROC-Kurve sind 1-Spezifität auf der X-Achse und Sensitivität auf der Y-Achse aufgetragen. Die Fläche unter der Kurve ist bei Patienten >75 kleiner als in allen anderen Altersgruppen, p=0,018.

Deskriptive Daten zeigten in einer Analyse, dass die Kalklast in Form des Calciumscores nach Agatston in den Koronararterien bei Patienten über 75 Jahren höher war als bei jüngeren Patienten (**Abbildung 9**).

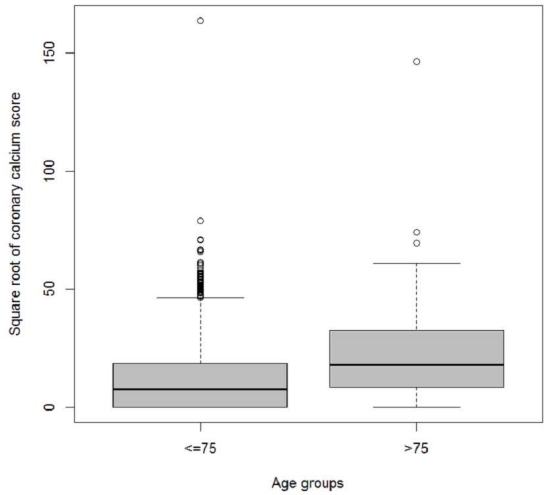


Abbildung 9. Calciumscore bei Patienten ≤ und >75 Jahre.[22] Die Boxplots zeigen die Wurzel des Agatston-Scores als Maß für die Kalklast (Y-Achse) für Patienten ≤75 Jahre und Patienten >75 Jahre (X-Achse). Der Median war bei Patienten ≤75 Jahren geringer (7,5; Interquartilsabstand 0,0-13,7) als bei Patienten >75 Jahren (17,9; Interquartilsabstand 8,4-32,3). Der Unterschied ist im Mann-Whitney-Test signifikant ($p<0.001$).

Die CCTA erzielte ähnliche Ergebnisse bei den verschiedenen Typen der Angina pectoris (klassische Angina pectoris 0.895 (0.873-0.917), atypische Angina pectoris 0.898 (0.884-0.913), Brustschmerzen 0.884 (0.870-0.899), andere Brustbeschwerden 0.915 (0.897-0.934)) (**Abbildung 10**).

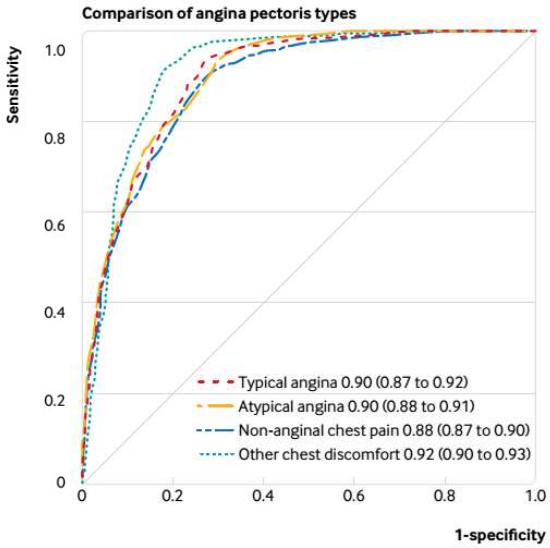


Abbildung 10. Diagnostische Genauigkeit der CCTA bei verschiedenen Typen der Angina pectoris.[22] In der ROC-Kurve sind 1-Spezifität auf der X-Achse und Sensitivität auf der Y-Achse aufgetragen. Die Fläche unter der Kurve ist zwischen den Typen der Angina pectoris ähnlich.

Unter Ausschluss der nicht-diagnostischen CCTA-Untersuchungen blieb die diagnostische Genauigkeit bei Patienten >75 Jahre schlechter (p=0.02). Die Art der Beschwerden hatte weiterhin keinen Einfluss auf die diagnostische Genauigkeit der CCTA.

4. Diskussion

Studienergebnisse im Kontext der aktuellen Leitlinien

In der aktuellen Version der europäischen Leitlinie wird erstmals eine Entscheidungshilfe des zu wählenden nicht-invasiven Erstlinientests anhand der PTP gegeben.[1] Dabei sollten Patienten mit geringer bis mittlerer PTP einer CCTA und Patienten mit hoher PTP einem funktionellen Test zugeführt werden.[1] Unsere Daten bieten erstmals Evidenz für diese Aussage bezüglich der Empfehlung zur CCTA für Patienten mit niedriger bis mittlerer PTP und unterstützen so die aktuelle Leitlinie der ESC. Die Empfehlung zur Durchführung einer CCTA kann sogar erweitert werden, wenn nach den Empfehlungen von 15 bis 50% ausgegangen wird. Die Ergebnisse zeigen, dass die CCTA eine KHK in Patienten zuverlässig ausschließen kann, wenn die Wahrscheinlichkeit für das Vorliegen einer KHK vor der Intervention zwischen 7 und 67% liegt. Auch der PPV zeigt in diesem Bereich gute Ergebnisse, sodass Posttestwahrscheinlichkeiten von 15 bis 50% erreicht werden.

Die aktuelle Richtlinie des National Institute for Health and Care Excellence (NICE) in Großbritannien hingegen empfiehlt für die Bewertung und Diagnostik bei Verdacht auf eine KHK in Patienten mit typischer oder atypischer Angina pectoris eine CCTA unabhängig von ihrer PTP durchzuführen.[23] Nach den Ergebnissen von COME-CCT sollte dieser Standpunkt überdacht werden, da die CCTA nicht in allen Patienten unabhängig ihrer PTP aufgrund zu niedriger prädiktiver Werte zu empfehlen ist.

Patienten mit einer hohen PTP (über 67%), bzw. einer Posttestwahrscheinlichkeit von >50%, profitieren weniger von der CCTA. Neben dem begrenzten NPV in dieser Patientengruppe wird die Mehrheit dieser Patienten aufgrund der relevanten Befunde einer KHK in der CCTA eine anschließende invasive Koronarangiographie erhalten („treat“ threshold). In diesen Fällen wäre für die Patienten die Belastung mit Kontrastmitteln und ionisierender Strahlen durch die zweifache Diagnostik unnötig hoch, sodass von einer CCTA abgeraten werden sollte. Der PPV ist relativ gering in Patienten mit einem niedrigen PTP (unter 7%), bzw. einer Posttestwahrscheinlichkeit von 15%, sodass bei diesen Patienten im Falle einer positiven CCTA die Durchführung einer invasiven Koronarangiographie bei Verdacht auf KHK mit relevanter Wahrscheinlichkeit in einer unnötigen invasiven Intervention resultiert („no treat“ threshold).

Aus klinischer Sicht ist es relevant, dass die diagnostische Genauigkeit der CCTA nicht von der Art der Angina pectoris beeinflusst wurde und in allen Arten eine vergleichbare Leistung erzielt hat. Auch wenn der Effekt gering war, ist es für die klinische Betrachtung wichtig zu wissen, dass die diagnostische Genauigkeit der CCTA in Patienten, die älter als 75 Jahre sind und bei Frauen im Vergleich zu Männern niedriger war. Eine Multicenter-Studie mit 291 Patienten[24] und zwei

Singlecenter-Studien mit 570 und 1372 eingeschlossenen Patienten[25, 26] resultierten in einer ähnlichen diagnostischen Genauigkeit der CCTA für Männer und Frauen. In der vorliegenden Metaanalyse mit 3473 Männern und 1859 Frauen konnte eine Verringerung der Fläche unter der ROC-Kurve von 0.023 für Frauen im Vergleich zu Männern gezeigt werden. Als Ursache für diesen Effekt ist der Umstand zu betrachten, dass die in COME-CCT partizipierenden Frauen eine höhere Herzfrequenz während der CT-Untersuchung hatten, was als signifikanter Faktor für nicht-diagnostische CT-Untersuchungen bestimmt werden konnte. Eine höhere Herzfrequenz während der CCTA bei Frauen konnte auch in einer anderen, noch unveröffentlichten, prospektiven randomisierten Studie der Arbeitsgruppe beobachtet werden. Interessanterweise war der Unterschied der diagnostischen Genauigkeit der CCTA zwischen Männern und Frauen in der vorliegenden Metaanalyse auch nicht mehr signifikant, wenn die nicht-diagnostischen Untersuchungen exkludiert wurden.

Limitationen der Arbeit

Metaanalysen auf Basis von IPD gelten als Goldstandard für systematische Übersichtsarbeiten.[27] Das COME-CCT-Projekt hatte die Zielsetzung, veröffentlichte und unveröffentlichte Evidenz zur diagnostischen Genauigkeit der CCTA umfänglich zusammenzuführen. Trotz des Einschlusses mehrerer Studienzentren weltweit sind diese global nicht gleich verteilt und Ethnien finden keine Berücksichtigung in den ausgewerteten Daten.

Eine wichtige Limitation der durchgeführten Metaanalyse besteht darin, dass die Daten von 78 der identifizierten 154 Studien nicht in die Analyse einbezogen werden konnten. Dabei haben trotz mehrmaliger Erinnerung eine relevante Zahl der Autoren nicht auf die Anfragen geantwortet (56 von 78, 71,8%) oder sie konnten die IPD nicht zur Verfügung stellen, da die Daten auf individueller Patientenbasis selbst bei den Autoren nicht vorlagen (7/78, 9,0%). Nach den Ergebnissen eines systematischen Reviews sind in 68% der IPD-Metaanalysen 80% der IPD aus im Median 14 eingeschlossenen Studien erhalten worden.[28] Mit 154 eingeschlossenen Studien in COME-CCT war die Studienbasis deutlich größer, was nachweislich mit einer schlechteren Antwortrate assoziiert ist.[28] Zudem zeigten IPD-Metaanalysen die höchsten Antwortraten wenn lediglich randomisierte kontrollierte Studien eingeschlossen wurden, sodass vor dem Hintergrund dieser Daten die Antwortrate in COME-CCT als verhältnismäßig angesehen werden kann.[28] Die hohe Anzahl der eingeschlossenen Studien spiegelte sich auch in einem hohen Aufwand wieder, die Daten zusammenzutragen und zu harmonisieren. Dabei zeigte sich der verwendete Einsatz unabhängiger Untersucher mit anschließendem Konsens als ein robustes Verfahren.

Im Vergleich der aggregierten Daten der Studien, von denen IPD erhalten wurden, mit den Studien, von denen keinen IPD erhalten wurden, zeigte sich kein Selektionsbias der in die Analyse eingeflossenen Studien. Zudem zeigte sich im Funnelplot kein Hinweis auf einen Publikationsbias. Man kann also davon ausgehen, dass die über COME-CCT erhobenen Daten eine realistische Abbildung der verfügbaren publizierten Daten zur diagnostischen Genauigkeit der CCTA schaffen. Unter Einsatz des QUADAS-2-Tools konnten zudem Bedenken in der Anwendbarkeit der zugrunde

liegenden Studien ausgeräumt werden. Auch zeigte sich kein hohes Risiko für einen Bias der beteiligten Studien. Um unveröffentlichte Studiendaten in die Metaanalyse einfließen lassen zu können, wurden alle Autoren nach weiteren geeigneten unpublizierten Daten gefragt. So konnten zwei unveröffentlichte Studien für die Metaanalyse gewonnen werden.

Als Metaanalyse diagnostischer Genauigkeitsstudien konnte methodisch bedingt keine Aussage zum klinischen Outcome der Patienten bezüglich der Morbidität und Mortalität im Langzeitverlauf erhoben werden. Dazu wurde durch unsere Arbeitsgruppe die internationale, von der Europäischen Union geförderte pragmatische randomisierte DISCHARGE-Studie entwickelt und durchgeführt, die kürzlich die Randomisierung der Patienten beenden konnte.[29]

Eine weitere Limitation der vorliegenden Metaanalyse ist die Tatsache, dass die diagnostische Genauigkeit lediglich anhand einer anatomischen Definition einer relevanten Stenose bestimmt wurde. Die Verwendung einer invasiven Koronarangiographie mit Bestimmung der FFR zur Beurteilung der Stenosen als signifikant flusslimitierend war keine Fragestellung der durchgeführten Metaanalyse. Aufgrund der tatsächlichen sowohl national als auch international seltenen Anwendung der FFR-Messung konnten diese Daten auch nicht über eine nachfolgende zusätzliche Erhebung, in für eine statistische Auswertung ausreichender Zahl, gewonnen werden.[4]

Prätestwahrscheinlichkeitsmodelle

Zur Berechnung der PTP verwendeten wir das aktualisierte Modell von Diamond und Forrester. Dieses beschränkt sich auf die Variablen Alter, Geschlecht und Typ der Angina pectoris. Die aus Belastungstests gewonnenen Patientendaten könnten ebenfalls in die klinische Vorhersage der PTP eingebracht werden. Die Ergebnisse von Belastungstest sind derzeit aber nicht in den validierten Programmen der Wahrscheinlichkeitsberechnung verfügbar.[16, 17, 30] Vielmehr indiziert eine Analyse des amerikanischen National Cardiovascular Data Registry, dass der niedrige PPV von Belastungstests zu vielen unnötigen invasiven Koronarangiographien führe.[6] Damit ist das verwendete Modell nicht nur eines der validierten, sondern kann in der klinischen Praxis schnell und einfach durch den behandelnden Arzt erhoben werden.

Unsere Ergebnisse zeigen, dass das verwendete und validierte Prediction Tool die PTP bis 40% über- und ab 50% unterschätzt. Eine Optimierung der Bestimmung der PTP über weitere Studien könnte das diagnostische Management der Patienten mit Verdacht auf eine KHK weiter verbessern.

Nicht-diagnostische CCTA-Untersuchungen

Metaanalysen, die aggregierte Studiendaten nutzen, schließen in der Regel Patienten mit nicht-diagnostischer CCTA aus oder betrachten diese als positiven Befund, wie durch eine durchschnittliche Sensitivität der CCTA von 97.2-100% und eine Spezifität von 87.4-89.0% in diesen Studien ersichtlich wird.[8, 31] COME-CCT zeigt niedrigere Werte für die Sensitivität und Spezifität, wenn nicht-diagnostische CCTA in einem Wort-Case-Szenario als falsch positiv oder

negativ angenommen und nicht ausgeschlossen werden.[15] Dabei konnte eine deutlich höhere Rate an nicht-diagnostischen CT-Untersuchungen bei CT-Scannern beobachtet werden, die ≤64 Detektorzeilen verwendeten.

In den gesammelten Studien im COME-CCT-Projekt wurden am häufigsten CT eingesetzt, die weniger als 64 Detektorzeilen haben. Daher wurde die höhere diagnostische Genauigkeit der CCTA durch CT mit mehr als 64 Detektorzeilen ausgehend von einer verhältnismäßig kleineren Anzahl in der Metaanalyse berechnet. Folglich hätte die diagnostische Leistung der CCTA noch besser sein können, wenn mehr oder ausschließlich modernste CT-Technologie in den Studien zur Anwendung gekommen wäre.

Vergleich mit weiteren nicht-invasiven kardialen diagnostischen Verfahren

Der Einfluss der PTP auf die diagnostische Leistung der CCTA kann nicht mit anderen Herzbildgebungsverfahren verglichen werden, da zum jetzigen Zeitpunkt keine weiteren Analysen auf Basis von IPD verfügbar sind. Eine ähnliche Analyse mit weiteren nicht-invasiven funktionellen Tests durchzuführen, könnte Aufschluss darüber geben, ob das CT im niedrigeren Bereich und ein funktioneller Test im höheren PTP-Bereich angewandt werden sollte, wie es derzeit von der ESC empfohlen und auch zumindest für die CCTA durch die Ergebnisse dieses Projekts unterstützt wird.

Vergleicht man die aggregierten Studiendaten der kardialen Funktionstests, so zeigt die unbereinigte Sensitivität pro Patient von Belastungs-Elektrokardiogrammen (EKG) und Einzelphotonen-Emissionscomputertomographie (SPECT) kürzlich Werte von 84% und 85%, beziehungsweise im 95% CI von 80-89% und 81-88%[32], welche signifikant niedriger sind als die ermittelte Sensitivität der CCTA (92.6-96.9%) in der vorliegenden Metaanalyse. Die Sensitivität des Belastungs-EKG und SPECT fiel sogar auf 34 und 38%, beziehungsweise im 95% CI auf 27-41% und 31-44% unter Anwendung der Bayeschen Statistik zur Bereinigung des „partial verification bias“, der in den EKG- und SPECT-Studien vorlag.[32]

Auch die Magnetresonanztomographie (MRT) inklusive Myokardszintigraphie und die Positronen-Emissions-Tomographie (PET) zeigten eine schlechtere diagnostische Leistung gegenüber der CCTA. Eine Metaanalyse, die 2125 Patienten aus 26 Studien inkludierte, kalkulierte eine Sensitivität pro Patient von 89% (95% CI 88-91%) für die MRT gegenüber der CCTA, wenn die invasive Koronarangiographie als Referenzstandard betrachtet wird.[8, 33] Die Sensitivität für die PET lag bei 92,6% (95% CI 88,3-95,5%) in einer Analyse, die 650 Patienten in neun Studien umfasste.[34]

Die Studienergebnisse im wissenschaftlichen Kontext

Die größte Stärke der CCTA ist ihr hoher NPV. Die Ergebnisse der Metaanalyse bescheinigen der CCTA, dass sie zuverlässig eine KHK ausschließt. Dadurch könnte das Patientenmanagement effizienter gestaltet und die Kosten in der Gesundheitsversorgung möglicherweise verringert werden, indem unnötige invasive Koronarangiographien durch nicht-invasive Diagnostik bei

Patienten mit niedrigem PTP für eine KHK ersetzt werden. Auch die kürzlich veröffentlichte randomisierte, klinische Studie PROMISE zeigte, dass in 52.5% der Patienten, die eine invasive Koronarangiographie erhalten haben, keine KHK diagnostiziert wurde. Im Vergleich dazu konnten nur in 27.9% der Patienten mit Verdacht auf eine KHK, die eine CCTA erhalten haben, die Diagnose nicht bestätigt werden.[35] In einer Analyse der sekundären Endpunkte der PROMISE-Studie zeigte die CCTA eine Reduktion der schweren kardiovaskulären Komplikationen, definiert als Tod, Myokardinfarkt und Hospitalisierung aufgrund instabiler Angina pectoris, um 50% nach einem mittleren Follow-Up von 26.1 Monaten im Vergleich zu einer initialen funktionellen Bildgebungsstrategie.[36]

Der SCOT-Heart-Trial verglich prospektiv die Standardversorgung mit der Standard-versorgung plus CCTA in Patienten mit neuartigen Brustschmerzen. Dabei trug die CCTA zu höherer diagnostischer Sicherheit bei, erhöhte die Rate an diagnostizierter obstruktiver und nicht-obstruktiver KHK und führte zur Verringerung der Durchführung weiterer diagnostischer Tests.[37] Darüber hinaus zeigte eine weitere Analyse nach fünf Jahren in Konkordanz zum PROMISE-Trial, dass sich die Rate an fatalen und nicht-fatalen Myokardinfarkten in der CCTA-Gruppe im Vergleich zur Kontrollgruppe halbierte, ohne die Rate an Koronarinterventionen zu erhöhen. Hingegen wurden in der CCTA-Gruppe mehr gerichtete präventive und antianginöse Therapien eingeleitet.[38]

Auch die in der Charité durchgeführte CAD-Man-Studie zeigte, dass die CCTA die Möglichkeit hat, bis zu 80% der durchgeführten Linksherzkatheteruntersuchungen zu ersetzen, da die Untersuchung eine KHK ausschließen konnte bzw. keine interventionellen therapeutischen Konsequenzen hatte.[39] Die von unserer Arbeitsgruppe initiierte und von der Europäischen Union geförderte DISCHARGE-Studie, die randomisiert die CCTA mit dem Herzkatheter in Patienten mit Verdacht auf eine KHK und einer PTP von 10 bis 60% hinsichtlich der klinischen Effektivität vergleicht, hat mittlerweile die Patientenrekrutierung abgeschlossen und wird darüber hinaus auch Aufschlüsse zur Kosteneffektivität der CCTA geben.[29]

Das CONFIRM Register wurde als eine große multinationale dynamische Beobachtungs-studie angelegt, deren primäres Ziel darin besteht, kardiale und nicht-kardiale CCTA-Befunde mit demographischen und klinischen Daten der Patienten zur Risikostratifizierung zu korrelieren. Trotz noch laufendem Patienteneinschluss konnte die CONFIRM Studie bereits zeigen, dass CCTA-Befunde die Risikostratifizierung der Patienten und die Prädiktion von kardialen Ereignissen verbesserte.[40]

Schlussfolgerung

Unsere Daten erlauben es erstmals, evidenzbasierte Empfehlungen zum Einsatz der CCTA anhand der PTP zu geben. Die CCTA schließt eine KHK zuverlässig bei Patienten mit einer PTP von 7 bis 67% aus und unterstützt so die Empfehlungen der aktuellen Leitlinie der ESC zum Management der Patienten mit Verdacht auf eine KHK zur Beschränkung auf Patienten mit einer niedrigen bis mittleren Prätestwahrscheinlichkeit. Bei Verwendung des Modells von Diamond und

Forrester zur Errechnung der Prätestwahrscheinlichkeit kann der empfohlene Bereich jedoch erweitert werden, wenn von 15-50% ausgegangen wird. CTs mit mehr als 64 Detektorzeilen zeigten eine höhere diagnostische Genauigkeit und deutlich weniger nicht-diagnostische Untersuchungen als CTs mit ≤64 Detektorzeilen und sollten primär zur CCTA verwendet werden. Bezieht man die nicht-diagnostischen CCTA-Untersuchungen im Intention-to-Diagnose-Prinzip in die Analyse ein, zeigt die CCTA statistisch eine etwas schlechtere diagnostische Genauigkeit in Frauen. Unabhängig der nicht-diagnostischen Untersuchungen nimmt die diagnostische Genauigkeit bei Patienten über 75 Jahre leicht ab. Die Art der Brustbeschwerden der Patienten hatte keinen Einfluss auf die diagnostische Performance der CCTA. Empfehlungen der NICE-Leitlinie, die CCTA unabhängig der PTP als primären kardialen diagnostischen Test einzusetzen, sollten nach unseren Daten überdacht und eingeschränkt werden.

Referenzen

1. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, Prescott E, Storey RF, Deaton C, Cuisset T, Agewall S, Dickstein K, Edvardsen T, Escaned J, Gersh BJ, Svitil P, Gilard M, Hasdai D, Hatala R, Mahfoud F, Masip J, Muneretto C, Valgimigli M, Achenbach S, Bax JJ, Group ESCSD. **2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes**. *Eur Heart J* 2020; 41(3):407-477.

2. WHO. **WHO GLOBAL BURDEN OF DISEASE. Global Health Estimates (GHE). Projections of mortality and causes of death, 2015 and 2030**. In.

3. Diamond GA. **A clinically relevant classification of chest discomfort**. *J Am Coll Cardiol* 1983; 1(2 Pt 1):574-575.

4. Gotberg M, Cook CM, Sen S, Nijjer S, Escaned J, Davies JE. **The Evolving Future of Instantaneous Wave-Free Ratio and Fractional Flow Reserve**. *J Am Coll Cardiol* 2017; 70(11):1379-1402.

5. Moschovitis A, Cook S, Meier B. **Percutaneous coronary interventions in Europe in 2006**. *EuroIntervention* 2010; 6(2):189-194.

6. Patel MR, Peterson ED, Dai D, Brennan JM, Redberg RF, Anderson HV, Brindis RG, Douglas PS. **Low diagnostic yield of elective coronary angiography**. *N Engl J Med* 2010; 362(10):886-895.

7. Dewey M, Hamm B. **Cost effectiveness of coronary angiography and calcium scoring using CT and stress MRI for diagnosis of coronary artery disease**. *Eur Radiol* 2007; 17(5):1301-1309.

8. Schuetz GM, Zacharopoulou NM, Schlattmann P, Dewey M. **Meta-analysis: noninvasive coronary angiography using computed tomography versus magnetic resonance imaging**. *Ann Intern Med* 2010; 152(3):167-177.

9. Dewey M, Zimmermann E, Deissenrieder F, Laule M, Dübel HP, Schlattmann P, Knebel F, Rutsch W, Hamm B. **Noninvasive Coronary Angiography by 320-Row CT with Lower Radiation Exposure and Maintained Diagnostic Accuracy: Comparison of Results with Cardiac Catheterization in a Head-To-Head Pilot Investigation**. *Circulation* 2009; 120(10):867-875.

10. Schönenberger E, Schnapauff D, Teige F, Laule M, Hamm B, Dewey M. **Patient Acceptance of Noninvasive and Invasive Coronary Angiography**. *PLoS ONE* 2007; 2(2):e246.

11. Leeflang MM, Bossuyt PM, Irwig L. **Diagnostic test accuracy may vary with prevalence: implications for evidence-based diagnosis**. *Journal of clinical epidemiology* 2009; 62(1):5-12.

12. Hunink MM, Weinstein MC, Wittenberg E, Drummond MF, Pliskin JS, Wong JB, Glasziou PP. **Decision making in health and medicine: integrating evidence and values**. Cambridge University Press; 2014.

13. Schuetz GM, Schlattmann P, Achenbach S, Budoff M, Garcia MJ, Roehle R, Pontone G, Meijboom WB, Andreini D, Alkadhi H, Honoris L, Bettencourt N, Hausleiter J, Leschka S, Gerber BL, Meijs MF, Shabestari AA, Sato A, Zimmermann E, Schoepf UJ, Diederichsen A, Halon DA, Mendoza-Rodriguez V, Hamdan A, Norgaard BL, Brodoefel H, Ovrehus KA, Jenkins SM, Halvorsen BA, Rixe J, Sheikh M, Langer C, Martuscelli E, Romagnoli A, Scholte AJ, Marcus RP, Ulimoen GR, Nieman K, Mickley H, Nikolaou K, Tardif JC, Johnson TR, Muraglia S, Chow BJ, Maintz D, Laule M, Dewey M. **Individual patient data meta-analysis for the clinical assessment of coronary computed tomography angiography: protocol of the Collaborative Meta-Analysis of Cardiac CT (CoMe-CCT)**. *Syst Rev* 2013; 2:13.

14. Stewart LA, Clarke M, Rovers M, Riley RD, Simmonds M, Stewart G, Tierney JF, Group P-ID. **Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data: the PRISMA-IPD Statement**. *JAMA* 2015; 313(16):1657-1665.

15. Schuetz GM, Schlattmann P, Dewey M. **Use of 3x2 tables with an intention to diagnose approach to assess clinical performance of diagnostic tests: meta-analytical evaluation of coronary CT angiography studies**. *BMJ* 2012; 345:e6717.

16. Diamond GA, Forrester JS. **Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease**. *N Engl J Med* 1979; 300(24):1350-1358.

17. Genders TS, Steyerberg EW, Alkadhi H, Leschka S, Desbiolles L, Nieman K, Galema TW, Meijboom WB, Mollet NR, de Feyter PJ, Cademartiri F, Maffei E, Dewey M, Zimmermann E, Laule M, Pugliese F, Barbagallo R, Sinitsyn V, Bogaert J, Goetschalckx K, Schoepf UJ, Rowe GW, Schuijf JD, Bax JJ, de Graaf FR, Knuuti J, Kajander S, van Mieghem CA, Meijs MF, Cramer MJ, Gopalan D, Feuchtner G, Friedrich G, Krestin GP, Hunink MG, Consortium CAD. **A clinical prediction rule for the diagnosis of coronary artery disease: validation, updating, and extension**. *Eur Heart J* 2011; 32(11):1316-1330.

18. Skrondal A, Rabe-Hesketh S. **Generalized Latent Variable Modeling: Multilevel, Longitudinal, and Structural Equation Models**. Chapman & Hall/CRC; 2004.

19. Skrondal A, Rabe-Hesketh S. **Prediction in multilevel generalized linear models**. *Journal of the Royal Statistical Society: Series A (Statistics in Society)* 2009; 172(3):659-687.

20. DeLong ER, DeLong DM, Clarke-Pearson DL. **Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach**. *Biometrics* 1988; 44(3):837-845.

21. Chu H, Cole SR. **Bivariate meta-analysis of sensitivity and specificity with sparse data: a generalized linear mixed model approach**. *J Clin Epidemiol* 2006; 59(12):1331-1332; author reply 1332-1333.

22. Haase R, Schlattmann P, Gueret P, Andreini D, Pontone G, Alkadhi H, Hausleiter J, Garcia MJ, Leschka S, Meijboom WB, Zimmermann E, Gerber B, Schoepf UJ, Shabestari AA, Norgaard BL, Meijs MFL, Sato A, Ovrehus KA, Diederichsen ACP, Jenkins SMM, Knuuti J, Hamdan A, Halvorsen BA, Mendoza-Rodriguez V, Rochitte CE, Rixe J, Wan YL, Langer C, Bettencourt N, Martuscelli E, Ghostine S, Buechel RR, Nikolaou K, Mickley H, Yang L, Zhang Z, Chen MY, Halon DA, Rief M, Sun K, Hirt-Moch B, Niinuma H, Marcus RP, Muraglia S, Jakamy R, Chow BJ, Kaufmann PA, Tardif JC, Nomura C, Kofoed KF, Laissy JP, Arbab-Zadeh A, Kitagawa K, Laham R, Jinzaki M, Hoe J, Rybicki FJ, Scholte A, Paul N, Tan SY, Yoshioka K, Rohle R, Schuetz GM, Schueler S, Coenen MH, Wieske V, Achenbach S, Budoff MJ, Laule M, Newby DE, Dewey M, Consortium C-C. **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:l1945.

23. National Institute for Health and Clinical Excellence. **Chest pain of recent onset: assessment and diagnosis**. In; 2016.

24. Dewey M, Vavere AL, Arbab-Zadeh A, Miller JM, Sara L, Cox C, Gottlieb I, Yoshioka K, Paul N, Hoe J, de Roos A, Lardo AC, Lima JA, Clouse ME. **Patient characteristics as predictors of image quality and diagnostic accuracy of MDCT compared with conventional coronary angiography for detecting coronary artery stenoses: CORE-64 Multicenter International Trial**. *AJR Am J Roentgenol* 2010; 194(1):93-102.

25. Dharampal AS, Papadopoulou SL, Rossi A, Weustink AC, Mollet NR, Meijboom WB, Neefjes LA, Nieman K, Boersma E, de Feijter PJ, Krestin GP. **Computed tomography coronary angiography accuracy in women and men at low to intermediate risk of coronary artery disease**. *Eur Radiol* 2012; 22(11):2415-2423.

26. Maffei E, Martini C, Tedeschi C, Spagnolo P, Zuccarelli A, Arcadi T, Guaricci A, Seitun S, Weustink A, Mollet N, Cademartiri F. **Diagnostic accuracy of 64-slice computed tomography coronary angiography in a large population of patients without revascularisation: registry data on the comparison between male and female population**. *Radiol Med* 2012; 117(1):6-18.

27. Stewart LA, Tierney JF. **To IPD or not to IPD? Advantages and disadvantages of systematic reviews using individual patient data**. *Eval Health Prof* 2002; 25(1):76-97.

28. Nevitt SJ, Marson AG, Davie B, Reynolds S, Williams L, Smith CT. **Exploring changes over time and characteristics associated with data retrieval across individual participant data meta-analyses: systematic review**. *BMJ* 2017; 357:j1390.

29. Napp AE, Haase R, Laule M, Schuetz GM, Rief M, Dreger H, Feuchtner G, Friedrich G, Spacek M, Suchanek V, Fuglsang Kofoed K, Engstroem T, Schroeder S, Drosch T, Gutberlet M, Woinke M, Maurovich-Horvat P, Merkely B, Donnelly P, Ball P, Dodd JD, Quinn M, Saba L, Porcu M, Francone M, Mancone M, Erglis A, Zvaigzne L, Jankauskas A, Sakalyte G, Haran T, Ilnicka-Suckiel M, Bettencourt N, Gama-Ribeiro V, Condrea S, Benedek I, Cemerlic Adjic N, Adjic O, Rodriguez-Palomares J, Garcia Del Blanco B, Roditi G, Berry C, Davis G, Thwaite E, Knuuti J, Pietila M, Kepka C, Kruk M, Vidakovic R, Neskovic AN, Diez I, Lecumberri I, Geleijns J, Kubiak C, Strenge-Hesse A, Do TH, Fromel F, Gutierrez-Ibarluzea I, Benguria-Arrate G, Keiding H, Katzer C, Muller-Nordhorn J, Rieckmann N, Walther M, Schlattmann P, Dewey M, Group DT. **Computed**

tomography versus invasive coronary angiography: design and methods of the pragmatic randomised multicentre DISCHARGE trial. *Eur Radiol* 2017; 27(7):2957-2968.

30. Jensen JM, Voss M, Hansen VB, Andersen LK, Johansen PB, Munkholm H, Norgaard BL. **Risk stratification of patients suspected of coronary artery disease: comparison of five different models**. *Atherosclerosis* 2012; 220(2):557-562.

31. von Ballmoos MW, Haring B, Juillerat P, Alkadhi H. **Meta-analysis: diagnostic performance of low-radiation-dose coronary computed tomography angiography**. *Ann Intern Med* 2011; 154(6):413-420.

32. Ladapo JA, Blecker S, Elashoff MR, Federspiel JJ, Vieira DL, Sharma G, Monane M, Rosenberg S, Phelps CE, Douglas PS. **Clinical implications of referral bias in the diagnostic performance of exercise testing for coronary artery disease**. *J Am Heart Assoc* 2013; 2(6):e000505.

33. Hamon M, Fau G, Nee G, Ehtisham J, Morello R, Hamon M. **Meta-analysis of the diagnostic performance of stress perfusion cardiovascular magnetic resonance for detection of coronary artery disease**. *Journal of cardiovascular magnetic resonance : official journal of the Society for Cardiovascular Magnetic Resonance* 2010; 12(1):29.

34. Parker MW, Iskandar A, Limone B, Perugini A, Kim H, Jones C, Calamari B, Coleman CI, Heller GV. **Diagnostic accuracy of cardiac positron emission tomography versus single photon emission computed tomography for coronary artery disease: a bivariate meta-analysis**. *Circulation Cardiovascular imaging* 2012; 5(6):700-707.

35. Douglas PS, Hoffmann U, Patel MR, Mark DB, Al-Khalidi HR, Cavanaugh B, Cole J, Dolor RJ, Fordyce CB, Huang M, Khan MA, Kosinski AS, Krucoff MW, Malhotra V, Picard MH, Udelson JE, Velazquez EJ, Yow E, Cooper LS, Lee KL, Investigators P. **Outcomes of anatomical versus functional testing for coronary artery disease**. *N Engl J Med* 2015; 372(14):1291-1300.

36. Hoffmann U, Ferencik M, Udelson JE, Picard MH, Truong QA, Patel MR, Huang M, Pencina M, Mark DB, Heitner JF, Fordyce CB, Pellikka PA, Tardif JC, Budoff M, Nahhas G, Chow B, Kosinski AS, Lee KL, Douglas PS, Investigators P. **Prognostic Value of Noninvasive Cardiovascular Testing in Patients With Stable Chest Pain: Insights From the PROMISE Trial (Prospective Multicenter Imaging Study for Evaluation of Chest Pain)**. *Circulation* 2017; 135(24):2320-2332.

37. SCOT-HEART Investigators. **CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open-label, parallel-group, multicentre trial**. *Lancet* 2015; 385(9985):2383-2391.

38. SCOT-HEART Investigators. **Coronary CT Angiography and 5-Year Risk of Myocardial Infarction**. *N Engl J Med* 2018.

39. Dewey M, Rief M, Martus P, Kendziora B, Feger S, Dreger H, Priem S, Knebel F, Bohm M, Schlattmann P, Hamm B, Schonenberger E, Laule M, Zimmermann E. **Evaluation of computed**

tomography in patients with atypical angina or chest pain clinically referred for invasive coronary angiography: randomised controlled trial. *BMJ (Clinical research ed)* 2016; 355:i5441.

40. Cho I, Al'Aref SJ, Berger A, B OH, Gransar H, Valenti V, Lin FY, Achenbach S, Berman DS, Budoff MJ, Callister TQ, Al-Mallah MH, Cademartiri F, Chinnaiyan K, Chow BJW, DeLago A, Villines TC, Hadamitzky M, Hausleiter J, Leipsic J, Shaw LJ, Kaufmann PA, Feuchtner G, Kim YJ, Maffei E, Raff G, Pontone G, Andreini D, Marques H, Rubinshtein R, Chang HJ, Min JK. **Prognostic value of coronary computed tomographic angiography findings in asymptomatic individuals: a 6-year follow-up from the prospective multicentre international CONFIRM study**. *Eur Heart J* 2018; 39(11):934-941.

Eidesstattliche Versicherung

Ich, Robert Haase, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: „Nicht-invasive kardiale Diagnostik bei Verdacht auf eine koronare Herzkrankheit: Metaanalyse individueller Patientendaten zur diagnostischen Genauigkeit der computertomographischen Koronarangiographie unter Einfluss der Prätestwahrscheinlichkeit“ selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.
Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren beruhen, sind als solche in korrekter Zitierung kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) werden von mir verantwortet.

Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem Betreuer, angegeben sind. Für sämtliche im Rahmen der Dissertation entstandenen Publikationen wurden die Richtlinien des ICMJE (International Committee of Medical Journal Editors; www.icmje.org) zur Autorenschaft eingehalten. Ich erkläre ferner, dass mir die Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis bekannt ist und ich mich zur Einhaltung dieser Satzung verpflichte.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§§156, 161 des Strafgesetzbuches) sind mir bekannt und bewusst.

_____

31.10.2020 Robert Haase

Anteilserklärung an der erfolgten Publikation

Publikation. Haase R, Schlattmann P, Gueret P, Andreini D, Pontone G, Alkadhi H, Hausleiter J, Garcia MJ, Leschka S, Meijboom WB, Zimmermann E, Gerber B, Schoepf UJ, Shabestari AA, Norgaard BL, Meijs MFL, Sato A, Ovrehus KA, Diederichsen ACP, Jenkins SMM, Knuuti J, Hamdan A, Halvorsen BA, Mendoza-Rodriguez V, Rochitte CE, Rixe J, Wan YL, Langer C, Bettencourt N, Martuscelli E, Ghostine S, Buechel RR, Nikolaou K, Mickley H, Yang L, Zhang Z, Chen MY, Halon DA, Rief M, Sun K, Hirt-Moch B, Niinuma H, Marcus RP, Muraglia S, Jakamy R, Chow BJ, Kaufmann PA, Tardif JC, Nomura C, Kofoed KF, Laissy JP, Arbab-Zadeh A, Kitagawa K, Laham R, Jinzaki M, Hoe J, Rybicki FJ, Scholte A, Paul N, Tan SY, Yoshioka K, Rohle R, Schuetz GM, Schueler S, Coenen MH, Wieske V, Achenbach S, Budoff MJ, Laule M, Newby DE, Dewey M, Consortium C-C.
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 :l1945

Beitrag im Einzelnen

Die Arbeit entstand in der Arbeitsgruppe Dewey unter Leitung von Prof. Dr. med. Marc Dewey. Der Promovend hat sowohl als Student als auch als wissenschaftlicher Mitarbeiter nach dem zweiten Staatsexamen in der Arbeitsgruppe und für das "Collaborative Meta-Analysis of Cardiac CT"-Projekt, kurz COME-CCT, gearbeitet. Dabei hat der Promovierende die primäre Suche und Identifikation der Primarstudien wiederholt und erweitert. Diese wurde initial 2010 durch Herrn Dr. med. Georg Schütz durchgeführt. In Zusammenarbeit mit Herrn Dr. Schütz und Herrn Robert Röhle, MSc, hat der Promovend die individuellen Patientendaten erhoben, validiert und die Datenbasis des Projektes erstellt. Für die veröffentlichte Analyse hat der Promovierende die aus dem Datensatz geeigneten Patienten identifiziert. Mit diesen Daten hat der Promovend das Flussdiagramm (Seite 5 der Publikation) erstellt und die deskriptive Statistik durchgeführt (siehe Seiten 5-7 der Publikation). Den Datensatz wurde vom Promovierenden zur Analyse im Modell für den Statistiker des COME-CCT-Projektes, Prof. Dr. med. Peter Schlattmann, vorbereitet und die Ergebnisse in Zusammenarbeit mit Prof. Schlattmann und Prof. Dewey für die Publikation aufgearbeitet. Die Abbildungen zum Modell erstellte Prof. Schlattmann (Seite 7, 9 und 10). Sämtliche Tabellen der Publikation sowie des Online Appendix der Publikation hat der Promovend erstellt. Der Promovend hat den Entwurf des Manuskriptes der Publikation erarbeitet und in Zusammenarbeit mit Prof. Dewey und Prof. Schlattmann finalisiert. Nach Bitte um Revision durch das Journal hat der Promovierende das Schwellenwertmodell von Hunink et al. für die Publikation erarbeitet und in Zusammenarbeit mit Prof. Dewey und Prof. Schlattmann umgesetzt.

Prof. Dr. med. Marc Dewey	Robert Haase

Auszug aus der Journal Summary List (ISI Web of Knowledge[SM])

Journal Data Filtered By: **Selected JCR Year: 2017** Selected Editions: SCIE,SSCI
Selected Categories: **"MEDICINE, GENERAL and INTERNAL"**
Selected Category Scheme: WoS
Gesamtanzahl: 154 Journale

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	NEW ENGLAND JOURNAL OF MEDICINE	332,830	79.258	0.702000
2	LANCET	233,269	53.254	0.435740
3	JAMA-JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION	148,774	47.661	0.299960
4	BMJ-British Medical Journal	109,303	23.259	0.150320
5	JAMA Internal Medicine	11,840	19.989	0.076280
6	ANNALS OF INTERNAL MEDICINE	53,689	19.384	0.099140
7	Nature Reviews Disease Primers	1,559	16.071	0.007250

Die Einreichung erfolgte am 5.9.2018. Sortiert nach Impact Factor belegte das British Medical Journal Platz 4 (von 154 Fachzeitschriften) im Fachgebiet "MEDICINE, GENERAL & INTERNAL" zu diesem Zeitpunkt.

Druckexemplar der Publikation

Die Arbeit ist als Open Access Publikation veröffentlicht worden. Die Originalarbeit lässt sich somit frei verfügbar von der Internetseite des British Medical Journal herunterladen: https://www.bmj.com/content/365/bmj.l1945

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

Robert Haase,[1] Peter Schlattmann,[2] Pascal Gueret,[3] Daniele Andreini,[4] Gianluca Pontone,[5] Hatem Alkadhi,[6] Jörg Hausleiter,[7] Mario J Garcia,[8] Sebastian Leschka,[9] Willem B Meijboom,[10] Elke Zimmermann,[1] Bernhard Gerber,[11] U Joseph Schoepf,[12] Abbas A Shabestari,[13] Bjarne L Nørgaard,[14] Matthijs F L Meijs,[15] Akira Sato,[16] Kristian A Ovrehus,[17] Axel C P Diederichsen,[18] Shona M M Jenkins,[18] Juhani Knuuti,[19] Ashraf Hamdan,[20] Bjørn A Halvorsen,[21] Vladimir Mendoza-Rodriguez,[22] Carlos E Rochitte,[23] Johannes Rixe,[24] Yung Liang Wan,[25] Christoph Langer,[26] Nuno Bettencourt,[27] Eugenio Martuscelli,[28] Said Ghostine,[29] Ronny R Buechel,[30] Konstantin Nikolaou,[31] Hans Mickley,[32] Lin Yang,[33] Zhaqoi Zhang,[33] Marcus Y Chen,[34] David A Halon,[35] Matthias Rief,[1] Kai Sun,[36] Beatrice Hirt-Moch,[31] Hiroyuki Niinuma,[37] Roy P Marcus,[32] Simone Muraglia,[38] Réda Jakamy,[39] Benjamin J Chow,[40] Philipp A Kaufmann,[31] Jean-Claude Tardif,[41] Cesar Nomura,[42] Klaus F Kofoed,[43] Jean-Pierre Laissy,[44] Armin Arbab-Zadeh,[45] Kakuya Kitagawa,[46] Roger Laham,[47] Masahiro Jinzaki,[48] John Hoe,[49] Frank J Rybicki,[50] Arthur Scholte,[51] Narinder Paul,[52] Swee Y Tan,[53] Kunihiro Yoshioka,[54] Robert Röhle,[1] Georg M Schuetz,[1] Sabine Schueler,[1] Maria H Coenen,[1] Viktoria Wieske,[1] Stephan Achenbach,[55] Matthew J Budoff,[56] Michael Laule,[1] David E Newby,[57] Marc Dewey,[1] On behalf of the COME-CCT Consortium

For numbered affiliations see end of the article.

Correspondence to: M Dewey
dewey@charite.de
(ORCID 0000-0002-4402-2733)

Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2019;365:l1945
http://dx.doi.org/10.1136/bmj.l1945

Accepted: 15 April 2019

ABSTRACT

OBJECTIVE

To determine whether coronary computed tomography angiography (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.

DESIGN

Prospectively designed meta-analysis of individual patient data from prospective diagnostic accuracy studies.

DATA SOURCES

Medline, Embase, and Web of Science for published studies. Unpublished studies were identified via direct contact with participating investigators.

ELIGIBILITY CRITERIA FOR SELECTING STUDIES

Prospective diagnostic accuracy studies that compared coronary CTA with coronary angiography as the reference standard, using at least a 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 generalised 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 less than 15% in case of negative CTA and above 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.

RESULTS

Individual patient data from 5332 patients from 65 prospective diagnostic accuracy studies were retrieved. For a pretest probability range of 7-67%, the treat threshold of more than 50% and the no-treat

WHAT IS ALREADY KNOWN ON THIS TOPIC

Coronary computed tomography angiography (CTA) is an accurate non-invasive alternative to invasive coronary angiography, and can rule out coronary artery disease (CAD) with high certainty

By contrast with recent guidelines from the National Institute for Health and Care Excellence, the European Society of Cardiology recommends not considering CTA in all patients with typical and atypical angina, but only in patients with a 15-50% pretest probability of CAD, estimated by clinical information such as sex, age, and chest pain type

WHAT THIS STUDY ADDS

According to a no-treat/treat threshold model, patients with a pretest probability of CAD ranging from 7% to 67% could benefit most from coronary CTA to rule out or confirm CAD

CTA using more than 64 detector rows was empirically more sensitive and specific than CTA using up to 64 detector rows

Performance of CTA was not influenced by the angina pectoris type and was slightly higher in men and lower in older patients

threshold of less than 15% post-test probability were obtained using CTA. At a pretest probability of 7%, the positive predictive value of CTA was 50.9% (95% confidence interval 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 the specificity was 79.2% (74.9% to 82.9%). CTA using more than 64 detector rows was associated with a higher empirical sensitivity than CTA using up to 64 rows (93.4% *v* 86.5%, P=0.002) and specificity (84.4% *v* 72.6%, P<0.001). 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) and was not significantly influenced by angina pectoris type (typical angina 0.895 (0.873 to 0.917), atypical angina 0.898 (0.884 to 0.913), non-anginal chest pain 0.884 (0.870 to 0.899), other chest discomfort 0.915 (0.897 to 0.934)).

CONCLUSIONS

In a no-treat/treat threshold model, 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%. Performance of CTA was not influenced by the angina pectoris type and was slightly higher in men and lower in older patients.

SYSTEMATIC REVIEW REGISTRATION

PROSPERO CRD42012002780.

Introduction

It is currently unclear in which subgroups of patients with suspected coronary artery disease (CAD) computed tomography angiography (CTA) has highest diagnostic clinical performance. Current guidelines recommend choosing the type of first line imaging test by taking the pretest probability of CAD into account, because it substantially affects diagnostic accuracy.[1-3] According to the most recent recommendation of the National Institute for Health and Care Excellence,[4] coronary CTA should be the primary imaging test in patients with suspected CAD and possible angina, while the guidelines of the European Society of Cardiology on the management of CAD recommend considering CTA only in patients with a CAD pretest probability of 15-50%.[3 4] Moreover, little is known about CTA's diagnostic performance in clinically important patient subgroups such as sex, age, and angina pectoris type and its association with the estimated clinical pretest probability of CAD.

Optimising the use of diagnostic imaging tests in patients with suspected CAD is crucial, given that about two thirds of invasive coronary angiograms performed in Europe and the United States show no evidence of obstructive CAD and increasing use of cardiac imaging tests poses a burden on healthcare costs.[5 6] CTA has the potential to reliably exclude obstructive CAD,[7 8] while halving the events of coronary heart disease after five years of follow-up[9] and improving the diagnostic yield of coronary angiography.[8 10] Its implementation as a first line diagnostic imaging test in patients with suspected CAD remains controversial. Since available diagnostic accuracy studies of CTA are moderate in size, data pooling can provide a more accurate assessment of its diagnostic performance. Individual patient data allow researchers to evaluate clinically important subgroups and individually estimate the pretest probability and to determine its effect on the diagnostic test performance of CTA. With the rationale to define the clinical context and clinical probability in which CTA has highest discriminative ability to diagnose or rule out CAD, we formed the COME-CCT (Collaborative Meta-Analysis of Cardiac CT) Consortium to pool patient level data from diagnostic accuracy studies of CTA enrolling patients with a clinical indication for coronary angiography as the reference standard for angiographic CAD.[11] This work will help clinicians identify those patients with stable chest pain for whom CTA is most suitable.

Methods

Study design and main objectives

COME-CCT is a collaborative meta-analysis using individual patient data (IPD) to summarise the published and unpublished evidence on the diagnostic performance of cardiac CTA, and the protocol has been published.[11] The main objective was to assess the influence of the clinical pretest probability of CAD on the diagnostic accuracy of cardiac CTA in order to define CTA's clinical discriminative ability for diagnosing or ruling out CAD depending on clinical risk. Therefore, we used a no-treat/treat threshold approach to define the pretest probability range for which CTA has highest diagnostic value and, vice versa, for which CTA is not appropriate, to better decide which patients to offer the test to.[12] Positive and negative predictive values (PPVs and NPVs) were chosen as primary outcome measures as a function of pretest probability.[13] Finally, the influence of sex, age, angina pectoris type, and number of CT detector rows on the diagnostic performance of coronary CTA was analysed in this primary outcomes publication. We used the PRISMA (preferred reporting items for systematic reviews and meta-analyses) statement for IPD systematic reviews for reporting this collaborative meta-analysis (checklist in web appendix 1).[14] COME-CCT was designed in a multicentric and multicontinental fashion according to a prespecified study protocol,[11] and the COME-CCT IPD meta-analysis was registered at PROSPERO.

Eligibility criteria and study selection

COME-CCT was designed as a prospective meta-analysis of IPD from prospective diagnostic accuracy studies comparing coronary CTA with invasive coronary angiography as the reference standard. Both tests used a diameter stenosis of at least 50% as the cutoff value to define angiographically obstructive CAD.

Eligible patients needed to have a clinical indication for coronary angiography due to suspected CAD because of stable chest pain, and both tests had to be performed in all patients to avoid verification bias.[15] Results had to be provided using 2×2 or 3×2 cross tabulations for the comparison of CTA with coronary angiography.[16] For the calculation of clinical pretest probability using an updated version of the Diamond and Forrester method,[17 18] the following information had to be provided: patient age, sex, and angina pectoris type.[19 20] Angina pectoris was classified as typical angina, atypical angina, non-anginal chest pain, or other chest discomfort according to Diamond and Forrester. The primary analysis included all patients irrespective of whether they had diagnostic or non-diagnostic (that is, unevaluable) CTA examinations.[16]

The search was performed in three databases (Medline, Embase, and Web of Science; sensitive search strategy described in web appendix 2).[21] The search strategy was implemented for every database by two independent investigators of the central data management team, as described in the published protocol.[11]

Collection and harmonisation of individual patient level data

When the search was completed, we started IPD collection and subsequent data harmonisation. As defined in the study protocol,[11] we emailed corresponding authors of eligible published studies identified by the search with a cover letter detailing the objectives of the collaborative meta-analysis and a CD containing a uniform IPD collection file (web appendix 3).[11] Other authors were contacted if the corresponding author did not respond. Data from unpublished studies that met the inclusion criteria were retrieved from corresponding authors of published studies.[22] The completed IPD collection files were sent back to the data management team.

Data harmonisation was performed by two independent readers at the site of the central data management team, who analysed data and searched for non-plausible data, including range checks, average and median checks (*v* published aggregated data results), minimum and maximum checks (*v* aggregated data results), wrong entries, non-logical values, and other data checks. Aggregate data of studies for which IPD were not provided were collected and compared with aggregate data of studies for which IPD were provided to rule out study selection bias. Aggregate data consisted of all data necessary for 2×2 tabulations to estimate sensitivity, specificity, and PPVs and NPVs, and to perform receiver operating characteristic curves analysis. Risk of bias and applicability concerns of the included studies were assessed by two independent readers of the central data management team, who were not involved in data harmonisation, using the QUADAS-2 tool.[23]

Primary and secondary outcomes

The primary outcomes of interest were the PPV and NPV of coronary CTA for the presence of obstructive CAD as measures of the post-test probability of disease needed for the no-treat/treat threshold model. PPV and NPV were evaluated as a function of the pretest probability of obstructive CAD and analysed by a generalised linear mixed model meta-regression including non-diagnostic CTA results.[11] To define the range of appropriate pretest probabilities of obstructive CAD for CTA, we used the no-treat/treat threshold method.[12] Following the European Society of Cardiology guidelines, the no-treat/treat thresholds for CTA were 15% and 50%, respectively, on the disease probability range. This means that for disease probabilities below 15%, other reasons for the chest pain should be considered, and for values above 50%, ischaemia testing should be recommended.[3]

Secondary outcomes were sensitivity and specificity analyses in women and men, in patients of different age groups, and with different angina pectoris types. Diagnostic performance of CTA was descriptively compared in computed tomography scanners with up to 64 detector rows versus those with more than 64 detector rows. A further post hoc analysis, which was not defined in the protocol of COME-CCT, were requested by reviewers: we analysed the use of core laboratories and quantitative coronary angiography in relation to diagnostic accuracy of CTA.

Statistical analysis

Using an intention-to-diagnose approach, we implemented a worst case scenario in which non-diagnostic CTA results were considered false positive if coronary angiography was negative, and considered false negative if coronary angiography was positive.[16] We calculated clinical pretest probability using the validated CAD Consortium prediction tool, which is an updated version of the Diamond and Forrester model.[17 18] Specifically, probability was estimated using all elements of the prediction tool: patient age, sex, and clinical presentation (angina pectoris type). Based on this model, mean logit PPVs and NPVs with their standard errors and 95% confidence intervals were estimated. These quantities were back-transformed to the original scale to obtain summary PPVs and NPVs. For the statistical analysis, we applied a univariate logistic regression model[24] extended by incorporating a random effect for study and a random slope for CTA or coronary angiography results, which is equivalent to a bivariate generalised linear mixed model.[25] To maintain equivalence, interaction terms of CTA and covariates of interest are necessary and were thus included into the model. Using these data and model, we performed a statistical prediction for a new cohort following the ideas presented by Skrondal and Rabe-Hasketh.[26 27]

To apply the no-treat/treat CAD probability thresholds for CTA, we chose two post-test probabilities to define the range when to offer CTA: below 15% when other reasons for the chest pain should then be considered (no treat threshold) and probabilities above 50% when ischaemia testing is then recommended (treat threshold). We then calculated the clinical

prediction score pretest probabilities that yielded post-test probabilities after negative CTA of below 15% (that is, a NPV of at least 85%) and those after positive CTA of above 50% (that is, a PPV of at least 50%). In addition to the model in which non-diagnostic CTA results were considered false positive if coronary angiography was negative and false negative if coronary angiography was positive, we also calculated NPVs and PPVs depending on pretest probabilities in a model excluding non-diagnostic CTA.

Based on the generalised linear mixed model with the test result as a dependent variable, we estimated mean logit sensitivity and specificity, between-study variability in logit sensitivity and specificity, and the covariance between them and the effect of covariates. Areas under the receiver operating characteristic curves were constructed using the observed data and model based predictions. These also included random effects, which reflect variability between studies and unobserved influential variables. The clinical performance of CTA was compared including non-diagnostic CTA results between women and men, between four age groups, and between the four angina pectoris types. Furthermore, it was compared with quantitative coronary angiography as the reference standard and the presence of core laboratories in the case of multicentre studies, to determine if this affected the primary outcomes. The influence of these covariates was evaluated by the likelihood ratio test. We did not search for the most parsimonious statistical model because, for clinical reasons, the type of chest pain, for instance, is pivotal and should be included. To compare the area-under-the-curve results for inclusion versus exclusion of non-diagnostic examinations, we applied DeLongs' test.[28] Performance of CTA using up to 64 or more than 64 detector rows was compared empirically. We investigated publication bias using the rank based method for the arcsine difference of study specific sensitivities and specificities.[29]

As recommended by the PRISMA statement, we compared aggregate data of studies for which IPD was provided with those aggregate data of studies for which IPD was not provided to identify or exclude differences between these data based on a bivariate generalised linear mixed model with IPD available as a covariate.[30] We calculated the likelihood ratio test for the models with and without this covariate. This model was estimated for aggregate 2×2 tables using the model of Chu and Cole.[31] In our analyses, non-diagnostic CTA results were treated using an intention-to-diagnose approach (see above) as suggested by Schuetz and colleagues.[16] Estimation was done with Stata 14, using the packages GLLAMM and gllapred for the predictions and MIDAS for the 2×2 diagnostic meta-analysis. Further statistical analyses were conducted by SAS version 9.4 (SAS Institute, Cary, NC, USA) and R 3.4,[32] and packages lme4,[33] meta,[34] and pROC.[35] Model based estimates of sensitivity and specificity were obtained by averaging over the random effects using the R package lsmeans.[36]

Patient and public involvement

We have insufficient evidence to comment on whether patients were actively involved in the design or management of the 76 studies included and for which IPD were provided. In this study, given the privacy concerns of IPD sharing, it was also not practical to involve patients in reviewing this data. The results of the study will be disseminated using press releases and the website of the study coordinator.

Results

Included studies and study participants

We identified 154 eligible published studies, for which we sought IPD by contacting authors (fig 1). Overall, we identified 76 studies (74 published, 2 unpublished) for which IPD were provided for a total of 7813 participants. Of these 76 studies, 11 (including 2481 patients) had to be excluded from this main COME-CCT analysis because no information on angina pectoris presentation was recorded, chest pain was unstable, or patients had coronary artery stents or bypasses. Finally, a total of 5332 patients from the remaining 65 studies (63 published and two unpublished; supplementary table 1 in web appendix 2) were included in the main collaborative analysis, including 554 patients with non-diagnostic CTA examinations (fig 1). Risk of bias was low for all items in most studies, and applicability concerns were not present in any of the included studies assessed by the QUADAS-2 tool (supplementary tables 2-4 and supplementary figures 1-2 in web appendix 2). In most of the 78 studies for which IPD were not provided (for a total of 6684 patients included), the corresponding authors did not respond (56/78, 72%) and aggregate data were available for 76 studies, or 6077 patients (fig 1).

Patient characteristics

Patient characteristics of the 5332 patients from 64 studies available for IPD analysis and their assignment to pretest probability categories are presented in table 1. Patient characteristics for each dataset including chest pain symptoms and risk factor distribution are listed in supplementary table 5 in web appendix 2. Technical characteristics of imaging tests for each dataset are summarised in supplementary table 6 in web appendix 2. Table 1 shows empirical results for true positives and negatives, false positives and negatives, as well as non-diagnostic CTA results for different categories of clinical pretest probability. Up to a pretest probability of 40%, pretest probability predictions overestimated true CAD prevalence by about 10 percentage points using the updated version of the Diamond and Forrester method. Above a pretest probability of 50%, true CAD prevalence was underestimated by about 10 percentage points. Above a pretest probability of about 70%, empirical diagnostic accuracy including specificity decreased (table 1). Also, CTA using up to 64 versus more than 64 detector rows led to significantly lower empirical sensitivity (86.5% *v* 93.4%, P=0.002) and specificity (72.6% *v* 84.4%, P<0.001, table 1). Non-diagnostic

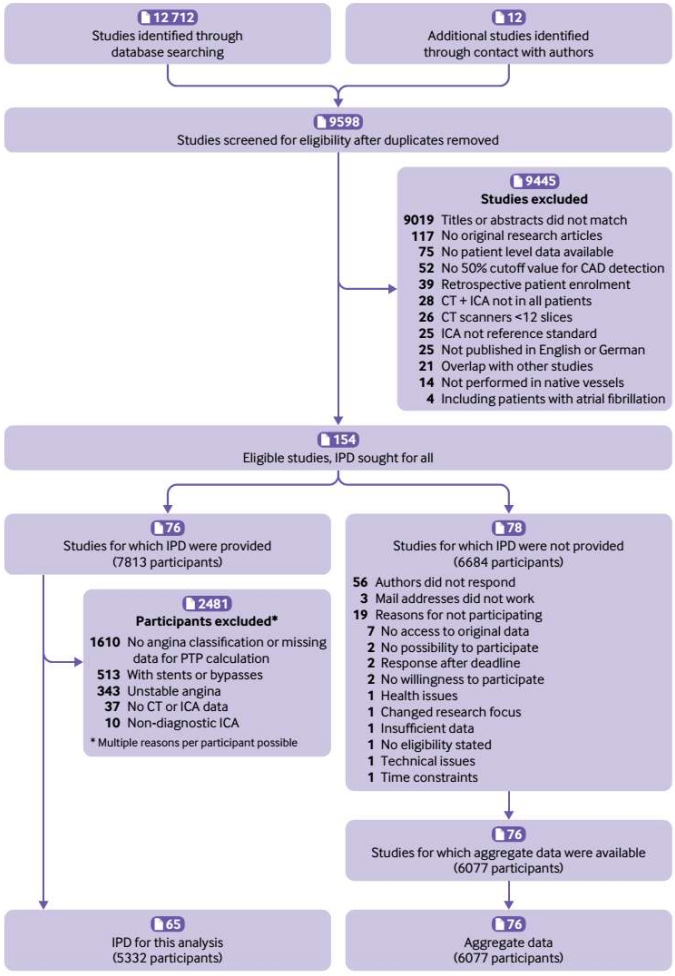


Fig 1 | PRISMA individual patient data (IPD) flow diagram. A total of 9598 studies were scanned after removing duplicates. After full text review of 580 publications, 154 studies remained for which IPD were sought. IPD were retrieved for 76 studies including 7813 participants. For this analysis, 2481 participants of 11 studies had to be excluded, mainly because angina pectoris type was not classified or other data for pretest probability (PTP) calculation were missing (1610). Further reasons for exclusion of participants from the main analysis included coronary stents or bypass grafts, unstable angina pectoris, and non-diagnostic, invasive, coronary angiography examinations. A total of 5332 patients were included in this IPD analysis. ICA=invasive coronary angiography

examinations were rare for scanners with more than 64 detector rows (2.9%), but considerably more frequent on those with up to 64 detector rows (11.5%, table 1).

Diagnostic performance of CTA depending on pretest probability

Figure 2 shows the relation between PPVs and NPVs of CTA and clinical pretest probability in the generalised linear mixed model including non-diagnostic examinations. Based on the statistical model, we found that for a pretest probability range of 7-67%, the treat threshold of more than 50% post-test probability (ischaemia testing recommended) and the no-treat threshold of less than 15% (consider other reasons for the chest pain) were obtained using CTA. At a pretest probability of 7%, the PPV of CTA was 50.9% (43.3% to 57.7%) and NPV was 97.8% (96.4% to 98.7%). At a pretest probability of 67%, the PPV was 82.7% (78.3% to 86.2%) and NPV was 85.0% (80.2% to 88.9%).

Table 1 | Baseline patient characteristics and empirical diagnostic performance of computed tomography angiography to diagnose coronary artery disease, stratified by pretest probability category and scanner detector rows

		Pretest probability categories									
	Overall (n=5332)	0 to <10% (n=86)	10 to <20% (n=530)	20 to <30% (n=601)	30 to <40% (n=727)	40 to <50% (n=745)	50 to <60% (n=752)	60 to <70% (n=590)	70 to <80% (n=535)	80 to <90% (n=698)	90 to 100% (n=68)
Demographic characteristics (median (range) or No (%))											
Median age (years)	61 (18-96)	47 (18-50)	56 (23-70)	59 (24-82)	57 (37-89)	55 (27-87)	63 (30-91)	70 (36-88)	55 (47-92)	66 (59-77)	80 (78-89)
Men	3473 (65)	0	29 (5)	211 (35)	509 (70)	576 (77)	507 (67)	391 (66)	484 (90)	698 (100)	68 (100)
Women	1859 (35)	86 (100)	501 (95)	390 (65)	218 (30)	169 (23)	245 (33)	199 (34)	51 (10)	0	0
Median body mass index	26.3 (14.3-57.1)	25.6 (17.9-39.3)	26.2 (14.3-47.3)	25.9 (16.1-44.8)	26.2 (16.9-41.8)	26.4 (17.5-45.2)	26.5 (17.2-57.1)	26.4 (15.5-56.2)	27.0 (17.5-42.5)	26.9 (16.9-56.7)	25.9 (16.8-35.2)
Clinical presentation (No)											
Typical angina	1967	0	0	4	43	137	247	306	464	698	68
Atypical angina	1592	1	138	269	235	280	339	260	70	0	0
Non-anginal chest pain	796	38	162	157	188	158	80	12	1	0	0
Other chest discomfort	977	47	230	171	261	170	86	12	0	0	0
Diagnostic performance (No or %)											
CAD prevalence (%)*	48.3	17.4	24.0	32.1	40.9	46.8	46.8	53.7	68.6	71.6	82.4
TP	2251	14	120	176	272	321	310	256	317	420	45
TN	2031	52	313	312	334	287	294	194	103	134	8
FP	728	19	90	96	96	109	106	79	65	64	4
FN	322	1	7	17	25	28	42	61	50	80	11
NDX†	554	13	58	50	54	67	76	79	60	85	12
NDX rate (%)†	10.4	15.1	10.9	8.3	7.4	9.0	10.1	13.4	11.2	12.2	17.6
PPV (%)	75.6	42.4	57.1	64.7	73.9	74.7	74.5	76.4	83.0	86.8	91.8
NPV (%)	86.3	98.1	97.8	94.8	93.0	91.1	87.5	76.1	67.3	62.6	42.1
Sensitivity (%)	87.5	93.3	94.5	91.2	91.6	92.0	88.1	80.8	86.4	84.0	80.4
Specificity (%)	73.6	73.2	77.7	76.5	77.7	72.5	73.5	71.1	61.3	67.7	66.7
Diagnostic accuracy (%)	80.3	76.7	81.7	81.2	83.4	81.6	80.3	76.3	78.5	79.4	77.9
LR+	3.32	3.49	4.23	3.88	4.10	3.34	3.32	2.79	2.23	2.60	2.41
LR–	0.17	0.09	0.07	0.12	0.11	0.11	0.16	0.27	0.22	0.24	0.29
CT scanners with ≤64 detector rows (No or %)											
No of patients	4666	80	452	529	651	634	637	530	472	619	62
CAD prevalence (%)	48.2	17.5	24.1	31.2	41.8	45.5	46.0	54.0	67.4	72.5	85.5
TP	1943	13	102	150	248	264	256	226	270	372	42
TN	1757	47	265	273	295	247	246	170	95	114	5
FP	662	19	78	91	84	99	98	74	59	56	4
FN	304	1	7	15	24	24	37	60	48	77	11
NDX†	538	13	54	50	50	65	75	77	58	84	12
NDX rate (%)†	11.5	16.3	11.9	9.5	7.7	10.3	11.8	14.5	12.3	13.6	19.4
PPV (%)	74.6	40.6	56.7	62.2	74.7	72.7	72.3	75.3	82.1	86.9	91.3
NPV (%)	85.2	97.9	97.4	94.8	92.5	91.1	86.9	79.9	66.4	59.7	31.3
Sensitivity (%)	86.5	92.9	93.6	90.9	91.2	91.7	87.4	79.0	84.9	82.9	79.2
Specificity (%)	72.6	71.2	77.3	75.0	77.8	71.4	71.5	69.7	61.7	67.1	55.6
Diagnostic accuracy (%)	79.3	75.0	81.2	80.0	83.4	80.6	78.8	74.7	77.3	78.5	75.8
LR+	3.16	3.23	4.12	3.64	4.11	3.20	3.07	2.61	2.22	2.52	1.78
LR–	0.19	0.10	0.08	0.12	0.11	0.12	0.18	0.30	0.24	0.26	0.37
CT scanners with >64 detector rows (No or %)											
No of patients	558	6	73	62	66	87	103	55	41	59	6
CAD prevalence (%)*	46.1	16.7	21.9	37.1	30.3	54.0	49.5	50.9	75.6	62.7	50.0
TP	240	1	16	21	19	44	46	27	29	34	3
TN	254	5	46	36	39	33	47	22	6	17	3
FP	47	0	11	3	7	7	5	5	4	5	0
FN	17	0	0	2	1	3	5	1	2	3	0
NDX†	16	0	4	0	4	2	1	2	2	1	0
NDX rate (%)†	2.9	0.0	5.5	0.0	6.1	2.3	1.0	3.6	4.9	1.7	0.0
PPV (%)	83.6	100	59.3	87.5	73.1	86.3	90.2	84.4	87.9	87.2	100
NPV (%)	93.7	100	100	94.7	97.5	91.7	90.4	95.7	75.0	85.0	100
Sensitivity (%)	93.4	100	100	91.3	95.0	93.6	90.2	96.4	93.5	91.9	100
Specificity (%)	84.4	100	80.7	92.3	84.8	82.5	90.4	81.5	60.0	77.3	100
Diagnostic accuracy (%)	88.5	100	84.9	91.9	87.9	88.5	90.3	89.1	85.4	86.4	100
LR+	5.98	∞	5.18	11.87	6.24	5.35	9.38	5.21	2.34	4.04	∞
LR–	0.08	0	0	0.09	0.06	0.08	0.11	0.04	0.11	0.10	0

TP=true positives; TN=true negatives; FP=false positives; FN=false negatives; PPV=positive predictive value; NPV=negative predictive value; LR+=positive likelihood ratio; LR–=negative likelihood ratio; NDX=non-diagnostic results.
The empirical results were derived from raw data and thus differ from the results of the statistical model.
*CAD prevalence was defined by coronary angiography.
†Non-diagnostic results were included in the estimation of diagnostic accuracy as false positives if the reference standard was negative, and as false negative if the reference standard was positive.

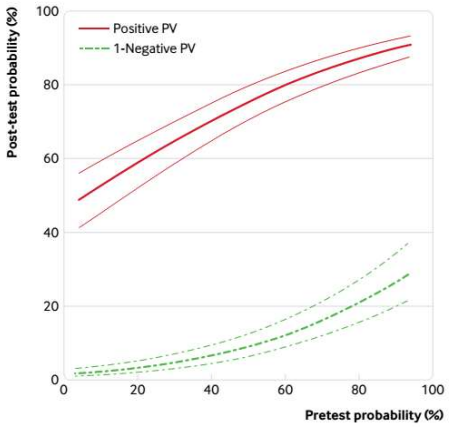


Fig 2 | Clinical diagnostic performance of computed tomography angiography to diagnose obstructive coronary artery disease as a function of pretest probability. The x axis represents the predicted clinical pretest probability, and the y axis shows the post-test probabilities and thus the positive predictive value (PV) and 1−negative PV with their 95% confidence intervals, based on the generalised linear mixed model including non-diagnostic CTA examinations. Results for the generalised linear mixed model excluding non-diagnostic CTA examinations are shown in supplementary figure 3 in web appendix 2. Disease probabilities were predicted by averaging over the random effects distribution. AUC=area under the curve

When excluding non-diagnostic examinations, the PPV at a pretest probability of 7% was 68.0% (60.5% to 74.6%) and NPV was 98.3% (97.0% to 99.1%; table 2); at a pretest probability of 67%, the PPV was 88.9% (85.3% to 91.7%) and NPV was 91.4% (87.8% to 94.2%). The relation between PPVs and NPVs of CTA and clinical pretest probability in the generalised linear mixed model after excluding non-diagnostic CTA examinations is shown in supplementary figure 3 in web appendix 2. The model based predictive values for 7% and 67% pretest probabilities as well as for 15% and 50% pretest probabilities as recommended by the European Society of Cardiology guidelines are listed in table 2 for both, including and excluding non-diagnostic CTA results.

Clinically important subgroups

The sensitivity of CTA for all patients was 95.2% (92.6% to 96.9%) and the specificity was 79.2% (74.9% to 82.9%, table 3). The sensitivity of CTA for women and men was 93.5% (89.6% to 96.0%) and 95.8% (93.4% to 97.4%), respectively, while the specificity was 80.6% (75.9% to 84.6%) and 77.4% (72.4% to 81.8%, likelihood ratio test11.28, df: 2, P<0.001, table 3). Empirical data of women and men and their assignment to pretest probability categories are tabulated in supplementary tables 7 and 8 in web appendix 2. For patients older than 75, the sensitivity of CTA was 93.2% (88.6% to 96.0%) and the specificity was 73.6% (65.7% to 80.2%, table 3).

In the receiver operating characteristic analysis, CTA including non-diagnostic results had an area under the curve of 0.897 (95% confidence interval 0.889 to 0.906) versus a significantly larger area under the curve when non-diagnostic results were excluded (0.949 (0.943 to 0.954), P<0.001, fig 3). All further results are provided for the analyses with inclusion of non-diagnostic CTA examinations. The diagnostic performance of CTA was lower in women than in men (area under the curve 0.874 (0.858 to 0.890) *v* 0.907 (0.897 to 0.916), P<0.001, fig 3). A descriptive analysis revealed that the heart rate during CTA was higher in women than in men (supplementary figure 4 in web appendix 2). Heart rate was the only factor significantly associated with a non-diagnostic CTA examination (supplementary table 9 in web appendix 2). The lowest diagnostic performance of CTA was found in patients older than 75 (0.864, 0.834 to 0.894, P=0.018 *v* all other age groups, fig 3). Empirical data of patients of different age groups and their assignment to pretest probability categories are listed in supplementary tables 10-13 in web appendix 2. In a descriptive analysis, patients older than 75 had significantly higher coronary artery calcium scores than younger patients (supplementary figure 5 in web appendix 2).[37] Accuracy of CTA was not significantly influenced by the angina pectoris type (area under the curve for typical angina 0.895 (0.873 to 0.917) *v* atypical angina 0.898 (0.884 to 0.913) *v* non-anginal chest pain 0.884 (0.870 to 0.899) *v* other chest discomfort: 0.915 (0.897 to 0.934), fig 3).

Further post hoc analyses

Empirical data of patients with different chest pain types and their assignment to pretest probability categories are tabulated in supplementary tables 14-17 in web appendix 2. The receiver operating characteristic analysis after excluding non-diagnostic CTA results showed that accuracy was significantly reduced only in patients older than 75, whereas sex was no longer a significant factor (supplementary figure 6 in web appendix 2). Overall, 3615 (69%)

Table 2 | Model based predictive values of computed tomography angiography for obstructive coronary artery disease, including and excluding non-diagnostic results

	Pretest probability of coronary artery disease (%)			
	7	15	50	67
Including non-diagnostic examinations				
PPV (%; 95% CI)	50.9 (43.3 to 57.7)	55.8 (48.6 to 62.3)	75.4 (70.5 to 79.5)	82.7 (78.3 to 86.2)
NPV (%; 95% CI)	97.8 (96.4 to 98.7)	97.1 (95.4 to 98.2)	90.9 (87.5 to 93.4)	85.0 (80.2 to 88.9)
Excluding non-diagnostic examinations				
PPV (%; 95% CI)	68.0 (60.5 to 74.6)	71.6 (64.7 to 77.5)	84.5 (80.0 to 87.9)	88.9 (85.3 to 91.7)
NPV (%; 95% CI)	98.3 (97.0 to 99.1)	97.9 (96.4 to 98.8)	94.4 (92.0 to 96.3)	91.4 (87.8 to 94.2)

PPV=positive predictive value, NPV=negative predictive value.

Table 3 | Model based sensitivity and specificity of computed tomography angiography for obstructive coronary artery disease, according to total population and subgroups

	Diagnostic performance estimate			
	Sensitivity		Specificity	
	Estimate (SE)	95% CI	Estimate (SE)	95% CI
Total	95.2 (1.1)	92.6 to 96.9	79.2 (2.1)	74.9 to 82.9
Sex				
Women	93.5 (1.6)	89.6 to 96.0	80.6 (2.2)	75.9 to 84.6
Men	95.8 (1.0)	93.4 to 97.4	77.4 (2.4)	72.4 to 81.8
Age				
>75	93.2 (1.8)	88.6 to 96.0	73.6 (3.7)	65.7 to 80.2
>65 to ≤75	95.0 (1.2)	92.0 to 96.9	77.3 (2.6)	71.8 to 82.0
>50 to ≤65	95.1 (1.2)	92.3 to 97.0	80.6 (2.1)	76.1 to 84.5
≤50	95.5 (1.4)	91.8 to 97.6	83.8 (2.4)	78.6 to 87.9

SE=standard error.

of 5266 patients were analysed with quantitative coronary angiography as the reference standard. We found no significant difference in diagnostic accuracy of CTA, irrespective of whether quantitative coronary angiography was used or not, while the use of core laboratories was associated with lower sensitivity and specificity (supplementary table 18).

Participation and publication bias

The comparison of the diagnostic accuracy studies for which IPD were provided with those studies for which only aggregate data were available (fig 1) showed no significant difference in diagnostic performance (P=0.73, fig 4 and table 4). We found no publication bias (supplementary figure 7 in web appendix 2), and heterogeneity analysis yielded variances of random effects of 0.673 for 1–specificity and 3.667 for sensitivity (table 5). We obtained similar values after adjusting age, sex, and type of chest pain (table 6), indicating that these covariates do not explain heterogeneity between studies. Table 6 also presents the model coefficients used for generating the receiver operating characteristic curves.

Discussion

In this pooled analysis of patient level data, we show that coronary CTA is most appropriately implemented for clinical decision making in patients with suspected obstructive CAD and a pretest probability ranging from 7% to 67%. In this low-to-intermediate clinical probability range, coronary CTA was able to accurately stratify patients into those with a disease post-test probability of below 15%, in whom other reasons for the chest pain should be considered, and those with a probability above 50%, in whom further testing is recommended.[3]

Our study also showed that the diagnostic performance of CTA was not significantly influenced by the angina pectoris type, but it was higher in men and lower in older patients. After we excluded non-diagnostic examinations from the analysis, the accuracy of CTA improved and the difference in diagnostic performance between female and male patients became non-significant. Moreover, diagnostic examinations are now more commonly conducted by computed tomography scanners with more than 64 detector rows, which had lower rates of non-diagnostic examinations.

Clinical context and guidelines

Current European and US guidelines recommend calculating patients' pretest probability of CAD to guide diagnostic decisions.[3 38] The European Society of Cardiology specifically recommends considering CTA in patients with 15-50% pretest probability of obstructive CAD,[3] whereas the NICE guideline recommends coronary CTA as the primary imaging test for all patients with possible angina and suspected obstructive CAD.[4] Our results show that using the no-treat/treat threshold approach, CTA offers good to excellent results in pretest probability range of 7% to 67%. The procedure yields a post-test probability below 15%, where other reasons for the chest pain should be considered, in case of negative CTA (that is, NPV ≥85%); and above 50%, where ischaemia testing is recommended, in case of positive CTA (that is, PPV ≥50%). Since no IPD meta-analysis has so far investigated in which patients CTA has the highest diagnostic performance, the results presented here might have important implications for current guidelines. The results of the diagnostic performance model can also be used to define the appropriate pretest probability range depending on the NPV and PPV deemed to be acceptable for the specific diagnostic purpose.

The main clinical strength of coronary CTA is its high NPV, and this is supported by our findings, which show that CTA can also detect both obstructive and non-obstructive CAD and therefore is a suitable imaging modality to guide subsequent management.[39] This may make patient management more efficient and can also lower costs, not least by reducing the high rate of negative coronary angiographies performed annually. Recently published randomised clinical trials support these assumptions. Although the PROMISE trial—which compared CTA with an initial functional testing strategy in the evaluation of chest pain—did not show a reduction in major adverse cardiovascular events (defined as death, myocardial infarction, and unstable angina needing hospital admissions, or a major procedural complication), subsequent invasive coronary angiography was more effective in the CTA group.[40]

The SCOT-HEART trial prospectively compared standard care with standard care plus CTA for the diagnosis of CAD in patients with recent onset chest pain.[41] In the trial, CTA was found to increase diagnostic certainty, increase the identification of obstructive and non-obstructive CAD, and eliminate the need for further downstream stress imaging tests.[41] Furthermore, the five year clinical outcome analysis of SCOT-HEART showed that standard care plus CTA resulted in a halving of fatal and non-fatal myocardial infarction without increasing the five year rate of coronary revascularisations but initiating more targeted preventive and anti-anginal treatments.[9] However, some controversy remains about the use of

doi: 10.1136/bmj.l1945 | BMJ 2019;365:l1945 | the bmj

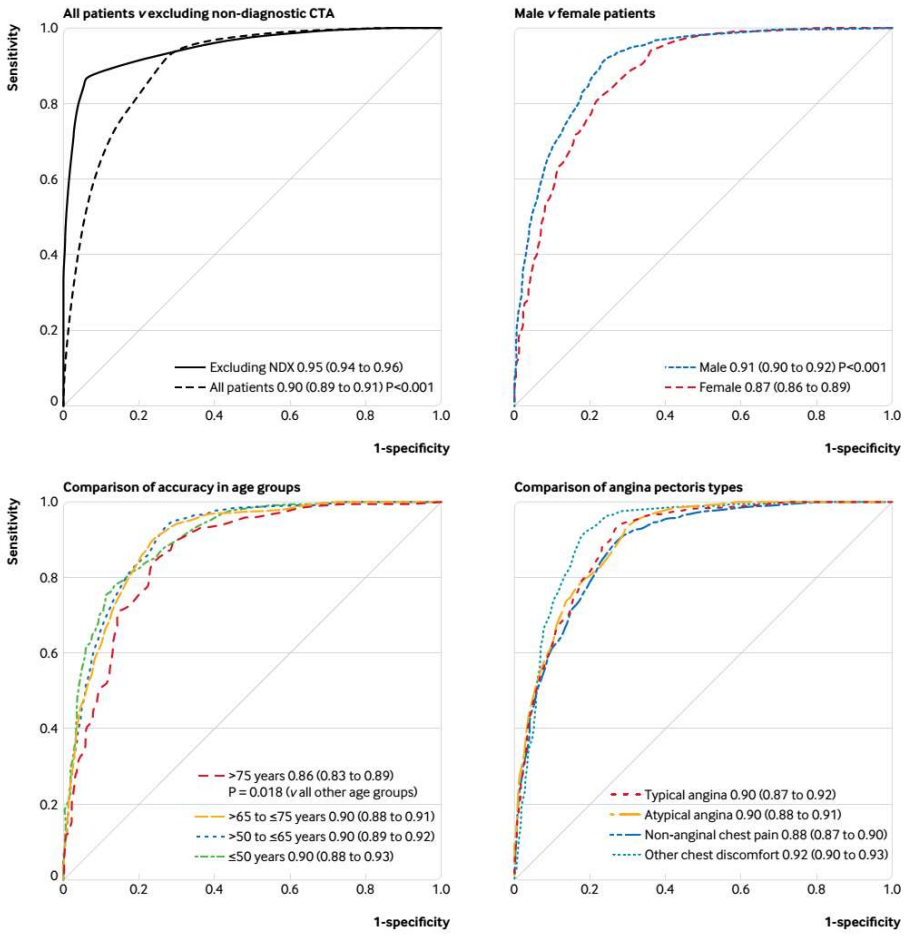


Fig 3 | Receiver operating characteristic curves of computed tomography angiography for obstructive coronary artery disease, by subgroup and after excluding non-diagnostic examinations (NDX). Diagnostic performance results are shown for all patients versus results obtained after exclusion of non-diagnostic test results. The inclusion of all patients (top left panel) resulted in lower performance, which is a more accurate prediction of the real world performance to be expected. Thus, all subgroup comparisons in the other three panels are provided for all patients (including non-diagnostic examinations): diagnostic performance was higher in men and lower in patients older than 75, and angina pectoris types were not significantly associated with performance. Curves were generated by a generalised linear mixed model and predictions based on these models. Computations were performed with the statistical package R and packages lme4 and pROC. Areas under the curve were constructed by use of the observed data and model based predictions, which also included the random effects reflecting variability between studies and unobserved influential variables

coronary CTA as the first line diagnostic test in patients with stable chest pain and suspected CAD,[42] and our IPD meta-analysis provides insights about in which patients CTA has highest predictive values.

Our IPD meta-analysis data can thus help physicians in better identifying the patients for whom coronary CTA is the most appropriate diagnostic test. Whether CTA can further improve clinical effectiveness in patients with a clinical indication for coronary angiography is an important question. The CAD-Man study showed that coronary CTA can reduce the need for invasive coronary angiography by up to 80% and can reduce procedural complications.[8] A similar safety profile with non-inferiority of CTA versus invasive coronary angiography in terms of major cardiovascular events at one year was found in the CONSERVE trial.[43] However, coronary CTA still has to be analysed in a multicentre study of patients with a clinical indication for invasive coronary angiography, and

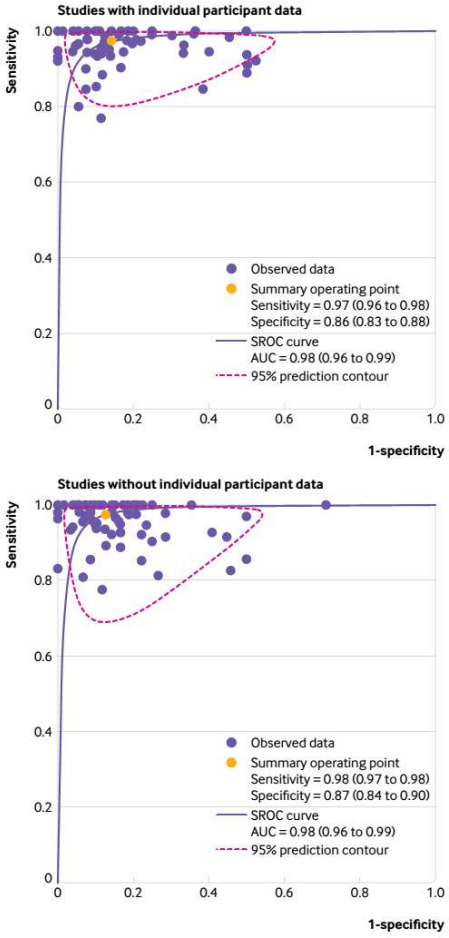


Fig 4 | Summary receiver operating characteristic (SROC) curves for studies using computed tomography angiography to diagnose obstructive coronary artery disease, with and without individual participant data (IPD) available. Curves are shown for studies with IPD available versus studies for which no IPD were available. Curves were calculated by aggregated data methodology (SROC curves) both for panels and after excluding non-diagnostic test results, which were not consistently available in publications of studies that did not provide IPD. Of 76 studies that provided IPD, aggregate data were not available for seven studies (two unpublished), leaving 69 for the analysis of studies with IPD; of 78 studies that did not provide IPD, 76 had aggregate data available (fig 1); there was no significant difference in diagnostic performance between these two groups of diagnostic accuracy studies (P=0.73). Further details shown in table 4. For study number details, see supplementary figure 8. AUC=area under the curve

the randomised DISCHARGE trial will provide more data in this regard.[44]

Comparison with other studies

Meta-analyses using aggregated data from studies that mostly excluded patients with non-diagnostic CTA examinations or considered them positive have reported a mean sensitivity for CTA per patient of 97.2% to 100% and a specificity of 87.4% to 89%.[21 45] We found lower sensitivities and specificities when including non-diagnostic tests as false positives or negatives in our IPD analysis in a worst case scenario, confirming that the performance of diagnostic tests is lower when non-diagnostic test results are considered and not merely excluded from the analysis.[16] Our data also confirm the findings of a study level meta-regression analysis suggesting a hyperbolic decrease and increase of the NPVs and PPVs with increasing pretest probability, respectively.[7] We also showed that pretest probability overestimated true CAD prevalence by about 10 percentage points up to a pretest probability of 40%; while above a pretest probability of 50%, true CAD prevalence was underestimated by about 10 percentage points. Future trials should address how to improve the accuracy of pretest probability estimation in patients with suspected CAD. Also, CTA using more than 64 detector rows led to significantly higher empirical sensitivity and specificity, indicating that recent CTA technology with more than 64 rows should be used.

Criteria have been proposed to ensure a reasonable use of coronary CTA.[46 47] Our study can help refine these criteria by allowing to individually define the appropriateness of coronary CTA based on the patient's clinical pretest probability. Moreover, according to our findings, one should be cautious to use CTA in patients with a clinical pretest probability exceeding 67% since the NPV drops below 85%. In addition, the odds to find obstructive CAD on CTA (and thus also the likelihood to require another invasive test after non-invasive CTA) increases with the pretest probability. On the other hand, the PPV of coronary CTA becomes rather low in patients with a pretest probability of less than 7%, so that, in this situation, about half of the positive CTA examinations would result in unnecessary further testing. For ease of understanding, we visualised the predictive values of coronary CTA depending on pretest probability in figure 2. The European Society of Cardiology guidelines suggest a pretest probability range of 15-50% for diagnostic testing with coronary CTA. In this narrower range of pretest probability, CTA had an NPV and PPV of at least 90.9% and 55.8%, respectively.

From a clinical perspective, the diagnostic performance of CTA was not influenced by the angina pectoris type and was equally effective in ruling out angiographic CAD in patients with different angina pectoris types. Even though the reductions in diagnostic performance of CTA were small, decision makers should be aware that CTA has a slightly lower accuracy in patients older than 75, and in women compared with men, if non-diagnostic CTA results are included in the analysis. As mentioned above, non-diagnostic examinations are rarely seen when using computed tomography scanners with more than 64 detector rows; and when excluding non-diagnostic examinations, performance of CTA was similar in women and men.

doi: 10.1136/bmj.l1945 | *BMJ* 2019;365:l1945 | the bmj

Table 4 | Study specific diagnostic accuracy of computed tomography angiography for coronary artery disease, comparing aggregated data from studies with individual participant data (IPD) versus aggregated data from studies without IPD

	Estimate (95% CI)	
	Sensitivity	Specificity
All studies	0.97 (0.97 to 0.98)	0.87 (0.85 to 0.88)
Studies with IPD*	0.97 (0.96 to 0.98)	0.86 (0.83 to 0.88)
Studies without IPD*	0.98 (0.97 to 0.98)	0.87 (0.84 to 0.90)
Heterogeneity analysis, IPD=1	Likelihood ratio test, x^2=0.62	P=0.73

*Studies with IPD=studies for which IPD were provided; studies without IPD=studies for which IPD were not provided. There was no relevant difference between these two groups of studies.

Similarly, our results showed that women had higher heart rates than men when examined by CTA and higher rates were the only factor associated with non-diagnostic examinations. Similar diagnostic accuracy of coronary CTA in men and women was reported by a multicentre study including 291 patients[48] and by two single centre studies including 570 and 1372 patients.[49 50] In our IPD analysis of 3473 men and 1859 women including non-diagnostic examinations, we showed a small reduction in the area under the curve of CTA in women by 0.023 compared with men (fig 3). This difference might be explained by women being more likely to have high heart rates during CTA, which was the only factor significantly associated with non-diagnostic CTA results.

Strength and limitations of study

Our study had strengths and limitations. IPD meta-analyses are considered the gold standard of systematic reviews. 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,[51] making the findings relevant for current clinical practice.

To define no-treat and treat thresholds, we estimated pretest probabilities by using the updated Diamond and Forester model (also recommended by the current the European Society of Cardiology guidelines). This calculator is validated for patients with suspected CAD referred for invasive coronary angiography, which is also the setting of this analysis. Other prediction models for pretest probabilities do not focus on this cohort but on patients referred for non-invasive assessment, as in the CONFIRM study.[52] Furthermore, although results of exercise tests can also be included in pretest calculation, they are not included in currently validated probability calculators and could thus not be considered in our review.[53]

As shown in table 1, the most frequently used computed tomography scanners had 64 detector rows (2438 of 5332 patients); thus, CTA performance in clinical practice using state-of-the-art technology with more than 64 detector rows could have been even better. An important limitation of our 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. However, we sought to systematically retrieve all IPD from the studies identified by the systematic review and, despite several reminders, a relevant proportion of authors did not reply at all (56/154, 36%) or indicated that they could not participate in the COME-CCT Consortium because they had no access to original data (7/154, 5%). According to a systematic review of data retrieval in IPD meta-analyses, 68% of meta-analyses retrieved IPD from at least 80% of a median of only 14 eligible studies.[54] With 154 eligible studies, our study was relevantly larger, which has been shown to complicate retrieval.[54]

Diagnostic performance results were similar in studies for which IPD were available versus those for which no IPD were provided. To include unpublished grey literature, we systematically asked all corresponding authors of the identified published studies about further unpublished analyses and systematically searched clinicaltrials.gov for unpublished diagnostic accuracy studies of coronary CTA and invasive coronary angiography registered in this database. With this approach, we found two unpublished studies that could be included in the COME-CCT database. Our findings did not show evidence of publication bias, but we found heterogeneity between studies, pointing to potentially unknown site specific factors that might have influenced diagnostic accuracy. All studies included patients who had suspected CAD and were clinically indicated to undergo coronary angiography. This gave us the opportunity to compare results from research CTA with clinically indicated coronary angiography in all patients to avoid verification bias. But the results are representative for patients clinically

Table 5 | Heterogeneity analysis of diagnostic accuracy studies using computed tomography angiography to diagnose obstructive coronary artery disease: overall statistical model without covariates

	Generalised linear mixed model fit by maximum likelihood
Fixed effects*	
Intercept	Estimate (SE), −1.336 (0.125); z=−10.72; P<0.001
CAD present	Estimate (SE), 4.313 (0.294); z=14.69; P<0.001
Random effects†	
Study No (intercept)	Variance, 0.673; SD, 0.8203
CAD present	Variance, 3.667; SD, 1.9149; correlation, −0.75

SE=standard error; SD=standard deviation; CAD=coronary artery disease.
*Data for fixed effects are estimates (standard error) of regression coefficients, z value, and P value. The intercept is 1−specificity, and the sum of the intercept and CAD represents sensitivity.
†Data are for random effects are variance, standard deviation, and correlation. Random effects quantify the variability between studies. The variance of the random effects of the intercept corresponds to the between study variability of 1−specificity, and the random effects variance of CAD denotes the between study variability of sensitivity.

Table 6 | Heterogeneity analysis of diagnostic accuracy studies using computed tomography angiography to diagnose obstructive coronary artery disease: analysis of potential effects of covariates in statistical model

	Generalised linear mixed model fit by maximum likelihood		
Covariates	**Estimate (SE)**	**z value**	**P value**
Fixed effects*			
Intercept	−1.566 (0.218)	−7.188	<0.001
CAD present	4.401 (0.492)	8.944	<0.001
Male sex	0.194 (0.096)	2.027	<0.05
Typical angina	−0.303 (0.192)	−1.579	0.11
Atypical angina	−0.192 (0.170)	−1.125	0.26
Non-anginal chest pain	−0.196 (0.175)	−1.116	0.26
Age			
50-65	0.215 (0.140)	1.538	0.12
65-75	0.417 (0.154)	2.716	0.01
>75	0.618 (0.198)	3.117	0.002
CAD present†			
+Sex	0.265 (0.187)	1.417	0.16
+Typical angina	0.494 (0.399)	1.237	0.22
+Atypical angina	−0.021 (0.359)	−0.059	0.95
+Non-anginal	0.153 (0.349)	0.438	0.66
+Age >50 to ≤65	−0.290 (0.285)	−1.016	0.31
+Age >65 to ≤75	−0.517 (0.302)	−1.708	0.09
+Age >75	−1.055 (0.356)	−2.966	0.003
Random effects‡			
Study No (intercept)	Variance, 0.703	SD, 0.838	—
CAD present	Variance, 3.802	SD, 1.950	Correlation, −0.77

SE=standard error; SD=standard deviation; CAD=coronary artery disease.
*Data for fixed effects are estimates (standard error) of regression coefficients, z value, and P value.
†The variable "CAD present" describes the invasive coronary angiography result (1=positive). "+Sex" describes the interaction between the invasive coronary angiography results and sex, and so on. These interactions are needed to maintain the bivariate structure of the diagnostic accuracy data.
‡Rather than estimates (standard error) of regression coefficients, z value, and P value, data for random effects are variance, standard deviation, and correlation, respectively. The variance of the random effects quantifies the variability between studies for sensitivity and specificity. The variance of the random effects of the intercept corresponds to the between study variability of 1−specificity and the random effects variance of CAD present to between study variability of sensitivity.

referred for coronary angiography, and there was likely to be bias particularly at the extremes of pretest probability. For instance, individuals with low pretest probability were likely to have other unmeasured risk factors that increased their clinical probability, which could have overestimated PPVs of CTA.

Conclusions

In a no-treat/treat threshold model, 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%. Performance of CTA was not influenced by the angina pectoris type, was slightly higher in men, and was lower in older patients.

AUTHOR AFFILIATIONS

[1]Department of Radiology, Charité - Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany
[2]Institute of Medical Statistics, Computer Sciences and Data Science, University Hospital of Friedrich Schiller University Jena, Jena, Germany
[3]Department of Cardiology, Henri Mondor Hospital, University Paris Est Créteil, Créteil, France
[4]Department of Cardiology and Radiology, Centro Cardiologico Monzino IRCCS, University of Milan, Milan, Italy
[5]Centro Cardiologico Monzino, IRCCS, Milan, Italy
[6]Department of Radiology, University Hospital Zurich, Zurich, Switzerland
[7]Medizinische Klinik und Poliklinik I, Ludwig-Maximilians-Universität München, Munich, Germany
[8]Department of Cardiology, Montefiore, University Hospital for the Albert Einstein College of Medicine, NY, USA
[9]Department of Radiology, Kantonsspital St Gallen, St Gallen, Switzerland
[10]Department of Cardiology, Erasmus University Medical Centre, Rotterdam, Netherlands
[11]Department of Cardiology, Clinique Universitaire St Luc, Institut de Recherche Clinique et Expérimentale, Brussels, Belgium
[12]Department of Radiology and Radiological Science, Medical University of South Carolina, Charleston, SC, USA
[13]Modarres Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[14]Department of Cardiology, Aarhus Universtity Hostipal, Aarhus, Denmark
[15]Department of Cardiology, University Medical Centre Utrecht, Utrecht, Netherlands
[16]Cardiovascular Division, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan
[17]Department of Cardiology, Odense University Hospital, Odense, Denmark
[18]Department of Cardiology, Glasgow Royal Infirmary and Stobhill Hospital, Glasgow, UK
[19]Turku University Hospital and University of Turku, Turku, Finland
[20]Department of Cardiovascular Imaging, Department of Cardiology, Rabin Medical Center, Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel
[21]Medical Department, Ostfold Hospital Trust, Grålum, Norway
[22]Department of Cardiology, National Institute of Cardiology and Cardiovascular Surgery, Havana, Cuba
[23]Heart Institute, InCor, University of São Paulo Medical School, São Paulo, Brazil
[24]Department of Cardiology, Kerckhoff Heart Centre, Bad Nauheim, Germany
[25]Medical Imaging and Radiological Sciences, College of Medicine, Chang Gung University, Chang Gung Memorial Hospital at Linkou, Taoyaun City, Taiwan
[26]Heart and Diabetes Center NRW in Bad Oeynhausen, University Clinic of the Ruhr-University Bochum, Bochum, Germany
[27]Department of Cardiology, Centro Hospitalar de Vila Nova de Gaia, Vila Nova de Gaia, Portugal
[28]Department of Internal Medicine, University of Rome Tor Vergata, Rome, Italy
[29]Department of Cardiology, Centre Chirurgical Marie Lannelongue, Le Plessis Robinson, France
[30]Department of Nuclear Medicine, University Hospital Zurich, Zurich, Switzerland
[31]Department of Diagnostic and Interventional Radiology, University Hospital of Tübingen, Tübingen, Germany
[32]Department of Cardiology, Odense University Hospital, Odense, Denmark
[33]Department of Radiology, Beijing Anzhen Hospital, Beijing, China
[34]National Heart and Blood Institute, National Institutes of Health, Bethesda, MD, USA
[35]Cardiovascular Clinical Research Unit, Lady Davis Carmel Medical Center, Haifa, Israel
[36]Department of Radiology, Baotou Central Hospital, Inner Mongolia Province, China
[37]St Luke's International Hospital, Tokyo, Japan
[38]Department of Cardiology, S Chiara Hospital, Trento, Italy
[39]Department of Cardiology, University Hospital Pitié-Salpêtrière, Paris, France
[40]University of Ottawa, Heart Institute, Ottawa, Ontario, Canada
[41]Montreal Heart Institute, Université de Montréal, Montréal, Canada
[42]Albert Einstein Hospital, São Paulo, Brazil
[43]The Heart Centre, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark
[44]Department of Diagnostic Imaging and Interventional Radiology, Bichat University Hospital, Paris, France

[45]Division of Cardiology, Johns Hopkins Hospital, Johns Hopkins University, Baltimore, MD, USA
[46]Mie University Hospital, Tsu, Japan
[47]BIDMC/Harvard Medical School, Department of Cardiology, Beth Israel Deaconess Medical Center, Harvard University, Boston, MA, USA
[48]Department of Radiology, Keio University Hospital, Tokyo, Japan
[49]Department of Radiology, Mount Elizabeth Hospital, Singapore
[50]Department of Radiology, University of Ottawa, Ottawa, Ontario, Canada
[51]Department of Cardiology, Leiden University Medical Centre, Leiden, Netherlands
[52]Department of Medical Imaging, Western University, London, Ontario, Canada
[53]National Heart Centre, Singapore, Singapore
[54]Iwate Medical University, Morioka, Japan
[55]Department of Cardiology, Friedrich-Alexander University Erlangen-Nuremberg, Erlangen, Germany
[56]University of California Los Angeles, Los Angeles, CA, USA
[57]British Heart Foundation, University of Edinburgh, Edinburgh, UK

Contributors: The COME-CCT investigators shared data, approved the manuscript after reviewing the findings and interpretation, provided critical revisions of the manuscript for important intellectual content, and gave final approval of the version to be published; and are accountable for the work. RH, PS, and MD drafted the report. RH, RR, GMS, and VW undertook literature searches, and gathered and harmonised data. All members of the writing committee participated in the drafting of the original manuscript. All members of the coordinating centre participated in the data collection and analysis. The data management team harmonised all data. PS performed the statistical analysis. MD is the guarantor. The corresponding author affirms that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Funding: This study was funded by the joint programme of the German Research Foundation (DFG) and the German Federal Ministry of Education and Research (BMBF, 01KG1110) to PS and MD. All researchers are independent of the funding bodies. The funding bodies had no role in the study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the manuscript for publication.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: PS and MD had support from the joint programme of the German Research Foundation and the German Federal Ministry of Education and Research for the submitted work; PS has support from the German Research Foundation, grants from the European Union and grants from Bayer Pharma AG; GP reports grants from General Electric and is on the speakers bureau for Medtronic and Bracco; JH is on the speakers bureau for Abbott Vascular and Edwards Life Sciences; BG reports that the Cliniques St Luc UCL holds a master research agreement with Philips Medical Systems; UJS reports institutional grants, personal fees, and non-financial support from Astellas, Bayer, General Electric, Guerbet, HeartFlow, and Siemens; BLN reports grants from Siemens and HeartFlow, JKreports grants from CardiRad and personal fees from GE Healthcare; RRB reports that the University Hospital Zurich holds a research agreement with GE Healthcare; MYC reports an institutional research agreement with Canon Medical, formerly Toshiba Medical (no financial support/funding); DAH reports institutional support from Philips Healthcare during the conduct of the primary study; BH-M reports that the University Hospital Zurich holds a research agreement with GE Healthcare; BJC reports grants from CV Diagnostix and non-financial support from TeraRecon during the conduct of the study; PAK reports that the University Hospital Zurich holds a research agreement with GE Healthcare; KFK reports grants from Toshiba Medical Corporation, grants from the Danish Heart Foundation, grants from AP Møller og hustru Chastine McKinney Møllers Fond, and grants from the Danish Agency for Science, Technology and Innovation by the Danish Council for Strategic Research; AA-Z reports grants and non-financial support from Toshiba Medical Systems; JH reports grants from Toshiba Medical Systems during the conduct of the study; AS reports personal fees from General Electric and Toshiba; NP is on the speakers bureau for Toshiba Medical Systems and reports grants from Toshiba Medical Systems; GMS reports grants from the German Federal Ministry of Education and Research (BMBF), during the conduct of the study; DEN reports grants from Toshiba Medical Systems; MD is supported by the FP7 programme of the European Commission for the randomised multicentre DISCHARGE trial (603266-2, HEALTH-2012.2.4.-2) from the Heisenberg programme of the German Research Foundation (DE 1361/14-1), and the Digital Health Accelerator of the Berlin Institute of Health, has received lecture fees from Canon Medical Systems, Guerbet, Cardiac MR Academy Berlin, and Bayer, is the editor of *Cardiac CT* (Springer), and offers hands-on workshops on cardiac CT imaging (http://herz-kurs.de/); Charité institutional master research agreements exist with Siemens Medical Solutions, General Electric, Philips Medical Systems, and Canon Medical Systems, and the terms of these arrangements are managed by the legal department of Charité - Universitätsmedizin Berlin.

Ethical approval: All original studies operated under supervision of an appropriate human ethics committee. This meta-analysis is exempt from ethics approval because the study collected data from previous clinical studies in which informed consent was already obtained.

Data sharing: Requests for patient level data will be considered by the COME-CCT Consortium.

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

1 Diamond GA, Denton TA, Berman DS, Cohen I. Prior restraint: a Bayesian perspective on the optimization of technology utilization for diagnosis of coronary artery disease. *Am J Cardiol* 1995;76:82-6. doi:10.1016/S0002-9149(99)80809-1
2 Leeflang MM, Bossuyt PM, Irwig L. Diagnostic test accuracy may vary with prevalence: implications for evidence-based diagnosis. *J Clin Epidemiol* 2009;62:5-12. doi:10.1016/j.jclinepi.2008.04.007
3 Montalescot G, Sechtem U, Achenbach S, et al, Task Force Members, ESC Committee for Practice Guidelines, Document Reviewers. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J* 2013;34:2949-3003. doi:10.1093/eurheartj/eht296
4 National Institute for Health and Care Excellence. Chest pain of recent onset: assessment and diagnosis. Secondary chest pain of recent onset: assessment and diagnosis 2016. https://www.nice.org.uk/guidance/cg95.
5 Moschovitis A, Cook S, Meier B. Percutaneous coronary interventions in Europe in 2006. *EuroIntervention* 2010;6:189-94. doi:10.4244/EIJV6I2A31
6 Patel MR, Peterson ED, Dai D, et al. Low diagnostic yield of elective coronary angiography. *N Engl J Med* 2010;362:886-95. doi:10.1056/NEJMoa0907272
7 Schlattmann P, Schuetz GM, Dewey M. Influence of coronary artery disease prevalence on predictive values of coronary CT angiography: a meta-regression analysis. *Eur Radiol* 2011;21:1904-13. doi:10.1007/s00330-011-2142-2
8 Dewey M, Rief M, Martus P, et al. Evaluation of computed tomography in patients with atypical angina or chest pain clinically referred for invasive coronary angiography: randomised controlled trial. *BMJ* 2016;355:i5441. doi:10.1136/bmj.i5441
9 Newby DE, Adamson PD, Berry C, et al, SCOT-HEART Investigators. Coronary CT angiography and 5-year risk of myocardial infarction. *N Engl J Med* 2018;379:924-33.
10 Patel MR, Dai D, Hernandez AF, et al. Prevalence and predictors of nonobstructive coronary artery disease identified with coronary angiography in contemporary clinical practice. *Am Heart J* 2014;167:846-52.e2.
11 Schuetz GM, Schlattmann P, Achenbach S, et al. Individual patient data meta-analysis for the clinical assessment of coronary computed tomography angiography: protocol of the Collaborative Meta-Analysis of Cardiac CT (CoMe-CCT). *Syst Rev* 2013;2:13. doi:10.1186/2046-4053-2-13
12 Hunink MM, Weinstein MC, Wittenberg E, et al. *Decision making in health and medicine: integrating evidence and values.* Cambridge University Press, 2014. doi:10.1017/CBO9781139506779
13 Sox HCJr. Probability theory in the use of diagnostic tests. An introduction to critical study of the literature. *Ann Intern Med* 1986;104:60-6. doi:10.7326/0003-4819-104-1-60
14 Stewart LA, Clarke M, Rovers M, et al, PRISMA-IPD Development Group. Preferred Reporting Items for Systematic Review and Meta-

Analyses of individual participant data: the PRISMA-IPD Statement. *JAMA* 2015;313:1657-65. doi:10.1001/jama.2015.3656
15 Whiting P, Rutjes AW, Reitsma JB, Glas AS, Bossuyt PM, Kleijnen J. Sources of variation and bias in studies of diagnostic accuracy: a systematic review. *Ann Intern Med* 2004;140:189-202. doi:10.7326/0003-4819-140-3-200402030-00010
16 Schuetz GM, Schlattmann P, Dewey M. Use of 3x2 tables with an intention to diagnose approach to assess clinical performance of diagnostic tests: meta-analytical evaluation of coronary CT angiography studies. *BMJ* 2012;345:e6717. doi:10.1136/bmj.e6717
17 Genders TS, Steyerberg EW, Alkadhi H, et al, CAD Consortium. A clinical prediction rule for the diagnosis of coronary artery disease: validation, updating, and extension. *Eur Heart J* 2011;32:1316-30. doi:10.1093/eurheartj/ehr014
18 Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease. *N Engl J Med* 1979;300:1350-8. doi:10.1056/NEJM197906143002402
19 Diamond GA. A clinically relevant classification of chest discomfort. *J Am Coll Cardiol* 1983;1:574-5. doi:10.1016/S0735-1097(83)80093-X
20 Diamond GA, Forrester JS, Hirsch M, et al. Application of conditional probability analysis to the clinical diagnosis of coronary artery disease. *J Clin Invest* 1980;65:1210-21. doi:10.1172/JCI109776
21 Schuetz GM, Zacharopoulou NM, Schlattmann P, Dewey M. Meta-analysis: noninvasive coronary angiography using computed tomography versus magnetic resonance imaging. *Ann Intern Med* 2010;152:167-77. doi:10.7326/0003-4819-152-3-201002020-00008
22 Ahmed I, Sutton AJ, Riley RD. Assessment of publication bias, selection bias, and unavailable data in meta-analyses using individual participant data: a database survey. *BMJ* 2012;344:d7762. doi:10.1136/bmj.d7762
23 Whiting PF, Rutjes AW, Westwood ME, et al, QUADAS-2 Group. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011;155:529-36. doi:10.7326/0003-4819-155-8-201110180-00009
24 Coughlin SS, Trock B, Criqui MH, Pickle LW, Browner D, Tefft MC. The logistic modeling of sensitivity, specificity, and predictive value of a diagnostic test. *J Clin Epidemiol* 1992;45:1-7. doi:10.1016/0895-4356(92)90180-U
25 Simmonds MC, Higgins JP. A general framework for the use of logistic regression models in meta-analysis. *Stat Methods Med Res* 2016;25:2858-77. doi:10.1177/0962280214534409
26 Skrondal A, Rabe-Hesketh S. *Generalized latent variable modeling: multilevel, longitudinal, and structural equation models.* Chapman & Hall/CRC, 2004. doi:10.1201/9780203489437.
27 Skrondal A, Rabe-Hesketh S. Prediction in multilevel generalized linear models. *J R Stat Soc Ser A Stat Soc* 2009;172:659-87. doi:10.1111/j.1467-985X.2009.00587.x.
28 DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 1988;44:837-45. doi:10.2307/2531595
29 Rücker G, Schwarzer G, Carpenter J. Arcsine test for publication bias in meta-analyses with binary outcomes. *Stat Med* 2008;27:746-63. doi:10.1002/sim.2971
30 Leeflang MM, Deeks JJ, Rutjes AW, Reitsma JB, Bossuyt PM. Bivariate meta-analysis of predictive values of diagnostic tests can be an alternative to bivariate meta-analysis of sensitivity and specificity. *J Clin Epidemiol* 2012;65:1088-97. doi:10.1016/j.jclinepi.2012.03.006
31 Chu H, Cole SR. Bivariate meta-analysis of sensitivity and specificity with sparse data: a generalized linear mixed model approach. *J Clin Epidemiol* 2006;59:1331-2, author reply 1332-3. doi:10.1016/j.jclinepi.2006.06.011
32 R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing. Secondary R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing. 2017. http://www.R-project.org/.
33 Bates D, Maechler M, Bolker B, et al. lme4: Linear mixed-effects models using Eigen and S4. R package version 1.1-7. 2014. https://cran.r-project.org/web/packages/lme4/index.html.
34 Schwarzer G. meta: Meta-Analysis with R. R package version 3.2-1. 2014. http://CRAN.R-project.org/package=meta.
35 Robin X, Turck N, Hainard A, et al. pROC: an open-source package for R and S+ to analyze and compare ROC curves. *BMC Bioinformatics* 2011;12:77. doi:10.1186/1471-2105-12-77
36 Length RV. Least-squares means: the R package lsmeans. *J Stat Softw* 2016;69:1-33.
37 Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte MJr, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol* 1990;15:827-32.
38 Fihn SD, Gardin JM, Abrams J, et al, American College of Cardiology Foundation, American Heart Association Task Force on Practice Guidelines, American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2012;60:e44-164. doi:10.1016/j.jacc.2012.07.013
39 Williams MC, Hunter A, Shah ASV, et al, SCOT-HEART Investigators. Use of coronary computed tomographic angiography to guide management of patients with coronary disease. *J Am Coll Cardiol* 2016;67:1759-68. doi:10.1016/j.jacc.2016.02.026
40 Douglas PS, Hoffmann U, Patel MR, et al, PROMISE Investigators. Outcomes of anatomical versus functional testing for coronary artery disease. *N Engl J Med* 2015;372:1291-300. doi:10.1056/NEJMoa1415516
41 SCOT-HEART investigators. CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open-label, parallel-group, multicentre trial. *Lancet* 2015;385:2383-91. doi:10.1016/S0140-6736(15)60291-4
42 Kaul S. Evaluating the evidence for coronary computed tomography angiography as the noninvasive test of choice for patients with stable chest pain. *JAMA Cardiol* 2019;4:199-200.
43 Chang HJ, Lin FY, Gebow D, et al. Selective referral using CCTA versus direct referral for individuals referred to invasive coronary angiography for suspected CAD: a randomized, controlled, open-label trial. *JACC Cardiovasc Imaging* 2018;S1936-878X(18)30921-5.
44 Napp AE, Haase R, Laule M, et al, DISCHARGE Trial Group. Computed tomography versus invasive coronary angiography: design and methods of the pragmatic randomised multicentre DISCHARGE trial. *Eur Radiol* 2017;27:2957-68. doi:10.1007/s00330-016-4620-z
45 von Ballmoos MW, Haring B, Juillerat P, Alkadhi H. Meta-analysis: diagnostic performance of low-radiation-dose coronary computed tomography angiography. *Ann Intern Med* 2011;154:413-20. doi:10.7326/0003-4819-154-6-201103150-00007
46 Carr JJ, Hendel RC, White RD, et al, American College of Cardiology Foundation, American College of Cardiology Foundation. 2013 appropriate utilization of cardiovascular imaging: a methodology for the development of joint criteria for the appropriate utilization of cardiovascular imaging by the American College of Cardiology Foundation and American College of Radiology. *J Am Coll Radiol* 2013;10:456-63. doi:10.1016/j.jacr.2013.03.019
47 Taylor AJ, Cerqueira M, Hodgson JM, et al, American College of Cardiology Foundation Appropriate Use Criteria Task Force, Society of Cardiovascular Computed Tomography, American College of Radiology, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, North American Society for Cardiovascular Imaging, Society for Cardiovascular Angiography and Interventions, Society for Cardiovascular Magnetic Resonance. ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR 2010 Appropriate Use Criteria for Cardiac Computed Tomography. A Report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the Society of Cardiovascular Computed Tomography, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the American Society of Nuclear Cardiology, the North American Society for Cardiovascular Imaging, the Society for Cardiovascular Angiography and Interventions, and the Society for Cardiovascular Magnetic Resonance. *Circulation* 2010;122:e525-55.
48 Dewey M, Vavere AL, Arbab-Zadeh A, et al. Patient characteristics as predictors of image quality and diagnostic accuracy of MDCT compared with conventional coronary angiography for detecting coronary artery stenoses: CORE-64 Multicenter International Trial. *AJR Am J Roentgenol* 2010;194:93-102. doi:10.2214/AJR.09.2833
49 Dharampal AS, Papadopoulou SL, Rossi A, et al. Computed tomography coronary angiography accuracy in women and men at low to intermediate risk of coronary artery disease. *Eur Radiol* 2012;22:2415-23. doi:10.1007/s00330-012-2503-5
50 Maffei E, Martini C, Tedeschi C, et al. Diagnostic accuracy of 64-slice computed tomography coronary angiography in a large population of patients without revascularisation: registry data on the comparison between male and female population. *Radiol Med* 2012;117:6-18. doi:10.1007/s11547-011-0693-6
51 Götberg M, Cook CM, Sen S, Nijjer S, Escaned J, Davies JE. The Evolving future of instantaneous wave-free ratio and fractional flow reserve. *J Am Coll Cardiol* 2017;70:1379-402. doi:10.1016/j.jacc.2017.07.770

52 Cheng VY, Berman DS, Rozanski A, et al. Performance of the traditional age, sex, and angina typicality-based approach for estimating pretest probability of angiographically significant coronary artery disease in patients undergoing coronary computed tomographic angiography: results from the multinational coronary CT angiography evaluation for clinical outcomes: an international multicenter registry (CONFIRM). *Circulation* 2011;124:2423-32, 1-8.
53 Jensen JM, Voss M, Hansen VB, et al. Risk stratification of patients suspected of coronary artery disease: comparison of five different models. *Atherosclerosis* 2012;220:557-62. doi:10.1016/j.atherosclerosis.2011.11.027
54 Nevitt SJ, Marson AG, Davie B, Reynolds S, Williams L, Smith CT. Exploring changes over time and characteristics associated with data retrieval across individual participant data meta-analyses: systematic review. *BMJ* 2017;357:j1390. doi:10.1136/bmj.j1390

Web appendix 1: PRISMA statement for IPD systematic reviews (PRISMA-IPD) (page numbers refer to accepted manuscript)
Web appendix 2: Supplementary materials
Web appendix 3: IPD collection file

Anhänge

Die Anhänge sind als „Web Appendix“ mit der Originalarbeit auf der Internetseite des British Medical Journal publiziert worden (https://www.bmj.com/content/365/bmj.l1945/related). Sie umfassen drei Dokumente:

- Web Appendix 1: Die ausgefüllte PRISMA-Checkliste für systematische Übersichtsarbeiten mit IPD (https://www.bmj.com/content/bmj/suppl/2019/06/12/bmj.l1945.DC1/haar046861.ww1.pdf)

- Web Appendix 2: Zusätzliche, nicht in der Publikation abgebildete Tabellen und Abbildungen (https://www.bmj.com/content/bmj/suppl/2019/06/12/bmj.l1945.DC1/haar046861.ww2.pdf)

- Web Appendix 3: Die an Koautoren versandte Excel-Datei zur Erhebung der IPD (https://www.bmj.com/content/bmj/suppl/2019/06/12/bmj.l1945.DC1/haar046861.ww3.pdf)

Web Appendix 1

Die ausgefüllte PRISMA-Checkliste für systematische Übersichtsarbeiten mit IPD

PRISMA-IPD Checklist of items to include when reporting a systematic review and meta-analysis of individual participant data (IPD)

PRISMA-IPD Section/topic	Item No	Checklist item	Reported on page
Title			
Title	1	Identify the report as a systematic review and meta-analysis of individual participant data.	1
Abstract			
Structured summary	2	Provide a structured summary including as applicable: **Background:** state research question and main objectives, with information on participants, interventions, comparators and outcomes. **Methods:** report eligibility criteria; data sources including dates of last bibliographic search or elicitation, noting that IPD were sought; methods of assessing risk of bias. **Results:** provide number and type of studies and participants identified and number (%) obtained; summary effect estimates for main outcomes (benefits and harms) with confidence intervals and measures of statistical heterogeneity. Describe the direction and size of summary effects in terms meaningful to those who would put findings into practice. **Discussion:** state main strengths and limitations of the evidence, general interpretation of the results and any important implications. **Other:** report primary funding source, registration number and registry name for the systematic review and IPD meta-analysis.	5-6
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	7-8
Objectives	4	Provide an explicit statement of the questions being addressed with reference, as applicable, to participants, interventions, comparisons, outcomes and study design (PICOS). Include any hypotheses that relate to particular types of participant-level subgroups.	Supplementary PRISMA items 1 in Appendix B
Methods			
Protocol and registration	5	Indicate if a protocol exists and where it can be accessed. If available, provide registration information including registration number and registry name. Provide publication details, if applicable.	8
Eligibility criteria	6	Specify inclusion and exclusion criteria including those relating to participants, interventions, comparisons, outcomes, study design and characteristics (e.g. years when conducted, required minimum follow-up). Note whether these were applied at the study or individual level i.e. whether eligible participants were included (and ineligible participants excluded) from a study that included a wider population than specified by the review inclusion criteria. The rationale for criteria should be stated.	9

Identifying studies - information sources	7	Describe all methods of identifying published and unpublished studies including, as applicable: which bibliographic databases were searched with dates of coverage; details of any hand searching including of conference proceedings; use of study registers and agency or company databases; contact with the original research team and experts in the field; open adverts and surveys. Give the date of last search or elicitation.	9
Identifying studies - search	8	Present the full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary PRISMA items 2 in Appendix B
Study selection processes	9	State the process for determining which studies were eligible for inclusion.	9
Data collection processes	10	Describe how IPD were requested, collected and managed, including any processes for querying and confirming data with investigators. If IPD were not sought from any eligible study, the reason for this should be stated (for each such study).	9/10
		If applicable, describe how any studies for which IPD were not available were dealt with. This should include whether, how and what aggregate data were sought or extracted from study reports and publications (such as extracting data independently in duplicate) and any processes for obtaining and confirming these data with investigators.	
Data items	11	Describe how the information and variables to be collected were chosen. List and define all study level and participant level data that were sought, including baseline and follow-up information. If applicable, describe methods of standardising or translating variables within the IPD datasets to ensure common scales or measurements across studies.	Supplementary PRISMA items 3 in Appendix B
IPD integrity	A1	Describe what aspects of IPD were subject to data checking (such as sequence generation, data consistency and completeness, baseline imbalance) and how this was done.	8, Supplementary PRISMA items 4
Risk of bias assessment in individual studies.	12	Describe methods used to assess risk of bias in the individual studies and whether this was applied separately for each outcome. If applicable, describe how findings of IPD checking were used to inform the assessment. Report if and how risk of bias assessment was used in any data synthesis.	10 (QUADAS-s), 15 (publication bias)

Specification of outcomes and effect measures	13	State all treatment comparisons of interests. State all outcomes addressed and define them in detail. State whether they were pre-specified for the review and, if applicable, whether they were primary/main or secondary/additional outcomes. Give the principal measures of effect (such as risk ratio, hazard ratio, difference in means) used for each outcome.	9-13
Synthesis methods	14	Describe the meta-analysis methods used to synthesise IPD. Specify any statistical methods and models used. Issues should include (but are not restricted to): • Use of a one-stage or two-stage approach. • How effect estimates were generated separately within each study and combined across studies (where applicable). • Specification of one-stage models (where applicable) including how clustering of patients within studies was accounted for. • Use of fixed or random effects models and any other model assumptions, such as proportional hazards. • How (summary) survival curves were generated (where applicable). • Methods for quantifying statistical heterogeneity (such as I^2 and τ^2). • How studies providing IPD and not providing IPD were analysed together (where applicable). • How missing data within the IPD were dealt with (where applicable).	11-13
Exploration of variation in effects	A2	If applicable, describe any methods used to explore variation in effects by study or participant level characteristics (such as estimation of interactions between effect and covariates). State all participant-level characteristics that were analysed as potential effect modifiers, and whether these were pre-specified.	11-13
Risk of bias across studies	15	Specify any assessment of risk of bias relating to the accumulated body of evidence, including any pertaining to not obtaining IPD for particular studies, outcomes or other variables.	12/13
Additional analyses	16	Describe methods of any additional analyses, including sensitivity analyses. State which of these were pre-specified.	11-13
Results			
Study selection and IPD obtained	17	Give numbers of studies screened, assessed for eligibility, and included in the systematic review with reasons for exclusions at each stage. Indicate the number of studies and participants for which IPD were sought and for which IPD were obtained. For those studies where IPD were not available, give the numbers of studies and participants for which aggregate data were available. Report reasons for non-availability of IPD. Include a flow diagram.	13/14
Study characteristics	18	For each study, present information on key study and participant characteristics (such as description of interventions, numbers of participants, demographic data, unavailability of outcomes, funding source, and if applicable duration of follow-up). Provide (main) citations for each study. Where applicable, also report similar study characteristics for any studies not providing IPD.	Supplementary table 1 in Appendix B
IPD integrity	A3	Report any important issues identified in checking IPD or state that there were none.	Supplementary

			PRISMA items 4
Risk of bias within studies	19	Present data on risk of bias assessments. If applicable, describe whether data checking led to the up-weighting or down-weighting of these assessments. Consider how any potential bias impacts on the robustness of meta-analysis conclusions.	14 (QUADAS-s)
Results of individual studies	20	For each comparison and for each main outcome (benefit or harm), for each individual study report the number of eligible participants for which data were obtained and show simple summary data for each intervention group (including, where applicable, the number of events), effect estimates and confidence intervals. These may be tabulated or included on a forest plot.	12-15, tables 1-6
Results of syntheses	21	Present summary effects for each meta-analysis undertaken, including confidence intervals and measures of statistical heterogeneity. State whether the analysis was pre-specified, and report the numbers of studies and participants and, where applicable, the number of events on which it is based.	13-18
		When exploring variation in effects due to patient or study characteristics, present summary interaction estimates for each characteristic examined, including confidence intervals and measures of statistical heterogeneity. State whether the analysis was pre-specified. State whether any interaction is consistent across trials.	
		Provide a description of the direction and size of effect in terms meaningful to those who would put findings into practice.	
Risk of bias across studies	22	Present results of any assessment of risk of bias relating to the accumulated body of evidence, including any pertaining to the availability and representativeness of available studies, outcomes or other variables.	18 (publication bias)
Additional analyses	23	Give results of any additional analyses (e.g. sensitivity analyses). If applicable, this should also include any analyses that incorporate aggregate data for studies that do not have IPD. If applicable, summarise the main meta-analysis results following the inclusion or exclusion of studies for which IPD were not available.	13-18
Discussion			
Summary of evidence	24	Summarise the main findings, including the strength of evidence for each main outcome.	19-26
Strengths and limitations	25	Discuss any important strengths and limitations of the evidence including the benefits of access to IPD and any limitations arising from IPD that were not available.	19-26
Conclusions	26	Provide a general interpretation of the findings in the context of other evidence.	19-26
Implications	A4	Consider relevance to key groups (such as policy makers, service providers and service users). Consider implications for future research.	19-26
Funding			

Funding	27	Describe sources of funding and other support (such as supply of IPD), and the role in the systematic review of those providing such support.	6

A1 – A3 denote new items that are additional to standard PRISMA items. A4 has been created as a result of re-arranging content of the standard PRISMA statement to suit the way that systematic review IPD meta-analyses are reported.

Web Appendix 2

Zusätzliche, nicht in der Publikation abgebildete Tabellen und Abbildungen

Supplementary table 1 | Characteristics of studies included in this analysis.

Study characteristics and citation details					Study data contribution	
Study no.	**First author**	**Journal**	**Year**	**Title**	**Pts. in data set***	**Data set no.**
1	Leschka S	Eur Heart J	2005	Accuracy of MSCT coronary angiography with 64-slice technology: first experience	49	**1**
2	Alkadhi H	Heart	2010	Low-dose, 128-slice, dual-source CT coronary angiography: accuracy and radiation dose of the high-pitch and the step-and-shoot mode	99	**2**
3	Alkadhi H	Eur Heart J	2008	Dual-source computed tomography coronary angiography: influence of obesity, calcium load, and heart rate on diagnostic accuracy	150	**3**
4	Leschka S	AJR Am J Roentgenol	2008	Effect of decrease in heart rate variability on the diagnostic accuracy of 64-MDCT coronary angiography	80	**4**
5	Andreini D	J Am Coll Cardiol	2007	Diagnostic accuracy of multidetector computed tomography coronary angiography in patients with dilated cardiomyopathy	170	**5**
6	Andreini D	Circ Cardiovasc Imaging	2009	Sixty-four-slice multidetector computed tomography: an accurate imaging modality for the evaluation of coronary arteries in dilated cardiomyopathy of unknown etiology	127	**6**
7	Bettencourt N	Circ Cardiovasc Imaging	2009	Multislice computed tomography in the exclusion of coronary artery disease in patients with presurgical valve disease	65	**7**
8	Dewey M	Ann Intern Med	2006	Noninvasive detection of coronary artery stenoses with multislice computed tomography or magnetic resonance imaging	129	**8**
9	Dewey M	Circulation	2009	Noninvasive coronary angiography by 320-row computed tomography with lower radiation exposure and maintained diagnostic accuracy: comparison of results with cardiac catheterization in a head-to-head pilot investigation	29	**9**
10	Chow BJ	Can J Cardiol	2007	Comparison of computed tomographic angiography versus rubidium-82 positron emission tomography for the detection of patients with anatomical coronary artery disease	26	**10**

11	Diederichsen AC	Scand Cardiovasc J	2009	Diagnostic value of cardiac 64-slice computed tomography: importance of coronary calcium	99	**11**
12	Diederichsen AC	Unpublished study #1			50	**12**
13	Garcia MJ	JAMA	2006	Accuracy of 16-row multidetector computed tomography for the assessment of coronary artery stenosis	230	**13**
14	Watkins MW	Am J Cardiol	2007	Detection of coronary artery stenosis using 40-channel computed tomography with multi-segment reconstruction	8	**14**
15	Kefer J	J Am Coll Cardiol	2005	Head-to-head comparison of three-dimensional navigator-gated magnetic resonance imaging and 16-slice computed tomography to detect coronary artery stenosis in patients	41	**15**
16	Pouleur AC	Circ Cardiovasc Imaging	2008	Direct comparison of whole-heart navigator-gated magnetic resonance coronary angiography and 40- and 64-slice multidetector row computed tomography to detect the coronary artery stenosis in patients scheduled for conventional coronary angiography	75	**16**
17	Pouleur AC	European Radiology	2007	Usefulness of 40-slice multidetector row computed tomography to detect coronary disease in patients prior to cardiac valve surgery	15	**17**
18	Ghostine S	J Am Coll Cardiol	2006	Non-invasive detection of coronary artery disease in patients with left bundle branch block using 64-slice computed tomography	32	**18**
19	Halon DA	Cardiology	2007	Uses and limitations of 40 slice multi-detector row spiral computed tomography for diagnosing coronary lesions in unselected patients referred for routine invasive coronary angiography	42	**19**
20	Halvorsen BA	Tidsskr Nor Laegeforen	2008	Angiography with 64-channel CT upon suspicion of stable coronary disease	83	**20**
21	Hamdan A	JACC Cardiovasc Imaging	2011	A prospective study for comparison of MR and CT imaging for detection of coronary artery stenosis	88	**21**
22	Hausleiter J	Eur Heart J	2007	Non-invasive coronary computed tomographic angiography for patients with suspected coronary artery disease: the Coronary Angiography by Computed Tomography with the Use of a Submillimeter resolution (CACTUS) trial	243	**22**
23	Jenkins SM	QJM	2011	Limited clinical utility of CT coronary angiography in a district hospital setting	99	**23**

24	Langer C	J Comput Assist Tomogr	2009	Noninvasive coronary angiography focusing on calcification: multislice computed tomography compared with magnetic resonance imaging	68	**24**
25	Martuscelli E	Eur Heart J	2004	Accuracy of thin-slice computed tomography in the detection of coronary stenoses	64	**25**
26	Meijboom WB	Am J Cardiol	2007	Comparison of diagnostic accuracy of 64-slice computed tomography coronary angiography in women versus men with angina pectoris	178	**26 and 27**
27	Meijboom WB	Heart	2007	64-Slice CT coronary angiography in patients with non-ST elevation acute coronary syndrome		
28	Meijboom WB	J Am Coll Cardiol	2006	Pre-operative computed tomography coronary angiography to detect significant coronary artery disease in patients referred for cardiac valve surgery		
29	Mollet NR	Circulation	2005	High-resolution spiral computed tomography coronary angiography in patients referred for diagnostic conventional coronary angiography		
30	Pugliese F	Eur Radiol	2006	Diagnostic accuracy of non-invasive 64-slice CT coronary angiography in patients with stable angina pectoris		
31	Meijboom WB	J Am Coll Cardiol	2008	Diagnostic accuracy of 64-slice computed tomography coronary angiography: a prospective, multicenter, multivendor study	108	**28**
32	Mendoza-Rodriguez V	The Internet Journal of Cardiology	2009	Ischemic Heart Disease Diagnosed by 64 Slice Computed Tomography Coronary Angiography	81	**29**
33	Bonmassari R	J Cardiovasc Med (Hagerstown)	2006	Noninvasive detection of coronary artery stenosis with 16-slice spiral computed tomography in a population at low to moderate risk for coronary artery disease	33	**30**
34	Nikolaou K	AJR Am J Roentgenol	2006	Accuracy of 64-MDCT in the diagnosis of ischemic heart disease	60	**31**
35	Nikolaou K	AJR Am J Roentgenol	2006	Clinical value of MDCT in the diagnosis of coronary artery disease in patients with a low pretest likelihood of significant disease	33	**32**
36	Ovrehus KA	Am J Cardiol	2010	Comparison of usefulness of exercise testing versus coronary computed tomographic angiography for evaluation of patients suspected of having coronary artery disease	100	**33**

37	Ovrehus KA	JCCT	2010	Coronary computed tomographic angiography in patients suspected of coronary artery disease: impact of observer experience on diagnostic performance and interobserver reproducibility	110	**34**
38	Pontone G	Clin Radiol	2007	Accuracy of multidetector spiral computed tomography in detecting significant coronary stenosis in patient populations with differing pre-test probabilities of disease	116	**35**
39	Pontone G	Coron Artery Dis	2007	Diagnostic work-up of unselected patients with suspected coronary artery disease: complementary role of multidetector computed tomography, symptoms and electrocardiogram stress test	144	**36**
40	Pontone G	J Am Coll Cardiol	2009	Diagnostic accuracy of coronary computed tomography angiography: a comparison between prospective and retrospective electrocardiogram triggering	96	**37**
41	Rixe J	Circ J	2009	Detection of relevant coronary artery disease using dual-source computed tomography in a high probability patient series: comparison with invasive angiography	76	**38**
42	Sato A	J Nucl Cardiol	2010	Incremental value of combining 64-slice computed tomography angiography with stress nuclear myocardial perfusion imaging to improve noninvasive detection of coronary artery disease	107	**39**
43	Herzog C	Radiology	2007	Does two-segment image reconstruction at 64-section CT coronary angiography improve image quality and diagnostic accuracy?	98	**40**
44	Herzog C	Radiology	2007	Significant coronary artery stenosis: comparison on per-patient and per-vessel or per-segment basis at 64-section CT angiography		
45	Arnoldi E	Radiologe	2010	Coronary CT angiography using prospective ECG triggering: high diagnostic accuracy with low radiation dose	20	**41**
46	Shabestari AA	Am J Cardiol	2007	Diagnostic performance of 64-channel multislice computed tomography in assessment of significant coronary artery disease in symptomatic subjects	113	**42**
47	Ugolini P	Can J Cardiol	2009	Evaluation of coronary atheroma by 64-slice multidetector computed tomography: Comparison with intravascular ultrasound and angiography	13	**43**
48	Ugolini P	Unpublished study #2			3	**44**

49	Yang L	AJR Am J Roentgenol	2009	64-MDCT coronary angiography of patients with atrial fibrillation: influence of heart rate on image quality and efficacy in evaluation of coronary artery disease	60	**45**
50	Xu L	Eur Radiol	2011	Diagnostic performance of 320-detector CT coronary angiography in patients with atrial fibrillation: preliminary results	37	**46**
51	Sun K	Chinese Medical Sciences Journal	2012	Feasibility and diagnostic accuracy for assessment of coronary artery stenosis of prospectively electrocardiogram-gated high-pitch spiral acquisition mode dual-source ct coronary angiography in patients with relatively higher heart rates: In comparison with catheter coronary angiography	37	**47**
52	Jakamy R	Arch Cardiovasc Dis	2012	Accuracy of multislice computed tomography in the preoperative assessment of coronary disease in patients scheduled for heart valve surgery	32	**48**
53	Kajander	Circulation	2010	Cardiac positron emission tomography/computed tomography imaging accurately detects anatomically and functionally significant coronary artery disease	99	**49**
54	Pontone G	Am Heart J	2011	Feasibility and accuracy of a comprehensive multidetector computed tomography acquisition for patients referred for balloon-expandable transcatheter aortic valve implantation	39	**50**
55	Herzog BA	Eur Heart J	2008	Accuracy of low-dose computed tomography coronary angiography using prospective electrocardiogram-triggering: first clinical experience	22	**51**
56	Herzog BA	Heart	2009	First head-to-head comparison of effective radiation dose from low-dose 64-slice CT with prospective ECG-triggering versus invasive coronary angiography	36	**52**
57	Husmann L	Acad Radiol	2010	Usefulness of additional coronary calcium scoring in low-dose CT coronary angiography with prospective ECG-triggering impact on total effective radiation dose and diagnostic accuracy	61	**53**
58	Andreini D	Cardiovasc Diabetol	2010	Comparison of the diagnostic performance of 64-slice computed tomography coronary angiography in diabetic and non-diabetic patients with suspected coronary artery disease	210	**54**

59	Chen CC	Int J Cardiovasc Imaging	2011	The effect of calcium score on the diagnostic accuracy of coronary computed tomography angiography	75	**55**
60	Laissy JP	Heart	2007	Comprehensive evaluation of preoperative patients with aortic valve stenosis: usefulness of cardiac multidetector computed tomography	13	**56**
61	Scheffel H	Eur Radiol	2006	Accuracy of dual-source CT coronary angiography: First experience in a high pre-test probability population without heart rate control	24	**57**
62	Leschka S	Heart	2008	Combining dual-source computed tomography coronary angiography and calcium scoring: added value for the assessment of coronary artery disease	67	**58**
63	Gueret P	Am J Cardiol	2013	Diagnostic Performance of Computed Tomography Coronary Angiography (from the Prospective National Multicenter Multivendor EVASCAN Study)	574	**59**
64	Rochitte CE	Eur Heart J	2014	Computed tomography angiography and perfusion to assess coronary artery stenosis causing perfusion defects by single photon emission computed tomography: the CORE320 study	265	**60**
65	Ghostine S	Eur Heart J	2008	Non-invasive diagnosis of ischaemic heart failure using 64-slice computed tomography	31	**61**

Full study citations can be found in Supplementary table 18. Pts. = Number of patients *=number of patients in the data set for main analysis. Number in the whole COME-CCT data set may be higher. The data set number will be used in supplementary 5 and 6 for identification.

Supplementary table 2 | QUADAS-2 analysis

	Studies		Risk of Bias				Applicability Concerns			Risk of Bias	Applicability Concerns
#	First author	Journal, Year	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard	**Total**	**Total**
1	Alkadhi H	Eur Heart J 2008	Low	Low	Low	Low	Low	Low	Low	**Low**	**Low**
2	Alkadhi H	Heart 2010	Low	Low	Low	Low	Low	Low	Low	**Low**	**Low**
3	Andreini D	Cardiovasc Diabetol 2010	Low	Low	Low	Low	Low	Low	Low	**Low**	**Low**
4	Andreini D	Circ Cardiovasc Imaging 2009	Low	Low	Low	Low	Low	Low	Low	**Low**	**Low**
5	Andreini D	J Am Coll Cardiol 2007	Low	Low	Low	Low	Low	Low	Low	**Low**	**Low**
6	Arnoldi E	Radiologe 2010	Low	Unclear	Low	Unclear	Low	Low	Low	**Unclear**	**Low**
7	Bettencourt N	Circ Cardiovasc Imaging 2009	Low	Low	Low	Low	Low	Low	Low	**Low**	**Low**
8	Bonmassari R	J Cardiovasc Med (Hagerstown) 2006	Low	Unclear	Unclear	Unclear	Low	Low	Low	**Unclear**	**Low**
9	Chen CC	Int J Cardiovasc Imaging 2011	Low	Low	Unclear	High	Low	Low	Low	**High**	**Low**
10	Chow BJ	Can J Cardiol 2007	Unclear	Unclear	Unclear	Low	Low	Low	Low	**Unclear**	**Low**
11	Dewey M	Ann Intern Med 2006	Low	Low	Low	Low	Low	Low	Low	**Low**	**Low**
12	Dewey M	Circulation 2009	Low	Low	Low	Low	Low	Low	Low	**Low**	**Low**
13	Diederichsen AC	Scand Cardiovasc J 2009	Low	Low	Low	Low	Low	Low	Low	**Low**	**Low**
14	Garcia MJ	JAMA 2006	High	Low	Unclear	Low	Low	Low	Low	**High**	**Low**
15	Ghostine S	J Am Coll Cardiol 2006	Low	Low	Low	Low	Low	Low	Low	**Low**	**Low**

16	Ghostine S	Eur Heart 2008	Low	Low	Low	Low	Low	Low	Low	**Low**	**Low**
17	Gueret P	Am J Cardiol 2013	High	Low	Low	Low	Low	Low	Low	**High**	**Low**
18	Halon DA	Cardiology 2007	High	Low	Low	High	Low	Low	Low	**High**	**Low**
19	Halvorsen BA	Tidsskr Nor Laegeforen 2008	X	X	X	X	X	X	X	X	X
20	Hamdan A	JACC Cardiovasc Imaging 2011	High	Low	Low	Low	Low	Low	Low	**High**	**Low**
21	Hausleiter J	Eur Heart J 2007	Low	Low	Low	Low	Low	Low	Low	**Low**	**Low**
22	Herzog BA	Eur Heart J 2008	Low	Unclear	Low	Low	Low	Low	Low	**Low**	**Low**
23	Herzog BA	Heart 2009	Low	Unclear	Low	Low	Low	Low	Low	**Low**	**Low**
24	Herzog C	Radiology 2007*	Low	Low	Low	Unclear	Low	Low	Low	**Unclear**	**Low**
25	Herzog C	Radiology 2007**	Low	Unclear	Low	Low	Low	Low	Low	**Unclear**	**Low**
26	Husmann L	Acad Radiol 2010	High	Unclear	Low	Unclear	Low	Low	Low	**High**	**Low**
27	Jakamy R	Arch Cardiovasc Dis 2012	Low	Unclear	Low	High	Low	Low	Low	**High**	**Low**
28	Jenkins SM	QJM 2012	Low	Low	Low	High	Low	Low	Low	**Low**	**Low**
29	Kajander	Circulation 2010	Low	Low	Low	High	Low	Low	Low	**High**	**Low**
30	Kefer J	J Am Coll Cardiol 2005	Low	Low	Low	High	Low	Low	Low	**Low**	**Low**
31	Laissy JP	Heart 2007	Low	Unclear	Unclear	Low	Low	Low	Low	**Unclear**	**Low**
32	Langer C	J Comput Assist Tomogr 2007	Low	Low	Unclear	Low	Low	Low	Low	**Unclear**	**Low**
33	Leschka S	Eur Heart 2005	High	Low	Low	Low	Low	Low	Low	**High**	**Low**
34	Leschka S	Heart 2008	Low	Low	Low	Low	Low	Low	Low	**Low**	**Low**
35	Leschka S	AJR Am J Roentgenol 2008	High	Low	Low	Low	Low	Low	Low	**High**	**Low**
36	Martuscelli E	Eur Heart J 2004	Low	Low	Unclear	High	Low	Low	Low	**High**	**Low**
37	Meijboom WB	J Am Coll Cardiol 2008	Low	Low	Low	Low	Low	Low	Low	**Low**	**Low**

38	Meijboom WB	J Am Coll Cardiol 2006	Low	Low	Low	Low	Low	Low	Low	**Low**	**Low**
39	Meijboom WB	Heart 2007	Low	Low	Low	Low	Low	Low	Low	**Low**	**Low**
40	Meijboom WB	Am J Cardiol 2007	Low	Low	Low	Low	Low	Low	Low	**Low**	**Low**
41	Mendoza-Rodriguez V	The Internet Journal of Cardiology 2007	Low	Unclear	Low	Unclear	Low	Low	Low	**Unclear**	**Low**
42	Mollet NR	Circulation 2005	Low	Low	Low	Low	Low	Low	Low	**Low**	**Low**
43	Nikolaou K	AJR Am J Roentgenol[+]	High	Low	Low	High	Low	Low	Low	**High**	**Low**
44	Nikolaou K	AJR Am J Roentgenol[++]	Low	Low	Low	Low	Low	Low	Low	**Low**	**Low**
45	Ovrehus KA	Am J Cardiol 2010	Low	Low	Low	Low	Low	Low	Low	**Low**	**Low**
46	Ovrehus KA	J Cardiovasc Comput Tomogr 2010	Low	Low	Low	Low	Low	Low	Low	**Low**	**Low**
47	Pontone G	Coron Art Dis 2007	High	Unclear	Low	Unclear	Low	Low	Low	**Unclear**	**Low**
48	Pontone G	Am Heart J 2011	High	Unclear	Unclear	Unclear	Low	Low	Low	**High**	**Low**
49	Pontone G	J Am Coll Cardiol 2009	High	Low	Low	Low	Low	Low	Low	**High**	**Low**
50	Pontone G	Clin Radiol 2007	Low	Unclear	Low	High	Low	Low	Low	**High**	**Low**
51	Pouleur AC	Eur Radiol 2007	Low	Low	Low	Low	Low	Low	Low	**Low**	**Low**
52	Pouleur AC	Circ Cardiovasc Imaging 2008	Low	Low	Low	Low	Low	Low	Low	**Low**	**Low**
53	Pugliese F	Eur Radiol 2006	Low	Low	Low	Low	Low	Low	Low	**Low**	**Low**
54	Rixe J	Circ J 2009	Low	Unclear	Low	Low	Low	Low	Low	**Unclear**	**Low**
55	Rochitte CE	Eur Heart J 2014	High	Low	Low	Low	Low	Low	Low	**High**	**Low**
56	Sato A	J Nucl Cardiol 2010	Low	Low	Unclear	High	Low	Low	Low	**High**	**Low**
57	Scheffel H	Eur Radiol 2006	Low	Unclear	Low	High	Low	Low	Low	**High**	**Low**
58	Shabestari AA	Am J Cardiol 2007	High	Low	Unclear	High	Low	Low	Low	**High**	**Low**
59	Sun K	Chin Med Sci J 2012	Low	Low	Low	Unclear	Low	Low	Low	**Unclear**	**Low**
60	Ugolini P	Can J Cardiol 2009	Low	Low	Low	Low	Low	Low	Low	**Low**	**Low**

61	Watkins MW	Am J Cardiol 2007	High	Low	Low	Unclear	Low	Low	Low	**High**	**Low**
62	Xu L	Eur Radiol 2011	Low	Low	Low	Low	Low	Low	Low	**Low**	**Low**
63	Yang L	AJR Am J Roentgenol 2009	Low	Low	Low	Low	Low	Low	Low	**Low**	**Low**
64	Unpublished data	Diederichsen AC	X	X	X	X	X	X	X	X	X
65	Unpublished data	Ugolini P	X	X	X	X	X	X	X	X	X

* refers to study 24 in supplementary table 1. ** refers to study 25 in supplementary table 1. $^{+}$ refers to study 43 in supplementary table 1. $^{++}$ refers to study 44 in supplementary table 1. X = QUADAS assessment not possible because of study language (Norwegian, #19) or unpublished data (#64 and #65).

Supplementary table 3 | QUADAS-2 risk of bias summary

Risk of bias	Patient selection	Index test	Reference standard	Flow and timing	Total
Low	47	47	52	41	31
High	14	0	0	12	20
Unclear	1	15	10	9	11

Supplementary table 4 | QUADAS-2 applicability concerns summary

Applicability concerns	Patient selection	Index test	Reference standard	Total
Low	62	62	62	62
High	0	0	0	0
Unclear	0	0	0	0

Supplementary table 5 | Participant characteristics for each data set. Figures are numbers (percentages) unless stated otherwise.

Data set*	Patients	Age mean (SD)	Male sex	Chest pain symptoms				Risk factor distribution					Patients with CAD
				Typical AP	Atypical AP	Non-anginal CD	Other CD	Arterial HTN	DM	HLD	Active Smokers	Former Smokers	
1	49	56 (13)	35 (71.4)	18 (36.7)	22 (44.9)	9 (18.4)	0 (0.0)	26 (53.1)	5 (10.2)	21 (42.9)	17 (34.7)	3 (6.1)	30 (61.2)
2	99	63 (8)	73 (73.7)	17 (17.2)	37 (37.4)	45 (45.5)	0 (0.0)	46 (46.5)	23 (23.2)	35 (35.4)	38 (38.4)	31 (31.3)	35 (35.4)
3	150	64 (12)	103 (68.7)	32 (21.3)	91 (60.7)	27 (18.0)	0 (0.0)	75 (50.0)	29 (19.3)	57 (38.0)	62 (41.3)	7 (4.7)	59 (39.3)
4	80	61 (11)	46 (57.5)	12 (15.0)	32 (40.0)	27 (33.8)	9 (11.3)	41 (51.3)	12 (15.0)	40 (50.0)	32 (40.0)	7 (8.8)	39 (48.8)
5	170	54 (8)	121 (71.2)	0 (0.0)	20 (11.8)	19 (11.2)	131 (77.1)	37 (21.8)	1 (0.6)	45 (26.5)	22 (12.9)	25 (14.7)	84 (49.4)
6	127	56 (7)	79 (62.2)	0 (0.0)	5 (3.9)	3 (2.4)	119 (93.7)	49 (38.6)	14 (11.0)	41 (32.3)	17 (13.4)	0 (0.0)	46 (36.2)
7	65	70 (8)	38 (58.5)	62 (95.4)	0 (0.0)	0 (0.0)	3 (4.6)	45 (69.2)	12 (18.5)	33 (50.8)	5 (7.7)	8 (12.3)	22 (33.8)
8	129	63 (9)	34 (26.4)	61 (47.3)	32 (24.8)	13 (10.1)	23 (17.8)	93 (72.1)	21 (16.3)	66 (51.2)	30 (23.3)	59 (45.7)	67 (51.9)
9	29	60 (10)	9 (31.0)	7 (24.1)	10 (34.5)	2 (6.9)	10 (34.5)	26 (89.7)	5 (17.2)	17 (58.6)	4 (13.8)	14 (48.3)	11 (37.9)
10	26	56 (9)	18 (69.2)	17 (65.4)	4 (15.4)	1 (3.8)	4 (15.4)	15 (57.7)	4 (15.4)	19 (73.1)	4 (15.4)	16 (61.5)	19 (73.1)
11	99	62 (11)	53 (53.5)	77 (77.8)	0 (0.0)	0 (0.0)	22 (22.2)	49 (49.5)	9 (9.1)	43 (43.4)	25 (25.3)	32 (32.3)	31 (31.3)
12	50	62 (10)	26 (52.0)	13 (26.0)	19 (38.0)	18 (36.0)	0 (0.0)	30 (60.0)	3 (6.0)	18 (36.0)	13 (26.0)	24 (48.0)	20 (40.0)
13	230	60 (9)	156 (67.8)	134 (58.3)	59 (25.7)	37 (16.1)	0 (0.0)	102 (44.3)	14 (6.1)	98 (42.6)	47 (20.4)	100 (43.5)	72 (31.3)
14	8	61 (10)	6 (75.0)	5 (62.5)	3 (37.5)	0 (0.0)	0 (0.0)	6 (75.0)	0 (0.0)	7 (87.5)	0 (0.0)	0 (0.0)	3 (37.5)
15	41	64 (13)	32 (78.0)	21 (51.2)	4 (9.8)	5 (12.2)	11 (26.8)	23 (56.1)	5 (12.2)	20 (48.8)	15 (36.6)	4 (9.8)	24 (58.5)
16	75	60 (13)	56 (74.7)	12 (16.0)	4 (5.3)	5 (6.7)	54 (72.0)	40 (53.3)	13 (17.3)	45 (60.0)	23 (30.7)	10 (13.3)	17 (22.7)
17	15	62 (12)	9 (60.0)	3 (20.0)	0 (0.0)	0 (0.0)	12 (80.0)	8 (53.3)	0 (0.0)	4 (26.7)	4 (26.7)	0 (0.0)	5 (33.3)
18	32	70 (13)	15 (46.9)	20 (62.5)	12 (37.5)	0 (0.0)	0 (0.0)	23 (71.9)	10 (31.3)	19 (59.4)	13 (40.6)	0 (0.0)	15 (46.9)
19	42	56 (12)	35 (83.3)	0 (0.0)	0 (0.0)	0 (0.0)	42 (100.0)	18 (42.9)	8 (19.0)	0 (0.0)	11 (26.2)	9 (21.4)	22 (52.4)
20	83	61 (9)	46 (55.4)	46 (55.4)	35 (42.2)	0 (0.0)	2 (2.4)	42 (50.6)	12 (14.5)	53 (63.9)	15 (18.1)	34 (41.0)	39 (47.0)
21	88	64 (9)	56 (63.6)	25 (28.4)	28 (31.8)	17 (19.3)	18 (20.5)	62 (70.5)	20 (22.7)	53 (60.2)	16 (18.2)	40 (45.5)	44 (50.0)
22	243	62 (10)	158 (65.0)	38 (15.6)	136 (56.0)	0 (0.0)	69 (28.4)	0 (0.0)	0 (0.0)	152 (62.6)	38 (15.6)	46 (18.9)	101 (41.6)
23	99	58 (11)	55 (55.6)	55 (55.6)	0 (0.0)	38 (38.4)	6 (6.1)	53 (53.5)	11 (11.1)	87 (87.9)	24 (24.2)	32 (32.3)	38 (38.4)
24	68	64 (11)	38 (55.9)	0 (0.0)	68 (100.0)	0 (0.0)	0 (0.0)	57 (83.8)	11 (16.2)	51 (75.0)	7 (10.3)	22 (32.4)	26 (38.2)

25	64	59 (7)	59 (92.2)	33 (51.6)	16 (25.0)	2 (3.1)	13 (20.3)	61 (95.3)	37 (57.8)	52 (81.3)	24 (37.5)	24 (37.5)	43 (67.2)
26	38	60 (12)	33 (86.8)	18 (47.4)	11 (28.9)	9 (23.7)	0 (0.0)	20 (52.6)	7 (18.4)	21 (55.3)	10 (26.3)	0 (0.0)	21 (55.3)
27	140	60 (11)	95 (67.9)	58 (41.4)	35 (25.0)	47 (33.6)	0 (0.0)	74 (52.9)	15 (10.7)	67 (47.9)	37 (26.4)	0 (0.0)	72 (51.4)
28	108	61 (6)	75 (69.4)	61 (56.5)	17 (15.7)	10 (9.3)	20 (18.5)	65 (60.2)	24 (22.2)	67 (62.0)	28 (25.9)	0 (0.0)	69 (63.9)
29	81	56 (8)	61 (75.3)	25 (30.9)	56 (69.1)	0 (0.0)	0 (0.0)	52 (64.2)	20 (24.7)	41 (50.6)	39 (48.1)	0 (0.0)	18 (22.2)
30	33	69 (8)	23 (69.7)	0 (0.0)	0 (0.0)	6 (18.2)	27 (81.8)	16 (48.5)	8 (24.2)	17 (51.5)	7 (21.2)	11 (33.3)	14 (42.4)
31	60	60 (10)	33 (55.0)	3 (5.0)	22 (36.7)	35 (58.3)	0 (0.0)	NA	NA	NA	NA	NA	5 (8.3)
32	33	64 (11)	24 (72.7)	32 (97.0)	1 (3.0)	0 (0.0)	0 (0.0)	NA	NA	NA	NA	NA	21 (63.6)
33	100	61 (9)	50 (50.0)	31 (31.0)	28 (28.0)	41 (41.0)	0 (0.0)	50 (50.0)	3 (3.0)	69 (69.0)	14 (14.0)	38 (38.0)	29 (29.0)
34	110	61 (9)	72 (65.5)	64 (58.2)	46 (41.8)	0 (0.0)	0 (0.0)	70 (63.6)	15 (13.6)	82 (74.5)	24 (21.8)	45 (40.9)	44 (40.0)
35	116	63 (10)	86 (74.1)	10 (8.6)	39 (33.6)	67 (57.8)	0 (0.0)	76 (65.5)	14 (12.1)	71 (61.2)	25 (21.6)	27 (23.3)	63 (54.3)
36	144	62 (10)	109 (75.7)	58 (40.3)	86 (59.7)	0 (0.0)	0 (0.0)	88 (61.1)	21 (14.6)	105 (72.9)	49 (34.0)	47 (32.6)	95 (66.0)
37	96	65 (9)	81 (84.4)	24 (25.0)	37 (38.5)	4 (4.2)	31 (32.3)	64 (66.7)	17 (17.7)	54 (56.3)	27 (28.1)	40 (41.7)	90 (93.8)
38	76	63 (10)	47 (61.8)	22 (28.9)	35 (46.1)	12 (15.8)	7 (9.2)	64 (84.2)	25 (32.9)	51 (67.1)	9 (11.8)	14 (18.4)	40 (52.6)
39	107	67 (10)	69 (64.5)	69 (64.5)	21 (19.6)	10 (9.3)	7 (6.5)	73 (68.2)	49 (45.8)	65 (60.7)	44 (41.1)	21 (19.6)	59 (55.1)
40	98	60 (10)	49 (50.0)	75 (76.5)	20 (20.4)	0 (0.0)	3 (3.1)	86 (87.8)	27 (27.6)	0 (0.0)	24 (24.5)	24 (24.5)	45 (45.9)
41	20	60 (12)	15 (75.0)	20 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	11 (55.0)
42	113	64 (10)	81 (71.7)	1 (0.9)	2 (1.8)	80 (70.8)	30 (26.5)	87 (77.0)	48 (42.5)	63 (55.8)	49 (43.4)	9 (8.0)	90 (79.6)
43	13	62 (5)	8 (61.5)	7 (53.8)	4 (30.8)	1 (7.7)	1 (7.7)	4 (30.8)	0 (0.0)	12 (92.3)	2 (15.4)	6 (46.2)	5 (38.5)
44	3	54 (16)	2 (66.7)	1 (33.3)	1 (33.3)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (66.7)	0 (0.0)
45	60	58 (7)	23 (38.3)	2 (3.3)	6 (10.0)	14 (23.3)	38 (63.3)	4 (6.7)	1 (1.7)	6 (10.0)	10 (16.7)	1 (1.7)	8 (13.3)
46	37	60 (6)	16 (43.2)	6 (16.2)	3 (8.1)	6 (16.2)	22 (59.5)	12 (32.4)	6 (16.2)	19 (51.4)	3 (8.1)	10 (27.0)	10 (27.0)
47	37	59 (11)	25 (67.6)	5 (13.5)	3 (8.1)	24 (64.9)	5 (13.5)	6 (16.2)	4 (10.8)	11 (29.7)	15 (40.5)	16 (43.2)	27 (73.0)
48	32	65 (12)	21 (65.6)	1 (3.1)	0 (0.0)	0 (0.0)	31 (96.9)	19 (59.4)	4 (12.5)	14 (43.8)	5 (15.6)	13 (40.6)	6 (18.8)
49	99	64 (7)	56 (56.6)	53 (53.5)	39 (39.4)	7 (7.1)	0 (0.0)	39 (39.4)	13 (13.1)	65 (65.7)	16 (16.2)	9 (9.1)	43 (43.4)
50	39	80 (9)	10 (25.6)	3 (7.7)	0 (0.0)	5 (12.8)	31 (79.5)	26 (66.7)	2 (5.1)	13 (33.3)	7 (17.9)	3 (7.7)	11 (28.2)
51	22	58 (11)	13 (59.1)	6 (27.3)	10 (45.5)	2 (9.1)	4 (18.2)	10 (45.5)	3 (13.6)	7 (31.8)	10 (45.5)	0 (0.0)	12 (54.5)
52	36	62 (9)	24 (66.7)	7 (19.4)	19 (52.8)	9 (25.0)	1 (2.8)	21 (58.3)	3 (8.3)	19 (52.8)	18 (50.0)	0 (0.0)	20 (55.6)
53	61	61 (11)	37 (60.7)	35 (57.4)	11 (18.0)	12 (19.7)	3 (4.9)	36 (59.0)	4 (6.6)	28 (45.9)	28 (45.9)	0 (0.0)	33 (54.1)

54	210	61 (8)	184 (87.6)	38 (18.1)	45 (21.4)	34 (16.2)	93 (44.3)	137 (65.2)	105 (50.0)	104 (49.5)	60 (28.6)	0 (0.0)	180 (85.7)
55	75	61 (10)	61 (81.3)	31 (41.3)	31 (41.3)	6 (8.0)	7 (9.3)	48 (64.0)	15 (20.0)	23 (30.7)	14 (18.7)	14 (18.7)	50 (66.7)
56	13	69 (11)	7 (53.8)	3 (23.1)	1 (7.7)	1 (7.7)	8 (61.5)	6 (46.2)	2 (15.4)	4 (30.8)	2 (15.4)	0 (0.0)	2 (15.4)
57	24	63 (12)	18 (75.0)	15 (62.5)	2 (8.3)	7 (29.2)	0 (0.0)	17 (70.8)	13 (54.2)	14 (58.3)	19 (79.2)	0 (0.0)	9 (37.5)
58	67	61 (12)	44 (65.7)	34 (50.7)	15 (22.4)	7 (10.4)	11 (16.4)	39 (58.2)	16 (23.9)	16 (23.9)	17 (25.4)	0 (0.0)	29 (43.3)
59	574	60 (11)	387 (67.4)	320 (55.7)	189 (32.9)	65 (11.3)	0 (0.0)	296 (51.6)	136 (23.7)	180 (31.4)	157 (27.4)	0 (0.0)	274 (47.7)
60	265	62 (8)	156 (58.9)	92 (34.7)	118 (44.5)	6 (2.3)	49 (18.5)	NA	NA	NA	NA	NA	152 (57.4)
61	31	69 (10)	22 (71.0)	29 (93.5)	2 (6.5)	0 (0.0)	0 (0.0)	17 (54.8)	7 (22.6)	17 (54.8)	14 (45.2)	0 (0.0)	20 (64.5)

* data set numbers for studies are provided in supplementary Table 1.

Supplementary table 6 | Technical characteristics of imaging tests for each data set. Figures are numbers (percentages) unless stated otherwise.

Study ID	Patients	CT rows						CT gating	CTA showing CAD	Effective dose, mean (SD), mSv Effective dose, mean (SD), mSv	kV
		16	32	40	64	128	320				
1	49	0	49	0	0	0	0	retrospective	30	10.0 (1.8)	120
2	99	0	0	0	0	99	0	prospective	43	0.9 (0.2)	100
3	150	0	0	0	150	0	0	retrospective	78	8.0 (1.0)	120
4	80	0	80	0	0	0	0	retrospective	53	10.1 (1.9)	120
5	170	170	0	0	0	0	0	retrospective	106	14.5 (1.1)	120 to 140 according to the patient's body weight
6	127	0	0	0	127	0	0	both	66	19.8 (6.9)	120
7	65	0	65	0	0	0	0	retrospective	55	11.2 (3.1)	120
8	129	129	0	0	0	0	0	retrospective	91	11.9 (1.4)	120
9	29	0	0	0	0	0	29	prospective	12	6.3 (4.0)	120
10	26	26	0	0	0	0	0	retrospective	18	NA	120
11	99	0	0	0	99	0	0	retrospective	48	25.5 (6.5)	120
12	50	0	0	0	50	0	0	both	58	7.4 (6.0)	NA
13	230	230	0	0	0	0	0	retrospective	190	6.3 (2.5)	120 to 140 according to the patient's body weight
14	8	0	0	8	0	0	0	retrospective	3	10.5 (1.5)	120 to 140 according to the patient's body weight
15	41	41	0	0	0	0	0	retrospective	31	11.5 (2.1)	140
16	75	1	0	58	16	0	0	retrospective	30	13.6 (2.3)	120
17	15	0	0	15	0	0	0	retrospective	5	13.8 (2.1)	120
18	32	0	0	0	32	0	0	retrospective	17	7.2 (2.4)	120
19	42	0	0	42	0	0	0	retrospective	27	NA	120

20	83	0	0	0	83	0	0	retrospective	52	NA	120 to 135
21	88	0	88	0	0	0	0	retrospective	56	16.5 (3.8)	120
22	243	129	0	0	114	0	0	retrospective	136	7.3 (3.0)	Not explicitly stated*
23	99	0	0	99	0	0	0	retrospective	99	15.7 (3.0)	120 to 140 according to the patient's body weight
24	68	68	0	0	0	0	0	retrospective	65	7.7 (3.8)	120
25	64	64	0	0	0	0	0	retrospective	46	NA	120
26	38	0	38	0	0	0	0	retrospective	22	NA	120
27	140	0	140	0	0	0	0	retrospective	80	NA	120
28	108	0	0	0	0	0	0	retrospective	87	NA	120
29	81	0	81	0	0	0	0	retrospective	22	10.9 (1.8)	120
30	33	33	0	0	0	0	0	retrospective	36	NA	140
31	60	60	0	0	0	0	0	retrospective	39	14.3 (1.0)	120
32	33	33	0	0	0	0	0	retrospective	29	8.6 (1.5)	120
33	100	0	51	0	49	0	0	retrospective	47	NA	120
34	110	0	44	0	66	0	0	retrospective	61	14.5 (4.0)	120
35	116	116	0	0	0	0	0	retrospective	91	13.1 (2.3)	120
36	144	144	0	0	0	0	0	retrospective	117	13.2 (2.5)	120 to 140 according to the patient's body weight
37	96	0	0	0	96	0	0	both	91	14.1 (8.9)	120
38	76	0	0	0	76	0	0	retrospective	52	NA	120
39	107	0	0	0	107	0	0	retrospective	95	15.0 (0.0)	120
40	98	0	0	0	98	0	0	retrospective	38	NA	120
41	20	0	0	0	20	0	0	prospective	15	2.5 (1.1)	100 to 120 according to the patient's body weight
42	113	0	113	0	0	0	0	retrospective	94	14.1 (1.5)	120
43	13	0	0	0	13	0	0	retrospective	7	NA	120
44	3	0	0	0	3	0	0	retrospective	2	8.3 (4.4)	NA
45	60	0	0	0	60	0	0	retrospective	18	14.4 (4.2)	100 to 135

46	37	0	0	0	0	0	37	prospective	15	13.0 (4.7)	100 and 120
47	37	0	0	0	0	37	0	prospective	34	1.1 (0.1)	100
48	32	0	0	0	32	0	0	prospective	11	22.7 (14.4)	120
49	99	0	0	0	99	0	0	both	46	9.5 (5.2)	100 to 120, depending on patient size
50	39	0	0	0	39	0	0	retrospective	17	36.6 (13.9)	120
51	22	0	0	0	22	0	0	prospective	18	2.1 (0.8)	100 and 120, according to the patient's BMI
52	36	0	0	0	36	0	0	prospective	22	2.1 (0.7)	100 and 120, according to the patient's BMI
53	61	0	0	0	61	0	0	prospective	39	2.1 (0.7)	100 and 120, according to the patient's BMI
54	210	0	0	0	210	0	0	retrospective	192	14.6 (1.7)	120
55	75	0	0	0	75	0	0	retrospective	51	16.3 (1.8)	120
56	13	13	0	0	0	0	0	retrospective	3	NA	no information
57	24	0	0	0	0	24	0	retrospective	8	NA	120
58	67	0	0	0	0	67	0	retrospective	39	NA	120
59	574	0	0	0	574	0	0	prospective	608	18.3 (7.3)	100 to 140, according to the patient's body weight
60	79	0	0	0	0	0	79	retrospective	34	NA	120
61	31	0	0	0	31	0	0	retrospective	21	9.9 (5.0)	120

* original citations from the publication: "To decrease radiation exposure, we consequently used dose-saving algorithms including prospective ECG-gated tube current modulation and 100 kV acquisition protocols, whenever possible."

Supplementary Table 7 | Empiral data of female patients and their assignment to pretest probability categories

Female patients	Participants	Pretest probability categories									
	Overall	0 to <10%	10 to <20%	20 to < 30%	30 to <40%	40 to <50%	50 to <60%	60 to <70%	70 to <80%	80 to <90%	90 to 100%
N	1859	86	501	390	218	169	245	199	51	0	0
TP	533	14	114	97	69	52	90	68	29	-	-
TN	927	52	292	210	104	81	107	72	9	-	-
FP	147	6	35	40	21	11	17	12	5	-	-
FN	34	1	3	7	4	4	8	7	0	-	-
NDX	218	13	57	36	20	21	23	40	8	-	-
NDX rate (%)	11.7	15.1	11.4	9.2	9.2	12.4	9.4	20.1	15.7	-	-
PPV (%)	78.4	70.0	76.5	70.8	76.7	82.5	84.1	85.0	85.3	-	-
NPV (%)	96.5	98.1	99.0	96.8	96.3	95.3	93.0	91.1	100.0	-	-
Sensitivity (%)	94.0	93.3	97.4	93.3	94.5	92.9	91.8	90.7	100.0	-	-
Specificity (%)	86.3	89.7	89.3	84.0	83.2	88.0	86.3	85.7	64.3	-	-
Diagnostic accuracy (%)	89.0	90.4	91.4	86.7	87.4	89.9	88.7	88.1	88.4	-	-
LR+	6.87	9.02	9.10	5.83	5.63	7.77	6.70	6.35	2.80	-	-
LR-	0.07	0.07	0.03	0.08	0.07	0.08	0.09	0.11	0.00	-	-

Supplementary Table 8 |Empirical data of male patients and their assignment to pretest probability categories

Male patients	Participants	Pretest probability categories									
	Overall	0 to <10%	10 to <20%	20 to < 30%	30 to <40%	40 to <50%	50 to <60%	60 to <70%	70 to <80%	80 to <90%	90 to 100%
N	3473	0	29	211	509	576	507	391	484	698	68
TP	1718	-	6	79	203	269	220	188	288	420	45
TN	1104	-	21	102	230	206	187	122	94	134	8
FP	228	-	1	13	28	48	38	27	33	38	2
FN	87	-	0	3	14	7	9	15	17	21	1
NDX	336	-	1	14	34	46	53	39	52	85	12
NDX rate (%)	9,7	-	3.4	6.6	6.7	8.0	10.5	10.0	10.7	12.2	17.6
PPV (%)	88,3	-	85.7	85.9	87.9	84.9	85.3	87.4	89.7	91.7	95.7
NPV (%)	92,7	-	100.0	97.1	94.3	96.7	95.4	89.1	84.7	86.5	88.9
Sensitivity (%)	95,2	-	100.0	96.3	93.5	97.5	96.1	92.6	94.4	95.2	97.8
Specificity (%)	82,9	-	95.5	88.7	89.1	81.1	83.1	81.9	74.0	77.9	80.0
Diagnostic accuracy (%)	90,0	-	96.4	91.9	91.2	89.6	89.6	88.1	88.4	90.4	94.6
LR+	5,56	-	22.00	8.52	8.62	5.16	5.69	5.11	3.63	4.31	4.89
LR-	0,06	-	0.00	0.04	0.07	0.03	0.05	0.09	0.08	0.06	0.03

Supplementary table 9 | Predictors of non-diagnostic CTA results

Random effects		
Group	Variance	Standard deviation
Study_No (Intercept)	2.632	1.622

Fixed effects				
Group	Estimate	Standard error	Z value	P value
Intercept	-5.066	0.415	-12.242	<0.001
Age >75	-0.009	0.166	-0.055	0.9560
Male	-0.200	0.107	-1.877	0.605
Heart rate	0.028	0.005	5.990	<0.001

Supplementary Table 10 | Patients ≤50 years and their assignment to pretest probability categories

Patients ≤ 50 years	Participants	Pretest probability categories									
	Overall	0 to <10%	10 to <20%	20 to < 30%	30 to <40%	40 to <50%	50 to <60%	60 to <70%	70 to <80%	80 to <90%	90 to 100%
N	817	86	113	185	120	107	3	107	96	0	0
TP	255	14	19	69	26	39	0	40	48	-	-
TN	397	52	71	89	71	49	2	40	23	-	-
FP	51	6	5	12	6	7	1	7	7	-	-
FN	21	1	2	3	1	2	0	6	6	-	-
NDX	93	13	16	12	16	10	0	14	12	-	-
NDX rate (%)	11.4	15.1	14.2	6.5	13.3	9.3	0.0	13.1	12.5	-	-
PPV (%)	83.3	70.0	79.2	85.2	81.3	84.8	0.0	85.1	87.3	-	-
NPV (%)	95.0	98.1	97.3	96.7	98.6	96.1	100.0	87.0	79.3	-	-
Sensitivity (%)	92.4	93.3	90.5	95.8	96.3	95.1	n/a*	87.0	88.9	-	-
Specificity (%)	88.6	89.7	93.4	88.1	92.2	87.5	66.7	85.1	76.7	-	-
Diagnostic accuracy (%)	90.1	90.4	92.8	91.3	93.3	90.7	66.7	86.0	84.5	-	-
LR+	8.12	9.02	13.75	8.07	12.36	7.61	n/a*	5.84	3.81	-	-
LR-	0.09	0.07	0.10	0.05	0.04	0.06	n/a*	0.15	0.14	-	-

* n/a = not applicable (division by 0)

Supplementary Table 11 | Patients >50 to ≤65 years and their assignment to pretest probability categories

Patients >50 to ≤ 65 years	Participants	Pretest probability categories									
	Overall	0 to <10%	10 to <20%	20 to < 30%	30 to <40%	40 to <50%	50 to <60%	60 to <70%	70 to <80%	80 to <90%	90 to 100%
N	2619	0	344	242	432	425	538	0	317	321	0
TP	1100	-	83	50	186	171	215	-	201	194	-
TN	1039	-	201	140	182	172	223	-	54	67	-
FP	173	-	24	21	25	31	36	-	19	17	-
FN	48	-	1	3	14	7	11	-	8	4	-
NDX	259	-	35	28	25	44	53	-	35	39	-
NDX rate (%)	9.9	-	10.2	11.6	5.8	10.4	9.9	-	11.0	12.1	-
PPV (%)	86.4	-	77.6	70.4	88.2	84.7	85.7	-	91.4	91.9	-
NPV (%)	95.6	-	99.5	97.9	92.9	96.1	95.3	-	87.1	94.4	-
Sensitivity (%)	95.8	-	98.8	94.3	93.0	96.1	95.1	-	96.2	98.0	-
Specificity (%)	85.7	-	89.3	87.0	87.9	84.7	86.1	-	74.0	79.8	-
Diagnostic accuracy (%)	90.6	-	91.9	88.8	90.4	90.0	90.3	-	90.4	92.6	-
LR+	6.71	-	9.26	7.23	7.70	6.29	6.84	-	3.70	4.84	-
LR-	0.05	-	0.01	0.07	0.08	0.05	0.06	-	0.05	0.03	-

Supplementary Table 12 | Patients >65 to ≤ 75 years and their assignment to pretest probability categories

Patients >65 to ≤ 75 years	Participants	Pretest probability categories									
	Overall	0 to <10%	10 to <20%	20 to < 30%	30 to <40%	40 to <50%	50 to <60%	60 to <70%	70 to <80%	80 to <90%	90 to 100%
N	1434	0	73	116	133	180	160	434	0	338	0
TP	692	-	18	42	53	98	71	199	-	211	-
TN	451	-	41	48	57	56	56	138	-	55	-
FP	109	-	7	14	13	15	13	28	-	19	-
FN	38	-	0	4	2	2	3	13	-	14	-
NDX	144	-	7	8	8	9	17	56	-	39	-
NDX rate (%)	10.0	-	9.6	6.9	6.0	5.0	10.6	12.9	-	11.5	-
PPV (%)	86.4	-	72.0	75.0	80.3	86.7	84.5	87.7	-	91.7	-
NPV (%)	92.2	-	100.0	92.3	96.6	96.6	94.9	91.4	-	79.7	-
Sensitivity (%)	94.8	-	100.0	91.3	96.4	98.0	95.9	93.9	-	93.8	-
Specificity (%)	80.5	-	85.4	77.4	81.4	78.9	81.2	83.1	-	74.3	-
Diagnostic accuracy (%)	88.6	-	89.4	83.3	88.0	90.1	88.8	89.2	-	89.0	-
LR+	4.87	-	6.86	4.04	5.19	4.64	5.09	5.57	-	3.65	-
LR-	0.06	-	0.00	0.11	0.04	0.03	0.05	0.07	-	0.08	-

Supplementary Table 13 | Patients >75 years and their assignment to pretest probability categories

Patients >75 years	Participants	Pretest probability categories									
	Overall	0 to <10%	10 to <20%	20 to < 30%	30 to <40%	40 to <50%	50 to <60%	60 to <70%	70 to <80%	80 to <90%	90 to 100%
N	462	0	0	58	42	33	51	49	122	39	68
TP	204	-	-	15	7	13	24	17	68	15	45
TN	144	-	-	35	24	10	13	16	26	12	8
FP	42	-	-	6	5	6	5	4	12	2	2
FN	14	-	-	0	1	0	3	3	3	3	1
NDX	58	-	-	2	5	4	6	9	13	7	12
NDX rate (%)	12.6	-	-	3.4	11.9	12.1	11.8	18.4	10.7	17.9	17.6
PPV (%)	82.9	-	-	71.4	58.3	68.4	82.8	81.0	85.0	88.2	95.7
NPV (%)	91.1	-	-	100.0	96.0	100.0	81.3	84.2	89.7	80.0	88.9
Sensitivity (%)	93.6	-	-	100.0	87.5	100.0	88.9	85.0	95.8	83.3	97.8
Specificity (%)	77.4	-	-	85.4	82.8	62.5	72.2	80.0	68.4	85.7	80.0
Diagnostic accuracy (%)	86.1	-	-	89.3	83.8	79.3	82.2	82.5	86.2	84.4	94.6
LR+	4.14	-	-	6.83	5.08	2.67	3.20	4.25	3.03	5.83	4.89
LR-	0.08	-	-	0.00	0.15	0.00	0.15	0.19	0.06	0.19	0.03

Supplementary Table 14 | Patients with typical angina and their assignment to pretest probability categories

Typical angina	Participants	Pretest probability categories									
	Overall	0 to <10%	10 to <20%	20 to < 30%	30 to <40%	40 to <50%	50 to <60%	60 to <70%	70 to <80%	80 to <90%	90 to 100%
N	1967	0	0	4	43	137	247	306	464	698	68
TP	989	-	-	1	9	39	89	108	278	420	45
TN	547	-	-	3	23	72	109	112	86	134	8
FP	116	-	-	0	3	5	18	19	31	38	2
FN	62	-	-	0	1	4	8	13	14	21	1
NDX	253	-	-	0	7	17	23	54	55	85	12
NDX rate (%)	12.9	-	-	0.0	16.3	12.4	9.3	17.6	11.9	12.2	17.6
PPV (%)	89.5	-	-	100.0	75.0	88.6	83.2	85.0	90.0	91.7	95.7
NPV (%)	89.8	-	-	100.0	95.8	94.7	93.2	89.6	86.0	86.5	88.9
Sensitivity (%)	94.1	-	-	100.0	90.0	90.7	91.8	89.3	95.2	95.2	97.8
Specificity (%)	82.5	-	-	100.0	88.5	93.5	85.8	85.5	73.5	77.9	80.0
Diagnostic accuracy (%)	89.6	-	-	100.0	88.9	92.5	88.4	87.3	89.0	90.4	94.6
LR+	5.38	-	-	n/a*	7.80	13.97	6.47	6.15	3.59	4.31	4.89
LR-	0.07	-	-	0.00	0.11	0.10	0.10	0.13	0.07	0.06	0.03

* n/a = not applicable (division by 0)

Supplementary Table 15 | Patients with atypical angina and their assignment to pretest probability categories

Atypical angina	Participants	Pretest probability categories									
	Overall	0 to <10%	10 to <20%	20 to < 30%	30 to <40%	40 to <50%	50 to <60%	60 to <70%	70 to <80%	80 to <90%	90 to 100%
N	1592	1	138	269	235	280	339	260	70	0	0
TP	579	0	23	53	73	110	142	140	38	-	-
TN	691	1	86	150	120	108	136	73	17	-	-
FP	136	0	8	29	19	32	22	19	7	-	-
FN	27	0	2	5	2	4	4	7	3	-	-
NDX	159	0	19	32	21	26	35	21	5	-	-
NDX rate (%)	10.0	0.0	13.8	11.9	8.9	9.3	10.3	8.1	7.1	-	-
PPV (%)	81.0	n/a*	74.2	64.6	79.3	77.5	86.6	88.1	84.4	-	-
NPV (%)	96.2	100.0	97.7	96.8	98.4	96.4	97.1	91.3	85.0	-	-
Sensitivity (%)	95.5	n/a*	92.0	91.4	97.3	96.5	97.3	95.2	92.7	-	-
Specificity (%)	83.6	100.0	91.5	83.8	86.3	77.1	86.1	79.3	70.8	-	-
Diagnostic accuracy (%)	88.6	100.0	91.6	85.7	90.2	85.8	91.4	89.1	84.6	-	-
LR+	5.81	n/a*	10.81	5.64	7.12	4.22	6.99	4.61	3.18	-	-
LR-	0.05	n/a*	0.09	0.10	0.03	0.05	0.03	0.06	0.10	-	-

* n/a = not applicable (division by 0)

Supplementary Table 16 | Patients with non-anginal chest discomfort and their assignment to pretest probability categories

Non-anginal chest discomfort	Participants	Pretest probability categories									
	Overall	**0 to <10%**	**10 to <20%**	**20 to < 30%**	**30 to <40%**	**40 to <50%**	**50 to <60%**	**60 to <70%**	**70 to <80%**	**80 to <90%**	**90 to 100%**
N	796	38	162	157	188	158	80	12	1	0	0
TP	294	6	37	64	72	73	35	6	1	-	-
TN	347	19	87	71	83	58	27	2	0	-	-
FP	55	4	16	11	9	10	4	1	0	-	-
FN	17	1	1	2	9	1	3	0	0	-	-
NDX	83	8	21	9	15	16	11	3	0	-	-
NDX rate (%)	10.4	21.1	13.0	5.7	8.0	10.1	13.8	25.0	0.0	-	-
PPV (%)	84.2	60.0	69.8	85.3	88.9	88.0	89.7	85.7	100.0	-	-
NPV (%)	95.3	95.0	98.9	97.3	90.2	98.3	90.0	100.0	n/a*	-	-
Sensitivity (%)	94.5	85.7	97.4	97.0	88.9	98.6	92.1	100.0	100.0	-	-
Specificity (%)	86.3	82.6	84.5	86.6	90.2	85.3	87.1	66.7	n/a*	-	-
Diagnostic accuracy (%)	89.9	83.3	87.9	91.2	89.6	92.3	89.9	88.9	100.0	-	-
LR+	6.91	4.93	6.27	7.23	9.09	6.71	7.14	3.00	n/a*	-	-
LR-	0.06	0.17	0.03	0.03	0.12	0.02	0.09	0.00	n/a*	-	-

* n/a = not applicable (division by 0

Supplementary Table 17 | Patients with other chest discomfort and their assignment to pretest probability categories

Other chest discomfort	Participants	Pretest probability categories									
	Overall	0 to <10 %	10 to <20 %	20 to < 30%	30 to <40 %	40 to <50 %	50 to <60 %	60 to <70 %	70 to <80 %	80 to <90 %	90 to 100 %
N	977	47	230	171	261	170	86	12	0	0	0
TP	389	8	60	58	118	99	44	2	-	-	-
TN	446	32	140	88	108	49	22	7	-	-	-
FP	68	2	12	13	18	12	11	0	-	-	-
FN	15	0	0	3	6	2	2	2	-	-	-
NDX	59	5	18	9	11	8	7	1	-	-	-
NDX rate (%)	6,0	10,6	7,8	5,3	4,2	4,7	8,1	8,3	-	-	-
PPV (%)	85.1	80.0	83.3	81.7	86.8	89.2	80.0	100.0	-	-	-
NPV (%)	96.7	100.0	100.0	96.7	94.7	96.1	91.7	77.8	-	-	-
Sensitivity (%)	96.3	100.0	100.0	95.1	95.2	98.0	95.7	50.0	-	-	-
Specificity (%)	86.8	94.1	92.1	87.1	85.7	80.3	66.7	100.0	-	-	-
Diagnostic accuracy (%)	91.0	95.2	94.3	90.1	90.4	91.4	83.5	81.8	-	-	-
LR+	7.28	17.00	12.67	7.39	6.66	4.98	2.87	n/a*	-	-	-
LR-	0.04	0.00	0.00	0.06	0.06	0.02	0.07	0.50	-	-	-

* n/a = not applicable (division by 0)

Supplementary table18 | References of included studies in this analysis

1. Alkadhi H, Scheffel H, Desbiolles L, et al. Dual-source computed tomography coronary angiography: influence of obesity, calcium load, and heart rate on diagnostic accuracy. *European heart journal* 2008; **29**(6): 766-76.
2. Alkadhi H, Stolzmann P, Desbiolles L, et al. Low-dose, 128-slice, dual-source CT coronary angiography: accuracy and radiation dose of the high-pitch and the step-and-shoot mode. *Heart* 2010; **96**(12): 933-8.
3. Andreini D, Pontone G, Bartorelli AL, et al. Comparison of the diagnostic performance of 64-slice computed tomography coronary angiography in diabetic and non-diabetic patients with suspected coronary artery disease. *Cardiovascular diabetology* 2010; **9**: 80.
4. Andreini D, Pontone G, Bartorelli AL, et al. Sixty-four-slice multidetector computed tomography: an accurate imaging modality for the evaluation of coronary arteries in dilated cardiomyopathy of unknown etiology. *Circulation Cardiovascular imaging* 2009; **2**(3): 199-205.
5. Andreini D, Pontone G, Pepi M, et al. Diagnostic accuracy of multidetector computed tomography coronary angiography in patients with dilated cardiomyopathy. *Journal of the American College of Cardiology* 2007; **49**(20): 2044-50.
6. Arnoldi E, Ramos-Duran I, Abro JA, et al. [Coronary CT angiography using prospective ECG triggering: high diagnostic accuracy with low radiation dose]. *Der Radiologe* 2010; **50**(6): 500-6.
7. Bettencourt N, Rocha J, Carvalho M, et al. Multislice computed tomography in the exclusion of coronary artery disease in patients with presurgical valve disease. *Circulation Cardiovascular imaging* 2009; **2**(4): 306-13.
8. Bonmassari R, Muraglia S, Centonze M, Coser D, Stoppa G, Disertori M. Noninvasive detection of coronary artery stenosis with 16-slice spiral computed tomography in a population at low to moderate risk for coronary artery disease. *Journal of cardiovascular medicine* 2006; **7**(11): 817-25.
9. Chen CC, Chen CC, Hsieh IC, et al. The effect of calcium score on the diagnostic accuracy of coronary computed tomography angiography. *The international journal of cardiovascular imaging* 2011; **27 Suppl 1**: 37-42.
10. Chow BJ, Dennie C, Hoffmann U, et al. Comparison of computed tomographic angiography versus rubidium-82 positron emission tomography for the detection of patients with anatomical coronary artery disease. *The Canadian journal of cardiology* 2007; **23**(10): 801-7.
11. Dewey M, Teige F, Schnapauff D, et al. Noninvasive detection of coronary artery stenoses with multislice computed tomography or magnetic resonance imaging. *Annals of internal medicine* 2006; **145**(6): 407-15.
12. Dewey M, Zimmermann E, Deissenrieder F, et al. Noninvasive coronary angiography by 320-row computed tomography with lower radiation exposure and maintained diagnostic accuracy: comparison of results with cardiac catheterization in a head-to-head pilot investigation. *Circulation* 2009; **120**(10): 867-75.
13. Diederichsen AC, Petersen H, Jensen LO, et al. Diagnostic value of cardiac 64-slice computed tomography: importance of coronary calcium. *Scandinavian cardiovascular journal : SCJ* 2009; **43**(5): 337-44.
14. Garcia MJ, Lessick J, Hoffmann MH, Investigators CS. Accuracy of 16-row multidetector computed tomography for the assessment of coronary artery stenosis. *Jama* 2006; **296**(4): 403-11.
15. Ghostine S, Caussin C, Daoud B, et al. Non-invasive detection of coronary artery disease in patients with left bundle branch block using 64-slice computed tomography. *Journal of the American College of Cardiology* 2006; **48**(10): 1929-34.
16. Ghostine S, Caussin C, Habis M, et al. Non-invasive diagnosis of ischaemic heart failure using 64-slice computed tomography. *European heart journal* 2008; **29**(17): 2133-40.
17. Gueret P, Deux JF, Bonello L, et al. Diagnostic performance of computed tomography coronary angiography (from the Prospective National Multicenter Multivendor EVASCAN

Study). *The American journal of cardiology* 2013; **111**(4): 471-8.
18. Halon DA, Gaspar T, Adawi S, et al. Uses and limitations of 40 slice multi-detector row spiral computed tomography for diagnosing coronary lesions in unselected patients referred for routine invasive coronary angiography. *Cardiology* 2007; **108**(3): 200-9.
19. Halvorsen BA, Rodevand O, Hagen G, Herud E, Mielczarek W, Molstad P. [Angiography with 64-channel CT upon suspicion of stable coronary disease]. *Tidsskrift for den Norske laegeforening : tidsskrift for praktisk medicin, ny raekke* 2008; **128**(19): 2172-6.
20. Hamdan A, Asbach P, Wellnhofer E, et al. A prospective study for comparison of MR and CT imaging for detection of coronary artery stenosis. *JACC Cardiovascular imaging* 2011; **4**(1): 50-61.
21. Hausleiter J, Meyer T, Hadamitzky M, et al. Non-invasive coronary computed tomographic angiography for patients with suspected coronary artery disease: the Coronary Angiography by Computed Tomography with the Use of a Submillimeter resolution (CACTUS) trial. *European heart journal* 2007; **28**(24): 3034-41.
22. Herzog BA, Husmann L, Burkhard N, et al. Accuracy of low-dose computed tomography coronary angiography using prospective electrocardiogram-triggering: first clinical experience. *European heart journal* 2008; **29**(24): 3037-42.
23. Herzog BA, Wyss CA, Husmann L, et al. First head-to-head comparison of effective radiation dose from low-dose 64-slice CT with prospective ECG-triggering versus invasive coronary angiography. *Heart* 2009; **95**(20): 1656-61.
24. Herzog C, Nguyen SA, Savino G, et al. Does two-segment image reconstruction at 64-section CT coronary angiography improve image quality and diagnostic accuracy? *Radiology* 2007; **244**(1): 121-9.
25. Herzog C, Zwerner PL, Doll JR, et al. Significant coronary artery stenosis: comparison on per-patient and per-vessel or per-segment basis at 64-section CT angiography. *Radiology* 2007; **244**(1): 112-20.
26. Husmann L, Herzog BA, Burger IA, et al. Usefulness of additional coronary calcium scoring in low-dose CT coronary angiography with prospective ECG-triggering impact on total effective radiation dose and diagnostic accuracy. *Academic radiology* 2010; **17**(2): 201-6.
27. Jakamy R, Barthelemy O, Le Feuvre C, et al. Accuracy of multislice computed tomography in the preoperative assessment of coronary disease in patients scheduled for heart valve surgery. *Archives of cardiovascular diseases* 2012; **105**(8-9): 424-31.
28. Jenkins SM, Johnston N, Hawkins NM, et al. Limited clinical utility of CT coronary angiography in a district hospital setting. *QJM : monthly journal of the Association of Physicians* 2011; **104**(1): 49-57.
29. Kajander S, Joutsiniemi E, Saraste M, et al. Cardiac positron emission tomography/computed tomography imaging accurately detects anatomically and functionally significant coronary artery disease. *Circulation* 2010; **122**(6): 603-13.
30. Kefer J, Coche E, Legros G, et al. Head-to-head comparison of three-dimensional navigator-gated magnetic resonance imaging and 16-slice computed tomography to detect coronary artery stenosis in patients. *Journal of the American College of Cardiology* 2005; **46**(1): 92-100.
31. Laissy JP, Messika-Zeitoun D, Serfaty JM, et al. Comprehensive evaluation of preoperative patients with aortic valve stenosis: usefulness of cardiac multidetector computed tomography. *Heart* 2007; **93**(9): 1121-5.
32. Langer C, Peterschroder A, Franzke K, et al. Noninvasive coronary angiography focusing on calcification: multislice computed tomography compared with magnetic resonance imaging. *Journal of computer assisted tomography* 2009; **33**(2): 179-85.
33. Leschka S, Alkadhi H, Plass A, et al. Accuracy of MSCT coronary angiography with 64-slice technology: first experience. *European heart journal* 2005; **26**(15): 1482-7.
34. Leschka S, Scheffel H, Desbiolles L, et al. Combining dual-source computed tomography coronary angiography and calcium scoring: added value for the assessment of coronary artery disease. *Heart* 2008; **94**(9): 1154-61.

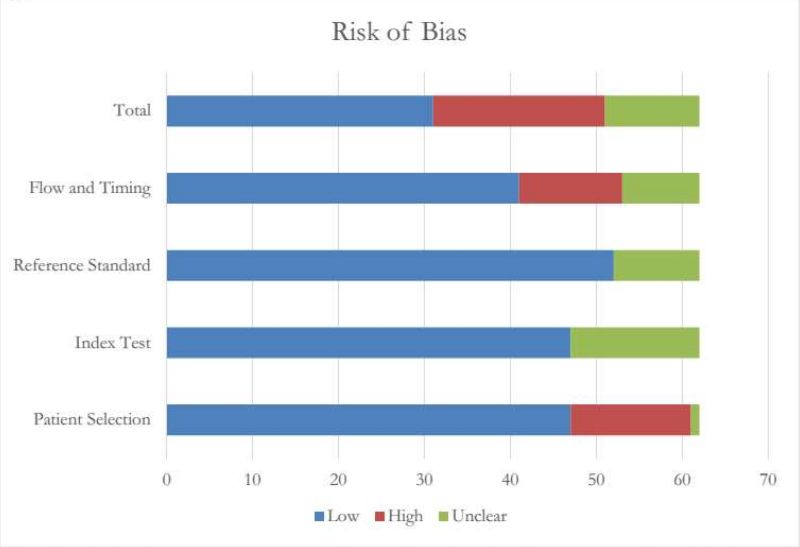
35. Leschka S, Scheffel H, Husmann L, et al. Effect of decrease in heart rate variability on the diagnostic accuracy of 64-MDCT coronary angiography. *AJR American journal of roentgenology* 2008; **190**(6): 1583-90.
36. Martuscelli E, Romagnoli A, D'Eliseo A, et al. Accuracy of thin-slice computed tomography in the detection of coronary stenoses. *European heart journal* 2004; **25**(12): 1043-8.
37. Meijboom WB, Meijs MF, Schuijf JD, et al. Diagnostic accuracy of 64-slice computed tomography coronary angiography: a prospective, multicenter, multivendor study. *Journal of the American College of Cardiology* 2008; **52**(25): 2135-44.
38. Meijboom WB, Mollet NR, Van Mieghem CA, et al. Pre-operative computed tomography coronary angiography to detect significant coronary artery disease in patients referred for cardiac valve surgery. *Journal of the American College of Cardiology* 2006; **48**(8): 1658-65.
39. Meijboom WB, Mollet NR, Van Mieghem CA, et al. 64-Slice CT coronary angiography in patients with non-ST elevation acute coronary syndrome. *Heart* 2007; **93**(11): 1386-92.
40. Meijboom WB, Weustink AC, Pugliese F, et al. Comparison of diagnostic accuracy of 64-slice computed tomography coronary angiography in women versus men with angina pectoris. *American Journal of Cardiology* 2007; **100**(10): 1532-7.
41. Mendoza V, Llerena L, Llerena L, Rodríguez L, Olivares E, Linares R. Ischemic heart disease diagnosed by 64 slice computed tomography coronary angiography. *The Internet Journal of Cardiology* 2009; **7**(1).
42. Mollet NR, Cademartiri F, van Mieghem CA, et al. High-resolution spiral computed tomography coronary angiography in patients referred for diagnostic conventional coronary angiography. *Circulation* 2005; **112**(15): 2318-23.
43. Nikolaou K, Knez A, Rist C, et al. Accuracy of 64-MDCT in the diagnosis of ischemic heart disease. *AJR American journal of roentgenology* 2006; **187**(1): 111-7.
44. Nikolaou K, Rist C, Wintersperger BJ, et al. Clinical value of MDCT in the diagnosis of coronary artery disease in patients with a low pretest likelihood of significant disease. *AJR American journal of roentgenology* 2006; **186**(6): 1659-68.
45. Ovrehus KA, Jensen JK, Mickley HF, et al. Comparison of usefulness of exercise testing versus coronary computed tomographic angiography for evaluation of patients suspected of having coronary artery disease. *The American journal of cardiology* 2010; **105**(6): 773-9.
46. Ovrehus KA, Munkholm H, Bottcher M, Botker HE, Norgaard BL. Coronary computed tomographic angiography in patients suspected of coronary artery disease: impact of observer experience on diagnostic performance and interobserver reproducibility. *Journal of cardiovascular computed tomography* 2010; **4**(3): 186-94.
47. Pontone G, Andreini D, Ballerini G, Nobili E, Pepi M. Diagnostic work-up of unselected patients with suspected coronary artery disease: complementary role of multidetector computed tomography, symptoms and electrocardiogram stress test. *Coronary artery disease* 2007; **18**(4): 265-74.
48. Pontone G, Andreini D, Bartorelli AL, et al. Feasibility and accuracy of a comprehensive multidetector computed tomography acquisition for patients referred for balloon-expandable transcatheter aortic valve implantation. *American heart journal* 2011; **161**(6): 1106-13.
49. Pontone G, Andreini D, Bartorelli AL, et al. Diagnostic accuracy of coronary computed tomography angiography: a comparison between prospective and retrospective electrocardiogram triggering. *Journal of the American College of Cardiology* 2009; **54**(4): 346-55.
50. Pontone G, Andreini D, Quaglia C, Ballerini G, Nobili E, Pepi M. Accuracy of multidetector spiral computed tomography in detecting significant coronary stenosis in patient populations with differing pre-test probabilities of disease. *Clinical radiology* 2007; **62**(10): 978-85.
51. Pouleur AC, le Polain de Waroux JB, Kefer J, et al. Usefulness of 40-slice multidetector row computed tomography to detect coronary disease in patients prior to cardiac valve surgery. *European radiology* 2007; **17**(12): 3199-207.
52. Pouleur AC, le Polain de Waroux JB, Kefer J, Pasquet A, Vanoverschelde JL, Gerber BL. Direct comparison of whole-heart navigator-gated magnetic resonance coronary angiography

and 40- and 64-slice multidetector row computed tomography to detect the coronary artery stenosis in patients scheduled for conventional coronary angiography. *Circulation Cardiovascular imaging* 2008; **1**(2): 114-21.
53. Pugliese F, Mollet NR, Runza G, et al. Diagnostic accuracy of non-invasive 64-slice CT coronary angiography in patients with stable angina pectoris. *European radiology* 2006; **16**(3): 575-82.
54. Rixe J, Rolf A, Conradi G, et al. Detection of relevant coronary artery disease using dual-source computed tomography in a high probability patient series: comparison with invasive angiography. *Circulation journal : official journal of the Japanese Circulation Society* 2009; **73**(2): 316-22.
55. Rochitte CE, George RT, Chen MY, et al. Computed tomography angiography and perfusion to assess coronary artery stenosis causing perfusion defects by single photon emission computed tomography: the CORE320 study. *European heart journal* 2014; **35**(17): 1120-30.
56. Sato A, Nozato T, Hikita H, et al. Incremental value of combining 64-slice computed tomography angiography with stress nuclear myocardial perfusion imaging to improve noninvasive detection of coronary artery disease. *Journal of nuclear cardiology : official publication of the American Society of Nuclear Cardiology* 2010; **17**(1): 19-26.
57. Scheffel H, Alkadhi H, Plass A, et al. Accuracy of dual-source CT coronary angiography: First experience in a high pre-test probability population without heart rate control. *European radiology* 2006; **16**(12): 2739-47.
58. Shabestari AA, Abdi S, Akhlaghpoor S, et al. Diagnostic performance of 64-channel multislice computed tomography in assessment of significant coronary artery disease in symptomatic subjects. *The American journal of cardiology* 2007; **99**(12): 1656-61.
59. Sun K, Han RJ, Cui LF, et al. Feasibility and Diagnostic Accuracy for Assessment of Coronary Artery Stenosis of Prospectively Electrocardiogram-gated High-pitch Spiral Acquisition Mode Dual-source CT Coronary Angiography in Patients with Relatively Higher Heart Rates: in Comparison with Catheter Coronary Angiography. *Chinese medical sciences journal = Chung-kuo i hsueh k'o hsueh tsa chih* 2013; **27**(4): 213-9.
60. Ugolini P, Pressacco J, Lesperance J, et al. Evaluation of coronary atheroma by 64-slice multidetector computed tomography: Comparison with intravascular ultrasound and angiography. *The Canadian journal of cardiology* 2009; **25**(11): 641-7.
61. Watkins MW, Hesse B, Green CE, et al. Detection of coronary artery stenosis using 40-channel computed tomography with multi-segment reconstruction. *The American journal of cardiology* 2007; **99**(2): 175-81.
62. Xu L, Yang L, Fan Z, Yu W, Lv B, Zhang Z. Diagnostic performance of 320-detector CT coronary angiography in patients with atrial fibrillation: preliminary results. *European radiology* 2011; **21**(5): 936-43.
63. Yang L, Zhang Z, Fan Z, et al. 64-MDCT coronary angiography of patients with atrial fibrillation: influence of heart rate on image quality and efficacy in evaluation of coronary artery disease. *AJR American journal of roentgenology* 2009; **193**(3): 795-801.
64. Unpublished study #1.
65. Unpublished study #2.

Supplementary table 19

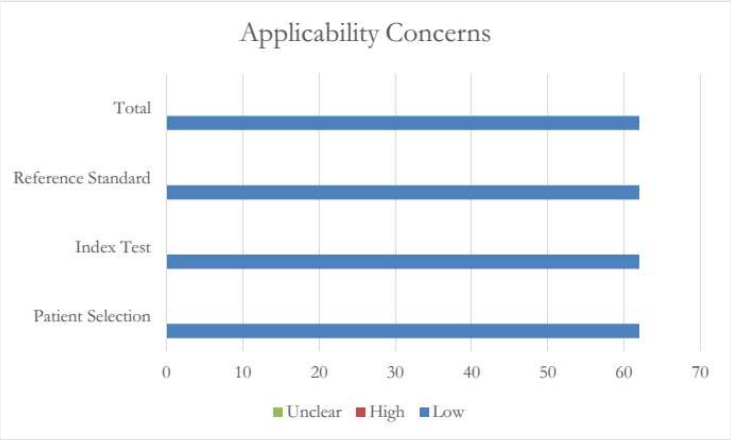
Studies without core labs		Studies with core labs	
Sensitivity (95% CI)	**Specificity (95% CI)**	**Sensitivity (95% CI)**	**Specificity (95% CI)**
95.2 (92.5 to 96.9)	80.8 (76.7 to 84.3)	73.9 (39.4 to 92.5)	61.7 (40.9 to 78.9)

Supplementary figure 1 | Proportion of studies with low, high or unclear risk of bias in QUADAS-2



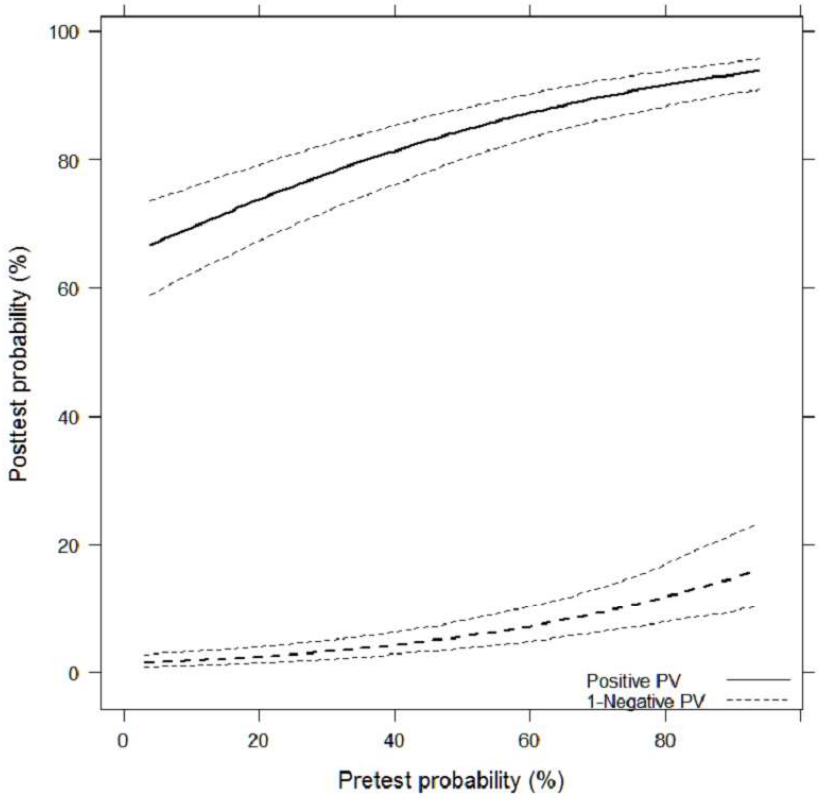
The X-axis displays the proportional rate of studies (in %) bearing a low (blue), high (red) or unclear (green) risk of bias regarding the items displayed on the Y-axis. In general, the risk of bias was low, especially regarding the both diagnostic tests, while it was highest in patient selection.

Supplementary figure 2 | Proportion of studies with low, high or unclear concerns regarding applicability in QUADAS-2



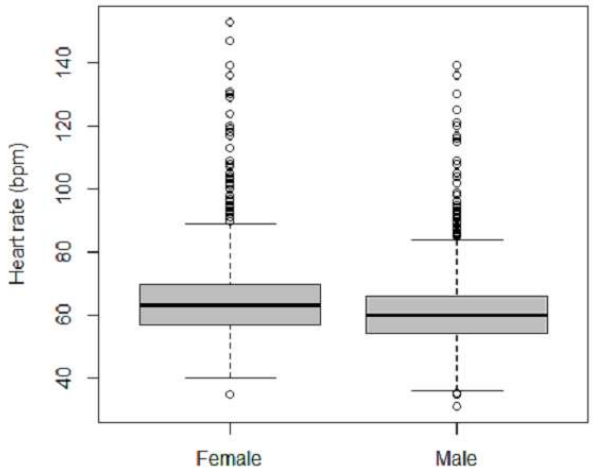
The X-axis displays the proportional rate of studies (in %) bearing a low (blue), high (red) or unclear (green) risk of bias regarding the items displayed on the Y-axis. There are only low concerns regarding the applicability of studies included in the analysis.

Supplementary figure 3| Clinical diagnostic performance of CTA as a function of pretest probability excluding non-diagnostic examinations



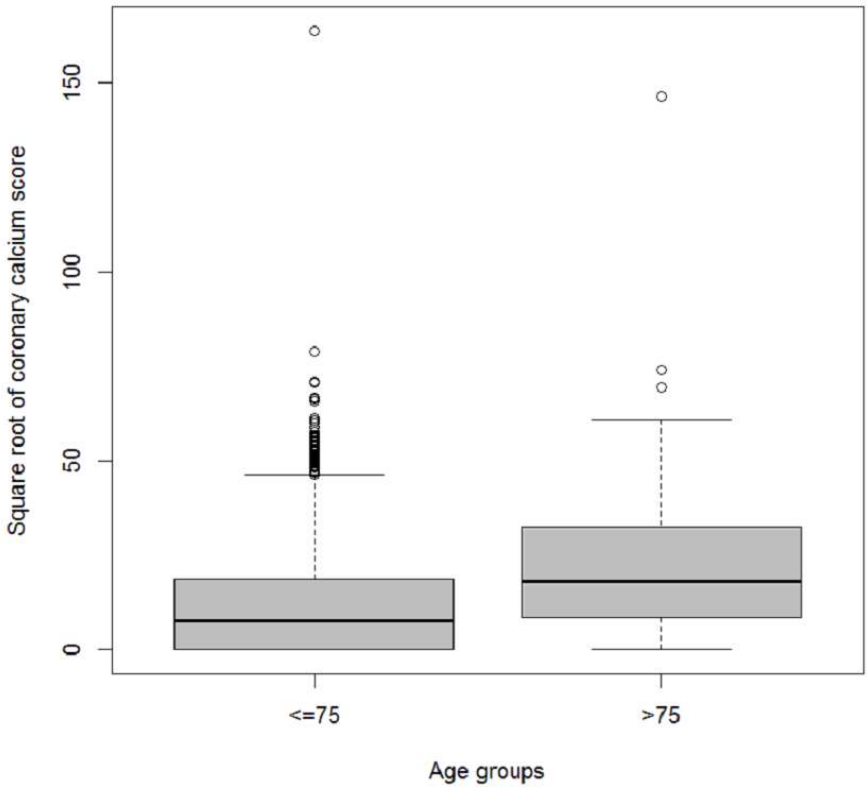
The X-axis represents the predicted clinical pretest probability and the Y-axis shows the positive predictive value (PV) and 1-Negative PV with their 95% CI based on the generalised linear mixed model excluding non-diagnostic CTA examinations. Disease probabilities were predicted by averaging over the random-effects distribution.

Supplementary figure 4 | Heart rate during CTA in female and male patients



Median heart rate was significantly higher in females during CTA (63 beats per minute [bpm], IQR: 57-70) compared with males (60 bpm, IQR: 54-66, MWM test: W = 3504600, p<0.001). Data on heart rate were missing for 62 of 1859 females and 151 of 3473 males.

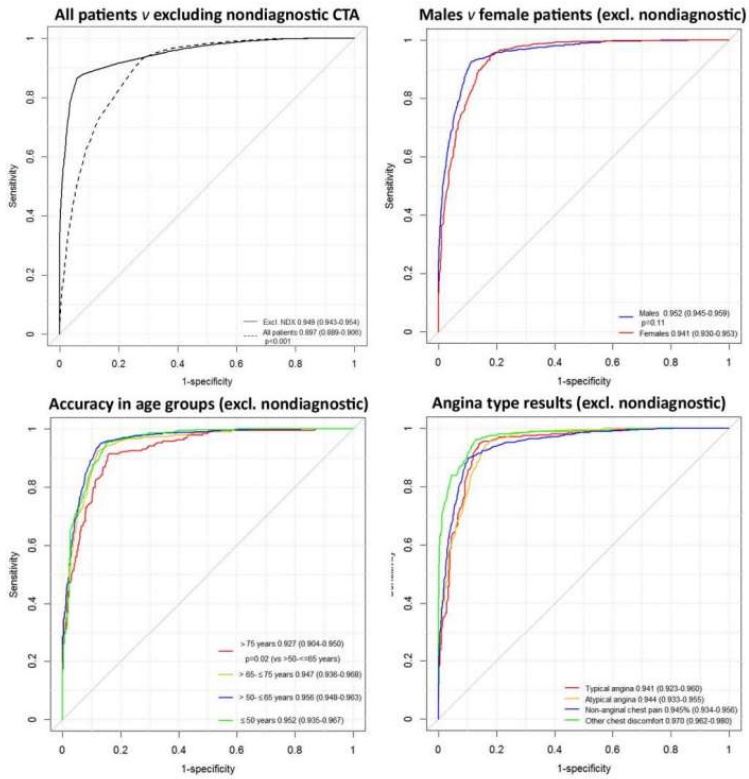
Supplementary figure 5 | Coronary calcium score in patients with up to 75 years of age vs older patients



Median calcium score (square root transformed) was significantly higher in patients above 75 years of age (17.916, IQR: 8.367-32.348) compared with younger patients (7.483, IQR: 0.000-13.74, p<0.001). Data on calcium score were missing for 311 of 552 patients above 75 years of age and 2567 of 4780 younger patients. The boxplot shows square root-transformed data of coronary calcium scores because of skewness of data.

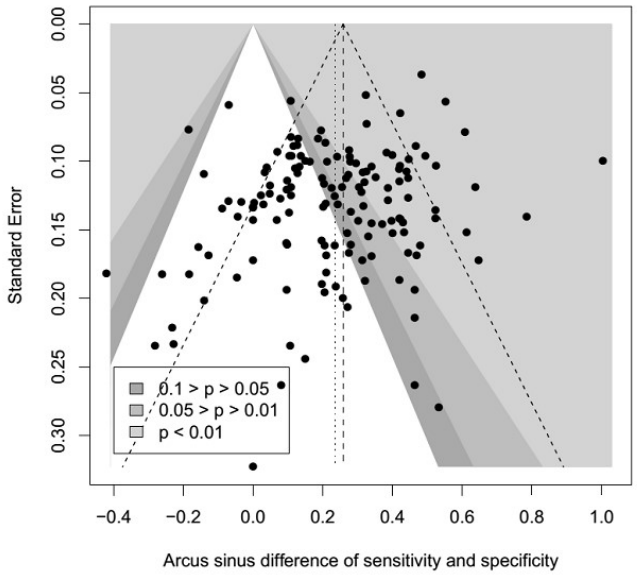
	Square root transformed data						
Groups	Min	1st Qu.	Median	Mean	3rd Qu.	Max	NA's
Age ≤75y	0.000	0.000	7.483	11.928	13.574	163.677	2567
Age >75y	0.000	8.367	17.916	21.916	32.348	146.595	311

Supplementary figure 6 | Receiver operating characteristic curves for CTA by subgroup excluding non-diagnostic CT examinationas



Subgroup comparisons in the three panels are provided for all patients after exclusion of non-diagnostic CT examinations. In the upper left panel diagnostic performance results are shown for all patients in comparison to results obtained after exclusion of non-diagnostic (NDX) test results like also demonstrated in the manuscript. Considering all patients resulted in lower performance, which is a more accurate prediction of the real-world performance to be expected. In contrast to the manuscript subgroup comparisons in the other three panels here are provided for patients after exclusion of non-diagnostic CT examinations: diagnostic performance is now similar in females and males. The other comparisons revealed similar results as when including non-diagnostic CT examinations: CTA's accuracy was lower in patients older than 75, and angina pectoris types were not significantly associated with performance. Like in the manuscript curves were generated using a generalised linear mixed model and predictions based on these models. Computations were performed with the statistical package R and the packages lme4 and pROC. AUC were constructed using the observed data and model-based predictions, which also included the random effects reflecting variability between studies and unobserved influential variables.

Supplementary figure 7 | Publication bias analysis using Funnel plot



This funnel plot shows the arc sinus difference of sensitivity and specificity *vs.* the corresponding standard error. The corresponding statistical test was performed using the method proposed by Rücker with a rank test: Kendal's tau = -661 s.e. = 584.973, z= -1.13, p=0.2585. There was no sign of publication bias.

Supplementary PRISMA item 1 | PICOS

Patients:	Patients with stable chest discomfort and a clinical indication to undergo invasive coronary angiography
Intervention:	Coronary computed tomography angiography
Comparison/Control:	Invasive coronary angiography
Outcomes:	Diagnostic accuracy as defined by positive and negative predictive values as a function of pretest probability and sensitivity and specificity
Setting:	Individual participant meta-analysis of diagnostic accuracy studies comparing coronary computed tomography angiography with invasive coronary as the reference standard.

Supplementary PRISMA items 2 | Search strategy for searching PubMed via Medline

((("tomography, x-ray computed"[MeSH Terms])OR ("computed tomography"[Text Words])OR ("CT"[Text Words])OR ("multidetector"[Text Words])OR ("multi-detector"[Text Words])OR ("multi detector"[Text Words])OR ("MDCT"[Text Words])OR ("multislice"[Text Words])OR ("multi-slice"[Text Words])OR ("MSCT"[Text Words])OR ("dual-source"[Text Words])OR ("dual source"[Text Words]) OR ("DSCT"[Text Words])OR ("multi-row"[Text Words])OR ("multi row"[Text Words]))AND(("coronary angiography"[Mesh Terms])OR ("coronary angiography"[Text Words]))AND(("coronary disease"[Mesh Terms])OR ("coronary artery disease"[Mesh Terms])OR ("coronary stenosis"[Mesh Terms])OR ("coronary disease"[Text Words])OR ("coronary artery disease"[Text Words])OR ("coronary stenosis"[Text Words])OR ("CAD"[Text Words])OR ("coronary heart disease"[Text Words])OR ("CHD"[Text Words]))
Further details have been reported in the study protocol.

Supplementary PRISMA items 3 | Data items and IPD collection file

Data items were predefined and collected using an IPD collection in a Microsoft Excel format that was sent to all corresponding authors of identified eligible diagnostic accuracy studies. Data items consisted of all data necessary to estimate patients' pretest probability (age, gender, angina pectoris classification), 3x2 cross tabulations (test positive, negative or non-diagnostic for both, coronary computed tomography angiography and invasive coronary angiography), details of each CT scan (number of detector rows, heart rate during scan) and patient information on cardiac medical history (stents or bypasses received, risk factors, stress tests performed). Please find the IPD collection file for all collected data items in Appendix C.

Supplementary PRISMA items 4 | Data revision process

Data harmonisation was performed by two independent readers who analysed data and searched for non-plausible data, including range checks, wrong entries, non-logical values and date checks etc. The two readers also recalculated 2x2 and/or 3x2 cross tabulations and compared these with the published data if possible and if available, non-diagnostic examinations were also recorded. After consensus the data management team solved contradictions. If not possible, new Excel files were created for the missing data and again sent to the corresponding author with comments on implausible data and the request to check. For any remaining implausibilities, further reminder mails were sent. Most revisions had to be done on angina type classification (dual or missing entries, rare cases of other classification), missing values for heart rate during CT, 3x2 cross tabulations (due to another definition of non-diagnostic examinations), missing values of CT characteristics, and typing errors.

Web Appendix 3

Die an Koautoren versandte Excel-Datei zur Erhebung der IPD. Zur besseren Lesbarkeit sind im Folgenden Ausschnitte aus der Excel-Datei dargestellt.

	A	B	C	D	E	F
1		Here is the list of your studies with the first author, journal, and year for which we would like to ask you to provide further information about individual patient results. Please use one Excel sheet on Characteristics for each of your studies if there are multiple.			Please provide start and end dates	
2	No.	Author	Journal	Year	Start of Study	End of Study
3	Study Example Please add missing information for your studies on the following lines.	Ropers D	Circulation	2003	14.03.01	15.10.02
4	1					
5	2					
6	3					

Tabellenblatt 1, „List of Your Publications“

	A	B	C	D	E	F	G	H	I	J
1		Please use 0=no; 1=yes if not otherwise indicated								
2	Comments and Explanations			Female=0 Male=1	Typical Angina Pectoris: 1. typical type of pain and 2. getting worse when exercising and 3. getting better during rest and/or nitro.	Atypical Angina Pectoris=2 out of the 3 criteria for Typical Angina	Chest Pain=1 out of the 3 criteria for Typical Angina			Average heart rate during scanning
3	Patient No.	Date of Birth	Date of Inclusion	Gender	Typical Angina Pectoris	Atypical Angina Pectoris	Chest Pain	No Pain	Pain Unknown	Heart Rate During CT (bpm)
4	Patient Example (67 years, male, true positive in CT with atypical angina. Please start your patients on the following line.)	07.03.1945	14.03.2001	1	0	1	0	0	0	55
5	1									
6	2									
7	3									
8	4									
9	5									

Tabellenblatt 2, „Data from Publication 1“, Daten zur Berechnung der PTP.

	A	K	L	M	N	O	P	Q	R	S	T
1											
2	Comments and Explanations		At least one coronary artery with at least one 50% diameter stenosis.	No coronary artery with at least one 50% diameter stenosis.	Nondiagnostic: if no stenosis is seen and at least one vessel is not fully evaluable	Please give reason why a patient was nondiagnostic, e.g., motion artifact, too much calcium etc.		At least one coronary artery with at least one 50% diameter stenosis.	No coronary artery with at least one 50% diameter stenosis.	Nondiagnostic: if no stenosis is seen and at least one vessel is not fully evaluable	Please give reason why a patient was nondiagnostic, e.g., no selective coronary injection possible
3	Patient No.	**CT**	Positive	Negative	Nondiagnostic	Comment on Nondiagnostic	**CATH**	Positive	Negative	Nondiagnostic	Comment on Nondiagnostic
4	Patient Example (67 years, male, true positive in CT with atypical angina. Please start your patients on the following line.)		1	0	0			1	0	0	
5	1										
6	2										
7	3										

Tabellenblatt 2, „Data from Publication 1“, Ergebnisse der CT und Herzkatheteruntersuchungen.

	A	U	V	W	X	Y	Z	AA	AB	AC	AD	AE	AF	AG	AH	AI	AJ	AK	AL	AM	AN
1																					
2	Comments and Explanations	The following information is nice to have, and everyone contributing will be an author on the resulting ancillary study but this is not a must for the primary analysis. Please provide the available information.	Please provide DLP or mSv																		
3	Patient No.	**Additional CT Characteristics**	DLP (mGy*cm)	mSv	Retrospective (=0) or Prospective (=1) Scanning	Number of Detector Rows Used	Oral Beta Blockade as Part of the CT Protocol	Type of Oral Beta Blocker	Dose of Oral Beta Blocker (mg)	IV Beta Blockade	Type of IV Beta Blocker	Dose of IV Beta Blocker (mg)	Sublingual Nitroglyerin	Dose of Sublingual Nitroglyerin (mg)	Contrast Agent Amount (ml)	Type of Contrast Agent	Contrast Agent Flow (ml/s)	Contrast Agent Concentration (Iodine mg/ml)	Breathhold Duration (s)	CAC score (Agatston)	CAC score (Volume)
4	Patient Example (67 years, male, true positive in CT with atypical angina. Please start your patients on the following			5	0	12	1	Atenolol	150	1	Esmolol	200	1	1,2	80	Iodixanol	5	320	8	365	Not available
5	1																				
6	2																				
7	3																				

Tabellenblatt 2, „Data from Publication 1“, zusätzliche CT-Daten.

	A	AO	AP	AQ
1				
2	Comments and Explanations	The following information is nice to have, and everyone contributing will be an author on the resulting ancillary study but this is not a must for the primary analysis. Please provide the available information.	0=CATH afterwards; 1=CATH before CT	
3	Patient No.	**Additional CATH Characteristics**	CATH after or before CT?	Days between CT and CATH
4	Example (67 years, male, true positive in CT with atypical angina. Please start your patients on the following line.)		0	1
5	1			
6	2			
7	3			

Tabellenblatt 2, „Data from Publication 1“, zeitlicher Bezug zwischen CT und Herzkatheter.

	A	AR	AS	AT	AU	AV	AW	AX	AY	AZ	BA	BB	BC	BD	BE
1															
2	Comments and Explanations	The following information is nice to have, and everyone contributing will be an author on the resulting ancillary study but this is not a must for the primary analysis. Please provide the available information.				yes=1 if rest angina (>20 min) within the last week, severe new-onset angina (at least CCS III that started in the last 2 months), or increasing angina (increased by at least 1 CCS class to CCS III in the last 2 months).			Defined as blood pressure consistently exceeding 140 mmHg (systolic) and/or 90 mmHg (diastolic) (≥grade 1) or use of anti hypertension medication.	Defined as having a fasting plasma glucose level of ≥126 mg/dL or being currently treated with either diet intervention, oral glucose-lowering agent or insulin.	Defined as having high total cholesterol (≥200 mg/dL) or treatment with lipid-lowering drugs.			Defined as presence of CAD in a first-degree female (<65 years) or male (<55 years) relative.	
3	Patient No.	**Additional Patient Characteristics**	Weight (kg)	Height (cm)	BMI	Unstable Angina	Coronary Stents Present	Coronary Bypasses Present	Hypertension	Diabetes	Hyperlipidemia	Current Smoker	Former Smoker	Positive Family History	Prior Myocardial Infarction
4	Example (67 years, male, true positive in CT with atypical angina. Please start your patients on the following line.)		85	174	28	0	0	0	1	0	1	0	1	1	1
5	1				#DIV/0!										
6	2				#DIV/0!										
7	3				#DIV/0!										

Tabellenblatt 2, „Data from Publication 1“, zusätzliche Patientendaten.

	A	BF	BG	BH	BI	BJ	BK	BL	BM	BN	BO	BP	BQ	BR
1														
2	Comments and Explanations	The following information is nice to have, and everyone contributing will be an author on the resulting ancillary study but this is not a must for the primary analysis. Please provide the available information.												
3	Patient No.	**Additional Tests Characteristics**	Rest ECG Done	Rest ECG: ST Changes	Rest ECG: Q waves		Stress ECG Done	Stress ECG: Significant ST Changes		Stress Echo Done	Stress Echo: Significant Signs of Ischemia		Stress SPECT Done	Stress SPECT: Significant Signs of Ischemia
4	Example (67 years, male, true positive in CT with atypical angina. Please start your patients on the following line.)		1	1	1		1	1		0	0		0	0
5	1													
6	2													
7	3													

Tabellenblatt 2, „Data from Publication 1“, Daten zu funktionellen kardiologischen Testergebnissen.

Lebenslauf

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

Publikationsliste

Haase R, Dodd JD, Kauczor HU, Kazerooni EA, Dewey M.
Developing a lung nodule management protocol specifically for cardiac CT: Methodology in the DISCHARGE trial.
Eur J Radiol Open 2020 Jun 25; 7:100235. doi: 10.1016/j.ejro.2020.100235.
Impact factor noch nicht vorhanden

Haase R, Schlattmann P, Gueret P, Andreini D, Pontone G, Alkadhi H, Hausleiter J, Garcia MJ, Leschka S, Meijboom WB, Zimmermann E, Gerber B, Schoepf UJ, Shabestari AA, Norgaard BL, Meijs MFL, Sato A, Ovrehus KA, Diederichsen ACP, Jenkins SMM, Knuuti J, Hamdan A, Halvorsen BA, Mendoza-Rodriguez V, Rochitte CE, Rixe J, Wan YL, Langer C, Bettencourt N, Martuscelli E, Ghostine S, Buechel RR, Nikolaou K, Mickley H, Yang L, Zhang Z, Chen MY, Halon DA, Rief M, Sun K, Hirt-Moch B, Niinuma H, Marcus RP, Muraglia S, Jakamy R, Chow BJ, Kaufmann PA, Tardif JC, Nomura C, Kofoed KF, Laissy JP, Arbab-Zadeh A, Kitagawa K, Laham R, Jinzaki M, Hoe J, Rybicki FJ, Scholte A, Paul N, Tan SY, Yoshioka K, Rohle R, Schuetz GM, Schueler S, Coenen MH, Wieske V, Achenbach S, Budoff MJ, Laule M, Newby DE, Dewey M, Consortium C-C.
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:l1945, doi: 10.1136/bmj.l1945.
Impact factor (2019): 30.223

Roehle R, Wieske V, Schuetz GM, Gueret P, Andreini D, Meijboom WB, Pontone G, Garcia M, Alkadhi H, Honoris L, Hausleiter J, Bettencourt N, Zimmermann E, Leschka S, Gerber B, Rochitte C, Schoepf UJ, Shabestari AA, Nørgaard B, Sato A, Knuuti J, Meijs MFL, Brodoefel H, Jenkins SMM, Øvrehus KA, Diederichsen ACP, Hamdan A, Halvorsen BA, Mendoza Rodriguez V, Wan YL, Rixe J, Sheikh M, Langer C, Ghostine S, Martuscelli E, Niinuma H, Scholte A, Nikolaou K, Ulimoen G, Zhang Z, Mickley H, Nieman K, Kaufmann PA, Buechel RR, Herzog BA, Clouse M, Halon DA, Leipsic J, Bush D, Jakamy R, Sun K, Yang L, Johnson T, Laissy JP, Marcus R, Muraglia S, Tardif JC, Chow B, Paul N, Maintz D, Hoe J, de Roos A, **Haase R**, Laule M, Schlattmann P, Dewey M.
Applicability and accuracy of pretest probability calculations implemented in the NICE clinical guideline for decision making about imaging in patients with chest pain of recent onset.
Eur Radiol. 2018 Sep;28(9):4006-4017. doi: 10.1007/s00330-018-5322-5. Epub 2018 Mar 19.
Erratum in: Eur Radiol. 2018 Jun 1; PMID: 29556770
Impact factor (2018): 3.962

Napp AE, **Haase R**, Laule M, Schuetz GM, Rief M, Dreger H, Feuchtner G, Friedrich G, Špaček M, Suchánek V, Fuglsang Kofoed K, Engstroem T, Schroeder S, Drosch T, Gutberlet M, Woinke M, Maurovich-Horvat P, Merkely B, Donnelly P, Ball P, Dodd JD, Quinn M, Saba L, Porcu M, Francone M, Mancone M, Erglis A, Zvaigzne L, Jankauskas A, Sakalyte G, Harań T, Ilnicka-Suckiel M, Bettencourt N, Gama-Ribeiro V, Condrea S, Benedek I, Čemerlić Adjić N, Adjić O, Rodriguez-Palomares J, Garcia Del Blanco B, Roditi G, Berry C, Davis G, Thwaite E, Knuuti J, Pietilä M, Kępka C, Kruk M, Vidakovic R, Neskovic AN, Díez I, Lecumberri I, Geleijns J, Kubiak C, Strenge-Hesse A, Do TH, Frömel F, Gutiérrez-Ibarluzea I, Benguria-Arrate G, Keiding H, Katzer C, Müller-Nordhorn J, Rieckmann N, Walther M, Schlattmann P, Dewey M; DISCHARGE Trial Group.
Computed tomography versus invasive coronary angiography: design and methods of the pragmatic randomised multicentre DISCHARGE trial.
Eur Radiol. 2017 Jul;27(7):2957-2968. doi: 10.1007/s00330-016-4620-z. Epub 2016 Nov 18. PMID: 27864607
Impact factor (2017): 4.027

Filip T, Schrother F, **Haase R**, Rudolph N, Claus T, Albes JM.
Patient Satisfaction and Clinical Complications after Endoscopic or Surgical Saphenous Vein Harvesting.
Thorac Cardiovasc Surg 2019 Apr 4. doi: 10.1055/s-0039-1683901. PMID: 30947354
Impact factor (2019): 1.209

Hartrumpf M, Kuehnel RU, Schroeter F, **Haase R**, Laux ML, Ostovar R, Albes JM.
Clinical Short-Term Outcome and Hemodynamic Comparison of Six Contemporary Bovine Aortic Valve Prostheses.
Thorac Cardiovasc Surg. 2019 Jan 22. doi: 10.1055/s-0038-1676853. PMID: 30669172
Impact factor (2019): 1.209

Ostovar R, Kuehnel RU, Erb M, Hartrumpf M, Claus T, **Haase R**, Albes JM.
How Do Transcatheter Heart Valves Fit in Mitral Annuloplasty Rings and Which Combination Can be Recommended?
Thorac Cardiovasc Surg. 2019 67(4):257-265. doi: 10.1055/s-0038-1645867. Epub 2018 May 8. PMID: 29739020
Impact factor (2019): 1.209

Danksagung

Ich danke Prof. Dewey für die lehrreichen Jahre und die Unterstützung nicht nur bei der Durchführung dieser Arbeit. Mein Dank gilt auch Prof. Schlattmann für den konstruktiven und herzlichen Austausch. Ich danke Herrn Dr. Márcio Sommer Bittencourt für den Vorschlag zur Verwendung des Modells nach Hunink et al. Steffen, Daniel, Sascha, Simon und Denise; danke, dass ihr die arbeitsame Zeit mit Leben gefüllt habt. Ich danke auch meiner Familie, Mama, Papa, Bine, Gunnar, Felix, Marina, Roman, Claudi, Jan und Flauschi, für die Geduld und die irgendwann ausbleibenden Fragen, wie lange es noch dauern wird. Denny, Daniel, Robert, Martin, danke für die Zeit von damals bis heute mit allem was dazu gehört. Achim, hier ist keine Musik drin, aber danke genau für diese ganzen Abende, in denen um Reisen, Musik und das Leben ging. Armando, gracias por todas las cosas que hemos bebido, fumado, bailado y hecho en Berlín y Múnich. Espero que nos vemos en cualquier lugar pronto. Mein größter Dank gilt Jessi und Fidel für ihren Rückhalt und die immerwährende Unterstützung. Ohne euch wäre meine Prätestwahrscheinlichkeit für das Vorliegen einer Promotionsverschleppung 100%.