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Research paper

Diagnostic performance of CCTA and CTP imaging for clinically suspected in-stent restenosis: A meta-analysis

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ABSTRACT

Aims: The objective of this study is to conduct a meta-analysis to assess the diagnostic performance of Coronary Computed Tomography Angiography (CCTA) and a hybrid approach that incorporates Computed Tomography Perfusion (CTP) in addition to CCTA (CCTA + CTP) for the detection of in-stent restenosis (ISR), as defined by angiography.

Methods: A comprehensive search of articles identified 18,513 studies. After removing duplicates, title/abstract screening, and full-text review, 17 CCTA and 3 CCTA + CTP studies were included. Only studies using ≥64-slices multidetector computed tomography (CT) were considered eligible.

Results: The per-patient ISR prevalence was 43 %, with 92 % of stents fully interpretable with CCTA. Meta-analysis exhibited a per-stent CCTA (n = 2674) sensitivity of 90 % (95 % CI; 84–94 %), specificity of 89 % (95 % CI; 86–92 %), positive likelihood ratio of 7.17 (95 % CI; 5.24–9.61), negative likelihood ratio of 0.17 (95 % CI; 0.10–0.25), and diagnostic odds ratio of 45.7 (95 % CI; 22.71–82.43). Additional sensitivity analyses revealed no influence of stent diameter or strut thickness on the diagnostic yield of CCTA. The per-stent diagnostic performance of CCTA + CTP (n = 752) did not show differences compared to CCTA.

Conclusions: With currently utilized scanners, CCTA and CCTA + CTP demonstrated high diagnostic performance for in-stent restenosis evaluation. Consequently, a history of previous stent implantation should not be an argument to preclude using these methods in clinically suspected patients.

1. Introduction

Percutaneous coronary intervention (PCI) using stents is the most common revascularization strategy worldwide, with over 3 million procedures performed annually.[1] One of the most frequent complications of modern PCI is in-stent restenosis (ISR).[2,3] This complication is traditionally defined by invasive coronary angiography (ICA) as a reduction in the luminal diameter ≥50 %, within or adjacent (5 mm proximal or

Abbreviations: PCI, percutaneous coronary intervention; ISR, in-stent restenosis; ICA, invasive coronary angiography; CCTA, coronary computed tomography angiography; CAD, coronary artery disease; CTP, computed tomography perfusion; CT, computed tomography; sROC, summary receiver operating characteristic; AUC, area under the curve.

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distal) to previous stented segments.[4] Although improvements in stent technology has decreased the incidence of ISR compared to the previous bare-metal stent era, the clinical burden of ISR is still high, accounting for approximately 5 % of all the PCI procedures performed in Europe.[5,6]

Coronary computed tomography angiography (CCTA) is a validated, non-invasive modality to evaluate patients with suspected coronary artery disease (CAD).[7–9] Nevertheless, its role in stent visualization remains a topic of debate.[10] This controversy emerges from the assumption that stent-related artifacts combined with a high atherosclerotic burden in segments without stents, hampers the diagnostic accuracy of CCTA. To overcome these limitations, it has been proposed that hybrid imaging, which integrates myocardial computed tomography perfusion (CTP) with the anatomical data provided by CCTA (CCTA + CTP), could enhance the diagnostic performance of the test. Hitherto, there is a paucity of large size studies evaluating the diagnostic yield of the hybrid CCTA + CTP strategy in the detection of ISR. Additionally, while the performance of CCTA to detect ISR has been the subject of numerous studies, many of these include routine follow-up CCTA scans in asymptomatic patients who have previously undergone PCI.[11,12] It is plausible to hypothesize that patients with clinically suspected ISR may exhibit a higher prevalence of disease and potentially a more complex spectrum of CAD than those undergoing routine follow-up CCTA. In this context, using CCTA or hybrid CCTA + CTP could be challenging, and there is limited information on how these imaging modalities perform in this high-risk clinical cohort. To address this knowledge gap, we conducted a meta-analysis to assess the diagnostic value of CCTA and hybrid CCTA + CTP in patients with clinically suspected ISR.

2. Methods

A systematic search was conducted in Pubmed, Embase, Web of Science, and the Cochrane library for studies from 2005 until June 2024. Articles published from 2005 onwards were considered eligible for inclusion to restrict the search to contemporary computed tomography (CT, ≥64-slice multidetector CT) hardware. Furthermore, the search was limited to studies published in English. The primary search was undertaken as part of a more extensive meta-analysis evaluating the diagnostic accuracy of cardiac imaging techniques in patients with a history of CAD (PROSPERO CRD42022322348). The complete search syntax is detailed in the Supplementary Material, Table S1. A manual reference check was performed to identify potential missed studies by our search strategy. If duplicated or overlapping studies were found, only the study with the largest cohort was included in the current analysis. Results of this meta-analysis were reported following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.[13]

2.1. Study eligibility

From the initial search, we screened titles and abstracts of studies that investigated the diagnostic utility of different non-invasive methods in patients with previous CAD. Subsequently, we performed a comprehensive full-text review of these studies. The final inclusion criteria encompassed the following: 1) Study population with clinically suspected ISR. 2) CCTA, hybrid CCTA + CTP, or both as index test. 3) ICA served as the reference standard. 4) Per-stent, per-patient or both ISR outcome. 5) Sufficient information was provided to construct a 2x2 contingency table. 6) ≥ 64-slice multidetector CT. Two independent reviewers (J.D. and R.J.) conducted the title and abstract screening and the full-text review. In case of disagreement between the two reviewers, a third experienced reviewer (I.D.) was consulted to achieve consensus.

2.2. Data collection

Data was collected by two reviewers (J.D. and R.J). Information regarding the study population, index test and reference standard was extracted. In studies which reported the diagnostic performance of CCTA and hybrid CCTA + CTP, both tests were included. If both only-interpretable and intention-to-diagnose (uninterpretable images censored as positive) analyses were reported, the intention-to-diagnose approach was extracted for the main analysis. Two by two contingency tables including true positive (TP), false positive (FP), true negative (TN) and false negative (FN) were derived from the published data. Furthermore, detailed information was collected when the studies reported the diagnostic performance stratified by CT hardware (64-slices vs. >64-slices multidetector CT), stent diameter, and strut thickness. The risk of bias and applicability was graded by two independent reviewers (J.D. and R.J.) according to the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2).[14] Discrepancies were resolved by consensus.

2.3. Statistical analysis

Agreement between reviewers was measured using the Cohen Kappa (κ) statistic. κ values are interpreted as: <0.40 (poor to fair), 0.41–0.80 (moderate to substantial), and >0.81 (almost perfect), accounting for chance agreement. The intention was to conduct per-patient and per-stent analyses for CCTA and CCTA + CTP. A random-effects model incorporating a logit transformation was used to meta-analyze the prevalence of ISR and the rate of interpretable images by CCTA. A Bayesian bivariate meta-analysis was used to pool the sensitivity and specificity of the studies. NLR and PRL were meta-analyzed according to Reitsma's approach for a bivariate model.[15,16] Pooled measures for sensitivity, specificity, positive negative likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR) along with 95 % confidence interval (CI) were reported. Forest plots were displayed to illustrate sensitivity and specificity. Summary receiver operating characteristic (sROC) curves for both modalities were constructed, with each point in the graph corresponding to an individual study. The area under curve (AUC) was used to compare the discriminative performance of the both tests. Additionally, a sensitivity analysis was performed for CCTA to assess the influence of CT hardware (64-slices vs. >64-slices multidetector CT), stent diameter and strut thickness on the diagnostic performance. Moreover, we evaluated the diagnostic performance of CCTA and CCTA + CTP in studies that compared these methods directly. The confidence intervals of the meta-analyzed diagnostic metrics for CCTA and CCTA + CTP, were employed to determine the presence of significant differences in the diagnostic yield between the two methods. Risk of publication bias was assessed with funnel plots and asymmetry was tested with the Eggers test.[17] A two-sided P value < 0.05 was considered indicative of statistical significance. All the statistical evaluations were conducted using RStudio software version 4.0.3 (R Foundation, Vienna, Austria) and SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

The systematic search yielded 18,513 studies. After removal of duplicates, initial screening based on title and abstract, and manual addition of relevant articles not included in the initial search, a total of 743 studied were selected for full-text review. Finally, 17 CCTA and 3 CCTA + CTP studies met the inclusion criteria (Fig. 1). A detailed overview of the included studies are depicted in Table 1. Six CCTA studies compromising 440 patients provided sufficient information for a per-patient analysis.[18–23] Only two studies reported the per-patient performance of CCTA + CTP for detecting ISR, precluding a pooled analysis.[23,24] A total of 17 CCTA studies including 2674 stents and 3 hybrid CCTA + CTP including 752 stents were used for the per-stent level analysis.[18–34] All the studies encompassed the occurrence of ISR as outcome. New lesions in non-stented areas were not included as an outcome. For the definition of ISR, all the studies used ICA with a diameter stenosis (DS) of ≥50 % as the reference standard (Table 1). The quality assessment of the included studies was summarized using the QUADAS-2 tool (Supplementary Material, Fig. S1). Almost perfect agreement between reviewers was observed ($k = 0.82$; $p < 0.01$) in the quality evaluation. A detailed

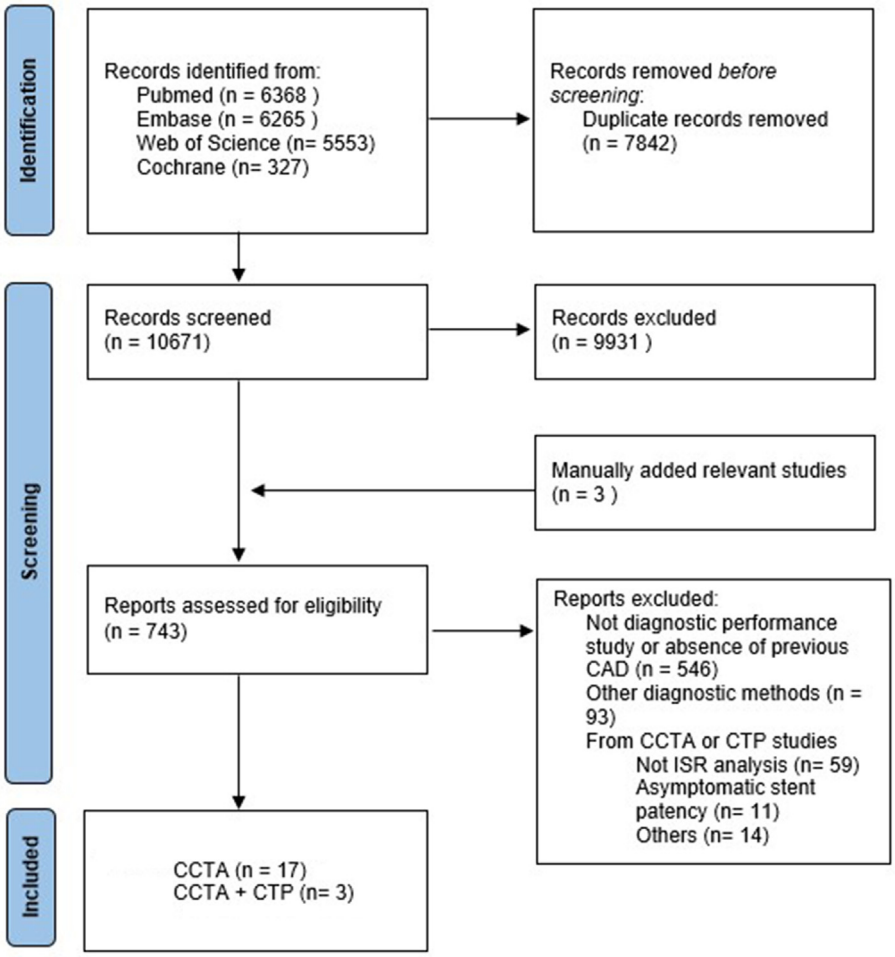

Fig. 1. Identification of studies via databases and registers.
The process of literature search and selection is described through this study flow chart.
CAD, coronary artery disease; ISR, in-stent restenosis; CCTA, coronary computed tomography angiography; CTP, computed tomography perfusion.

assessment of the items from the QUADAS-2 tool and the specific per-study grading are reported in Supplementary Materials, Fig. S2 and Table S2, respectively. The pooled prevalence of ISR at the per-patient level was 43 % (95 % CI: 23–66 %) as depicted in Fig. 2. In the per-stent analysis, the prevalence was 23 % (95 % CI: 16–32 %). The rate of stent interpretability using CCTA was 92 % (95 % CI: 87–95; see Fig. 3).

3.1. Diagnostic performance

Table 2 shows the performance of CCTA and hybrid CCTA + CTP for the diagnosis of ISR. At a per-patient level (n = 440) CCTA showed a pooled sensitivity, specificity, PLR, NLR and DOR of 93 % (95 % CI; 85–98 %), 80 % (95 % CI; 69–89 %), 4.35 (95 % CI; 2.41–7.69), 0.15 (95 % CI; 0.05–0.33) and 38.5 (95 % CI; 9.34–107.84), respectively (Supplementary Material, Fig. S3). The per-stent analysis of CCTA (n = 2674) showed a sensitivity of 90 % (95 % CI; 84–94 %), a specificity of 89 % (95 % CI; 86–92 %), a PLR of 7.17 (95 % CI; 5.24–9.61), a NLR of 0.17 (95 % CI; 0.10–0.25) and DOR of 45.7 (95 % CI; 22.71–82.43). Hybrid CCTA + CTP (n = 752) showed a per-stent sensitivity of 88 % (95 % CI; 80–94 %), specificity of 88 % (95 % CI; 84–93 %), a PLR of 7.23 (95 % CI; 5.34–9.64), a NLR 0.15 (95 % CI; 0.07–0.27) and a DOR of 53.59 (95 % CI; 24.69–102.08). Forest plots illustrating the sensitivity and specificity of the two diagnostic methods at a per-stent level are shown in Supplementary Material, Figs. S4–S5. The per-patient sROC AUC of CCTA to detect ISR was 0.97 (95 % CI; 0.95–0.99). At a per-stent level the sROC AUCs of CCTA and the hybrid CCTA + CTP are 0.96 (95 % CI; 0.94–0.97) and 0.96 (95 % CI; 0.89–1.00) respectively as shown in Fig. 4. In a sensitivity analysis evaluating the performance of CCTA at a per-stent level (Table 3), the number of CT slices (64 slices vs. > 64 slices) did not impact the diagnostic performance of the test. Similarly, stent diameter (<3 mm vs. ≥ 3 mm), and stent strut thickness (≥100 μm vs. < 100 μm) did not influence CCTA diagnostic yield. Furthermore, when focusing on the three studies (n = 752 stents) that directly compared CCTA and CCTA + CTP for ISR, we observed that, on a per-stent level, the performance of CCTA + CTP was numerically superior, but with an overlap in the confidence intervals (Table 4). Visual analysis of the funnel plots for per-stent and per-patient prevalence of ISR indicated no evidence of publication bias, as corroborated by the absence of asymmetry in the Egger's test (p = 0.26 for both analyses; see Supplementary Material, Fig. S6).

4. Discussion

The main findings of this meta-analysis can be described as follows: 1) Among patients clinically suspected of having ISR, the prevalence of ISR was 43 %. 2) CCTA and hybrid CCTA + CTP demonstrated a similar diagnostic performance for detecting ISR at a per-stent level (Graphical Abstract). For CCTA, the pooled sensitivity and specificity were 90 % (95 % CI: 84–94 %) and 89 % (95 % CI: 86–92 %), respectively. The hybrid

Table 1
General overview of CCTA and CCTA + CTP studies included.

CCTA studies											
First author	Year	Country of origin	Index test ISR diagnostic criteria (CCTA)	Gold standard ISR diagnostic criteria (ICA)	Mean Age	Sex (Men %)	Mean HR (SD)	Mean stent diameter (SD)	Month between PCI and scan	Days between scan and ICA	Scanner slices
Cademartiri[25]	2007	Italy	DS ≥ 50 %	DS ≥ 50 %	58	84	60 (8)	3.1 (0.4)	6	9	64
Das[26]	2007	Qatar	DS ≥ 50 %	DS ≥ 50 %	54	85	NR	2.7 (0.2)	25	28	64
Manghat[27]	2008	England	DS ≥ 50 %	DS ≥ 50 %	64	90	63 (11)	3.2 (0.7)	20	NR	64
Oncel[18]	2008	Turkey	DS ≥ 50 %	DS ≥ 50 %	65	71	74 (12)	3.3 (0.4)	37	1	2 × 32
Pugliese[28]	2008	Netherlands	DS ≥ 50 %	DS ≥ 50 %	62	78	67 (12)	3.2 (0.6)	35	NR	2 × 32
Andreini[19]	2009	Italy	DS ≥ 50 %	DS ≥ 50 %	64	88	58 (9)	3.1 (0.6)	7	4	64
Pflederer[20]	2009	Germany	DS ≥ 50 %	DS ≥ 50 %	65	63	60 (9)	3.3 (0.3)	16	NR	2 × 64
Wykrzykowska[29]	2010	USA	DS ≥ 50 %	DS ≥ 50 %	*61*	89	59 (7)	3.6 (0.5)	47	30	64
Andreini[30]	2011	Italy	DS ≥ 50 %	DS ≥ 50 %	63	90	57 (8)	3.1 (0.6)	6	4	64
Magalhães[31]	2011	Brazil	DS ≥ 50 %	DS ≥ 50 %	57	61	NR	NR	NR	NR	64
Eisentopf[21]	2013	Germany	DS ≥ 50 %	DS ≥ 50 %	63	82	60 (6)	3 (0.4)	NR	NR	2 × 128
Pan[22]	2013	China	DS ≥ 50 %	DS ≥ 50 %	68	67	NR	3.2 (0.3)	NR	4	64
Rief[23]	2013	Germany	DS ≥ 50 %	DS ≥ 50 %	64	80	53 (7)	3 (0.5)	41	1	320
Yoshimura[32]	2015	Japan	DS ≥ 50 %	DS ≥ 50 %	65	82	64 (14)	3 (0.8)	34	19	64
Li[33]	2018	China	DS ≥ 50 %	DS ≥ 50 %	69	93	66 (5)	2.9 (0.3)	NR	10	2 × 192
Andreini[34]	2019	Italy	DS ≥ 50 %	DS ≥ 50 %	67	85	67 (14)	3.1 (0.6)	12	7	256
Andreini[24]	2020	Italy	DS ≥ 50 %	DS ≥ 50 %	65	88	60 (5)	3.2 (0.2)	NR	NR	256

CCTA + CPT studies											
First author	Year	Country of origin	Index test ISR diagnostic criteria (CCTA + CTP)	Gold standard ISR diagnostic criteria (ICA)	Mean Age	Sex (Men %)	Mean HR (SD)	Mean stent diameter (SD)	Month between PCI and scan	Days between scan and ICA	Scan slices
Magalhães[31]	2011	Brazil	CCTA DS ≥ 50 % or reversible perfusion defects if CCTA was of limited quality or uninterpretable.	DS ≥ 50 %	57	90	NR	NR	NR	NR	64
Rief[23]	2013	Germany	CCTA DS ≥ 50 % or perfusion defects if CCTA was uninterpretable.	DS ≥ 50 %	64	80	53 (7)	3 (0.5)	41	1	320
Andreini[24]	2020	Italy	CCTA DS ≥ 50 % and/or reversible perfusion defects.	DS ≥ 50 %	65	88	60 (5)	3.2 (0.2)	NR	NR	256

CCTA, coronary computed tomography angiography; CTP, computed tomography perfusion; ISR, in-stent restenosis; ICA, invasive coronary angiography; PCI, percutaneous coronary intervention; HR, heart rate; NR, non-reported; SD, standard deviation.

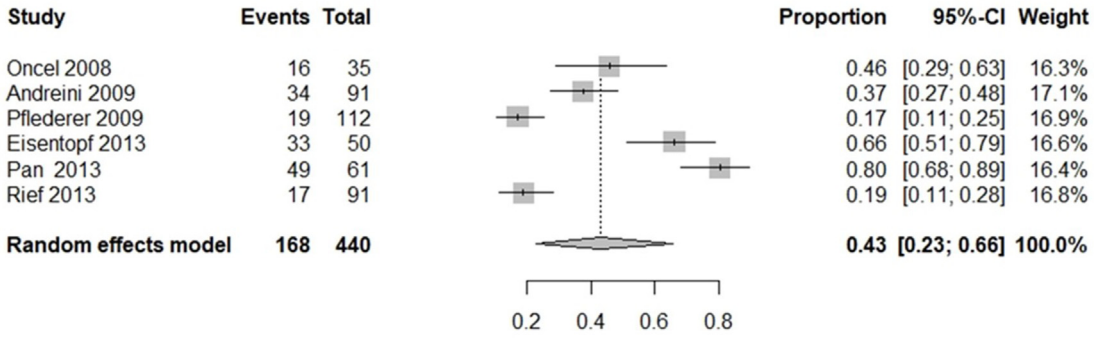

Fig. 2. Prevalence of ISR, per-patient level. ISR, in-stent restenosis.

approach showed a sensitivity and specificity of 88 % for both metrics. 3) With currently employed CT equipment, the prevalence of uninterpretable stents in clinical practice is low, approximately 8 %. 4) Small stent diameter (<3 mm) and thick stent struts (≥100 μm) did not impact the diagnostic accuracy of CCTA significantly.

4.1. Coronary computed tomography angiography

CCTA has gained recognition as a valuable imaging modality in low-to-intermediate risk patients for the exclusion of obstructive CAD. This method has proven to be the workhorse of non-invasive diagnostic work-

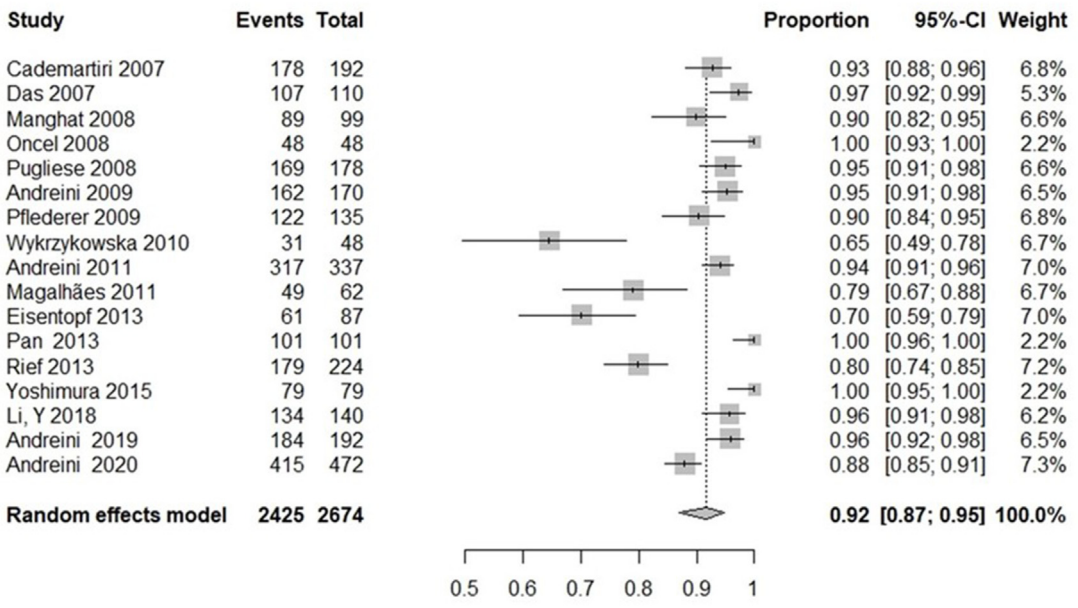

Fig. 3. Prevalence of interpretable stents by CCTA.
ISR, in-stent restenosis.

Table 2
Performance of CCTA and CCTA + CTP for ISR diagnosis.

	Number	Sensitivity	Specificity	PLR	NLR	DOR
PER-PATIENT						
CCTA	440	0.93 (0.85–0.98)	0.80 (0.69–0.89)	4.35 (2.41–7.69)	0.15 (0.05–0.33)	38.5 (9.34–107.84)
PER-STENT						
CCTA	2674	0.90 (0.84–0.94)	0.89 (0.86–0.92)	7.17 (5.24–9.61)	0.17 (0.10–0.25)	45.70 (22.71–82.43)
CCTA + CTP	752	0.88 (0.80–0.94)	0.88 (0.84–0.93)	7.23 (5.34–9.64)	0.15 (0.07–0.27)	53.59 (24.69–102.08)

CCTA, coronary computed tomography angiography; CTP, computed tomography perfusion; ISR, in-stent restenosis; PLR, positive likelihood ratio; NLR, negative likelihood ratio; DOR, diagnostic odds ratio.

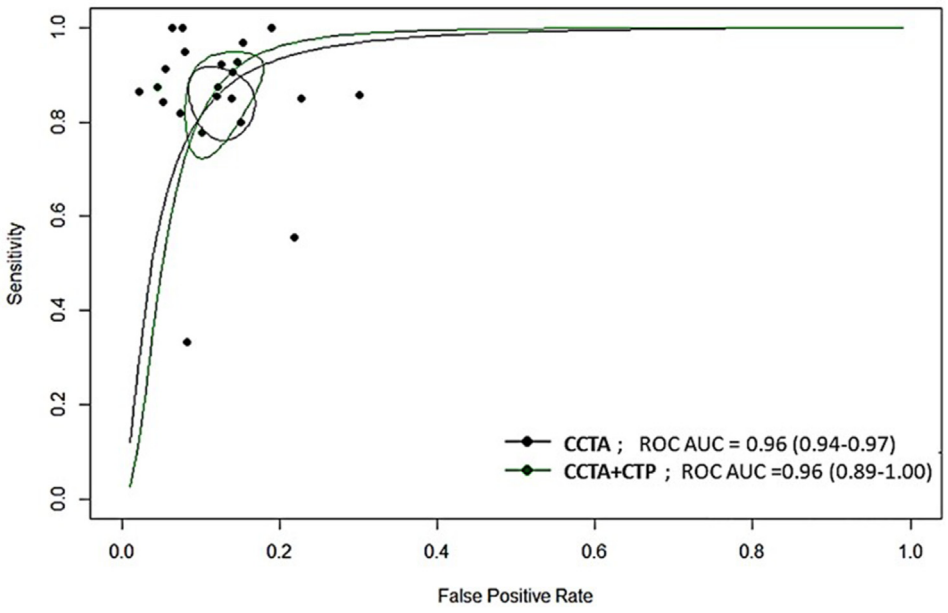

Fig. 4. CCTA and CCTA + CTP Summary Receiver Operating Characteristic Curve for the diagnosis of ISR, per-stent level.
ROC, receiver operating characteristic curve; AUC, area under the curve; CCTA, coronary computed tomography angiography; CTP, computed tomography perfusion.

Table 3
Performance of CCTA for ISR diagnosis, per-stent level sensitivity analysis.

	Number	Sensitivity	Specificity	PLR	NLR	DOR
64-SLICE CT vs. >64-SLICE CT						
64 slice CT	1424	0.91 (0.85–0.96)	0.91 (0.87–0.93)	8.44 (5.93–11.76)	0.14 (0.07–0.24)	66.05 (28.84–130.51)
>64 slice CT	1250	0.86 (0.76–0.93)	0.86 (0.80–0.91)	5.88 (3.26–9.76)	0.22 (0.10–0.39)	31.66 (8.65–83.01)
STENT DIAMETER						
<3 mm	396	0.90 (0.83–0.95)	0.90 (0.79–0.97)	8.48 (2.78–21.66)	0.16 (0.09–0.27)	59.84 (11.78–185.03)
≥3 mm	880	0.96 (0.92–0.98)	0.96 (0.93–0.99)	18.7 (6.92–42.07)	0.12 (0.06–0.19)	187.16 (41.13–545.65)
STENT STRUT THICKNESS						
≥100 μm	351	0.83 (0.72–0.91)	0.95 (0.91–0.98)	19.02 (7.48–41.2)	0.18 (0.097–0.30)	113.56 (34.03–282.75)
<100 μm	320	0.95 (0.89–0.98)	0.98 (0.95–1.00)	74.00 (3.01–348.93)	0.08 (0.03–0.18)	1219.26 (5.38–6625.20)

CCTA, coronary computed tomography angiography; ISR, in-stent restenosis; PLR, positive likelihood ratio; NLR, negative likelihood ratio; DOR, diagnostic odds ratio.

Table 4
Per-stent level performance of CCTA and CCTA + CTP for ISR diagnosis, sensitivity analysis including head to head comparison studies.

	Number	Sensitivity	Specificity	PLR	NLR	DOR
STUDIES WITH HEAD-TO-HEAD COMPARISON OF THE TESTS						
CCTA	752	0.77 (0.64–0.86)	0.82 (0.75–0.87)	4.36 (2.57–6.52)	0.31 (0.14–0.56)	16.95 (4.67–44.13)
CCTA + CTP		0.88 (0.80–0.94)	0.88 (0.84–0.93)	7.23 (5.34–9.64)	0.15 (0.07–0.27)	53.59 (24.70–101.96)

CCTA, coronary computed tomography angiography; CTP, computed tomography perfusion; ISR, in-stent restenosis; PLR, positive likelihood ratio; NLR, negative likelihood ratio; DOR, diagnostic odds ratio.

up of chronic coronary syndromes and it has been primarily regarded a useful tool in patients without a prior CAD history. However, this paradigm is quickly shifting to high-risk patients with complex CAD (e.g. coronary stenting, coronary artery bypass graft patients) due to advancements in hardware, software technology, and the higher image quality obtained with state-of-art systems. This is also supported by the Society of Cardiovascular Computed Tomography (SCCT) 2021 Expert Consensus document in which CCTA is considered an appropriate diagnostic method for patients with stable symptoms and known CAD (e.g. prior coronary stenting).[35] Despite guidelines supporting its use, CCTA has not achieved widespread adoption as a diagnostic tool in patients with pre-existing CAD. Data from a recently published U.S. registry, encompassing over 2.5 million patients who underwent non-invasive cardiac imaging, indicate that CCTA is infrequently employed (<2 %) in the cohort of patients with a history of CAD.[36] In contrast, single-photon emission computed tomography (SPECT) was the initial diagnostic test in over 80 % of these patients. Recent findings have underscored the limited diagnostic performance of various non-invasive myocardial perfusion imaging (MPI) techniques for identifying hemodynamically significant CAD in patients with prior CAD.[37,38] These limitations have been attributed to a higher prevalence of balanced ischemia, myocardial scarring and microvascular dysfunction within this patient cohort. Metal artifacts and partial volume effects have been reported to impair stent visualization impeding accurate grading of stent patency. Advances in CT technology have fulfilled the prerequisites for coronary stent imaging. Our meta-analysis shows that similar to patients without a prior history of CAD, CCTA was found to rule out significant lesions with high precision (per-patient NLR: 0.15 [95 % CI; 0.05–0.33]). Remarkably, the per-stent performance of this technique was comparable to the per-segment diagnostic yield reported in general patient populations with suspected CAD.[7–9] Of note, while characteristics such as smaller stent diameter and thicker stent struts—features associated with the occurrence of artifacts—appear to numerically reduce the performance of CCTA, this decrement was not significant in our pooled analysis.[11,12] Additionally, advancements in stent technology are also focusing on thinner stent struts to improve arterial healing and reduce ISR rates.[39] Currently, most commercially available stents have a strut thickness of less than 100 μm.[40] Such advancements in stent technology, combined with improved CT capabilities, provide further arguments for expanding the use of CCTA in this complex patient population.

Our pooled analysis revealed a marginally lower, though statistically non-significant, diagnostic performance in scanners with more than 64 slices compared to 64-slice scanners. This observed difference may be due to the use of bare-metal stents (BMS) during the early 64-slice CT era. It is known that ISR with BMS more commonly presents with a diffuse phenotype, involving the stented regions with more extensive disease.[41] In contrast, ISR associated with drug-eluting stents (DES), which are commonly used in contemporary clinical practice, typically presents with a focal pattern of disease.[3,42] This difference in the morphologic pattern of ISR may explain the marginal differences in CT performance, as diffuse ISR is likely to be more distinctly recognizable compared to the focal pattern typically observed with DES.

Although not part of this meta-analysis, emerging and novel technologies in the domain of CCTA have also been evaluated in patients with prior stent implantation. A machine-learning based FFR_{CT} algorithm recently demonstrated excellent correlation (r = 0.84) with invasive fractional flow reserve (FFR).[43] The accuracy of this algorithm for detecting hemodynamic significant stenosis at per-stent level was reported to be 86 %.[43] Moreover, recent advancements in CT hardware showed promise for assessing CAD in high-risk populations. Specifically, photon-counting detector CT systems offer an ultra-high-resolution (UHR), achieving an unprecedented maximum in-plane resolution of 0.11 mm and a maximum through-plane resolution of 0.16 mm.[44,45] UHR CCTA provides an outstanding plaque visualization with a significant reduction of blooming artifacts.[44,46] Consistent with these advancements Hagar et al. studied the diagnostic value of UHR CCTA to detect obstructive CAD in a high-risk cohort, reporting a per-patient accuracy of 88 % (95 % CI: 78–95) with a remarkably high specificity (84 %; 95 % CI: 58–95).[47] They also showed a subgroup of patients with prior coronary stenting, that photon-counting CT offered a diagnostic accuracy of 93 % (95 % CI: 68–100 %) for obstructive CAD.

4.2. Hybrid CCTA + CTP for ISR diagnosis

This is the first meta-analysis reporting on the diagnostic performance of hybrid CCTA + CTP for clinically suspected ISR. Within our main analysis, we found that a hybrid CCTA + CTP approach did not improve the performance of CCTA for detecting ISR. The absence of a diagnostic benefit might be attributed to the low prevalence of uninterpretable scans when using routinely employed cardiac CT hardware with improved temporal and spatial resolution, the specific subgroup that might benefit from the reclassification added by CTP. Interestingly, and in support of our findings, previous studies have indicated that the addition of perfusion imaging to the anatomical information garnered

from CCTA offers limited incremental value in diagnosing obstructive CAD.[48] In a meta-analysis conducted by Rizvi et al. hybrid cardiac imaging revealed a higher specificity but only a marginal improvement in the ROC AUC for detecting obstructive CAD on a per-patient basis when compared to stand-alone CCTA (0.97 vs. 0.93, p = 0.132).[49] It is noteworthy that even in the sensitivity analysis of three studies directly comparing CCTA and CCTA + CTP, the diagnostic yield observed with the hybrid technique was not significantly higher (Table 4).

5. Limitations

This study meta-analyzes current evidence and some limitations should be addressed. First, coronary angiography was used as a reference due to the absence of diagnostic studies systematically utilizing invasive functional outcomes. It is known that the angiographic appearance of a coronary stenosis does not always correspond with its functional significance.[50] Even though insufficient evidence supports the use of FFR for assessing ISR, some studies suggest that intermediate (DS 40–70 %) lesions with FFR ≥0.75 can be safely managed conservatively.[51,52] Diagnostic studies with FFR as reference standard are awaited. Secondly, within this study, we only assessed the performance of CT for detecting ISR. The performance of CT for the detecting new stenoses in non-stented segments or ISR was not subjected to meta-analysis due to its infrequent report in the literature. Thirdly, it should be noted that only three studies in this meta-analysis employed hybrid CCTA + CTP.[23,24,31] The ongoing PACIFIC III study (ClinicalTrials.gov Identifier: NCT04742933) aims to expand the existing body of literature on this particular subject, and it results are eagerly awaited.

6. Conclusion

Given the consistently high diagnostic accuracy of both CCTA and hybrid CCTA + CTP using contemporary clinical equipment, the presence of a stent should not be a reason to preclude the use of CCTA in patients with clinically suspected disease. Moreover, a hybrid CCTA + CTP imaging has a similar diagnostic yield than CCTA for the diagnosis of ISR. Given advancements in CT hardware, future guidelines may advocate for the use of either CCTA or a hybrid CCTA + CTP strategy for assessing stent patency in patients with previous stent implantation, irrespective of the stent diameter and strut thickness, thereby expanding its applicability to more complex patient populations.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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References

1. Gerber Y, Rihal CS, Sundt 3rd TM, et al. Coronary revascularization in the community. A population-based study, 1990 to 2004. *J Am Coll Cardiol*. 2007;50(13):1223–1229.
2. Cassese S, Byrne RA, Schulz S, et al. Prognostic role of restenosis in 10 004 patients undergoing routine control angiography after coronary stenting. *Eur Heart J*. 2015;36(2):94–99.
3. Alfonso F, Coughlan JJ, Giacoppo D, Kastrati A, Byrne RA. Management of in-stent restenosis. *EuroIntervention*. 2022;18(2):e103–e123.
4. Kuntz RE, Baim DS. Defining coronary restenosis. Newer clinical and angiographic paradigms. *Circulation*. 1993;88(3):1310–1323.
5. Alfonso F, Kastrati A. Clinical burden and implications of coronary interventions for in-stent restenosis. *EuroIntervention*. 2021;17(5):e355–e357.
6. Giustino G, Colombo A, Camaj A, et al. Coronary in-stent restenosis: JACC state-of-the-art review. *J Am Coll Cardiol*. 2022;80(4):348–372.
7. Mowatt G, Cummins E, Waugh N, et al. Systematic review of the clinical effectiveness and cost-effectiveness of 64-slice or higher computed tomography angiography as an alternative to invasive coronary angiography in the investigation of coronary artery disease. *Health Technol Assess*. 2008;12(17). iii-iv, ix-143.
8. Vanhoenacker PK, Heijenbrok-Kal MH, Van Heste R, et al. Diagnostic performance of multidetector CT angiography for assessment of coronary artery disease: meta-analysis. *Radiology*. 2007;244(2):419–428.
9. Li S, Ni Q, Wu H, et al. Diagnostic accuracy of 320-slice computed tomography angiography for detection of coronary artery stenosis: meta-analysis. *Int J Cardiol*. 2013;168(3):2699–2705.
10. Pontone G, Rossi A, Guglielmo M, et al. Clinical applications of cardiac computed tomography: a consensus paper of the European Association of Cardiovascular Imaging—part I. *European Heart Journal - Cardiovascular Imaging*. 2022;23(3):299–314.
11. Sun Z, Almutairi AM. Diagnostic accuracy of 64 multislice CT angiography in the assessment of coronary in-stent restenosis: a meta-analysis. *Eur J Radiol*. 2010;73(2):266–273.
12. Dai T, Wang JR, Hu PF. Diagnostic performance of computed tomography angiography in the detection of coronary artery in-stent restenosis: evidence from an updated meta-analysis. *Eur Radiol*. 2018;28(4):1373–1382.
13. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ*. 2009;339:b2700.
14. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med*. 2011;155(8):529–536.
15. Guo J, Riebler A. meta4diag: bayesian bivariate meta-analysis of diagnostic test studies for routine practice. *J Stat Software*. 2018;83(1):1–31.
16. Reitsma JB, Glas AS, Rutjes AW, Scholten RJ, Bossuyt PM, Zwinderman AH. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. *J Clin Epidemiol*. 2005;58(10):982–990.
17. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629.
18. Oncel D, Oncel G, Tastan A, Tamci B. Evaluation of coronary stent patency and in-stent restenosis with dual-source CT coronary angiography without heart rate control. *Am J Roentgenol*. 2008;191(1):56–63.
19. Andreini D, Pontone G, Bartorelli AL, et al. Comparison of feasibility and diagnostic accuracy of 64-slice multidetector computed tomographic coronary angiography versus invasive coronary angiography versus intravascular ultrasound for evaluation of in-stent restenosis. *Am J Cardiol*. 2009;103(10):1349–1358.
20. Pflederer T, Marwan M, Renz A, et al. Noninvasive assessment of coronary in-stent restenosis by dual-source computed tomography. *Am J Cardiol*. 2009;103(6):812–817.
21. Eisentopf J, Achenbach S, Ulzheimer S, et al. Low-Dose dual-source CT angiography with iterative reconstruction for coronary artery stent evaluation. *JACC (J Am Coll Cardiol): Cardiovascular Imaging*. 2013;6(4):458–465.
22. Pan J, Lu Z, Zhang J, Li M, Wei M. Angiographic patterns of in-stent restenosis classified by computed tomography in patients with drug-eluting stents: correlation with invasive coronary angiography. *Eur Radiol*. 2013;23(1):101–107.
23. Rief M, Zimmermann E, Stenzel F, et al. Computed tomography angiography and myocardial computed tomography perfusion in patients with coronary stents: prospective intraindividual comparison with conventional coronary angiography. *J Am Coll Cardiol*. 2013;62(16):1476–1485.
24. Andreini D, Mushtaq S, Pontone G, et al. CT perfusion versus coronary CT angiography in patients with suspected in-stent restenosis or CAD progression. *JACC (J Am Coll Cardiol): Cardiovascular Imaging*. 2020;13(3):732–742.
25. Cademartiri F, Schuijf JD, Pugliese F, et al. Usefulness of 64-slice multislice computed tomography coronary angiography to assess in-stent restenosis. *J Am Coll Cardiol*. 2007;49(22):2204–2210.
26. Das KM, El-Menyar AA, Salam AM, et al. Contrast-enhanced 64-section coronary multidetector CT angiography versus conventional coronary angiography for stent assessment. *Radiology*. 2007;245(2):424–432.
27. Manghat N, Van Lingen R, Hewson P, et al. Usefulness of 64-detector row computed tomography for evaluation of intracoronary stents in symptomatic patients with suspected in-stent restenosis. *Am J Cardiol*. 2008;101(11):1567–1573.
28. Pugliese F, Weustink AC, Mieghem CV, et al. Dual source coronary computed tomography angiography for detecting in-stent restenosis. *Heart*. 2008;94(7):848.
29. Wykrzykowska JJ, Arbab-Zadeh A, Godoy G, et al. Assessment of in-stent restenosis using 64-MDCT: analysis of the CORE-64 multicenter international trial. *AJR Am J Roentgenol*. 2010;194(1):85–92.

30. Andreini D, Pontone G, Bartorelli AL, et al. High diagnostic accuracy of prospective ECG-gating 64-slice computed tomography coronary angiography for the detection of in-stent restenosis. *Eur Radiol*. 2011;21(7):1430–1438.
31. Magalhães TA, Cury RC, Pereira AC, et al. Additional value of dipyridamole stress myocardial perfusion by 64-row computed tomography in patients with coronary stents. *Journal of Cardiovascular Computed Tomography*. 2011;5(6):449–458.
32. Yoshimura M, Nao T, Miura T, et al. New quantitative method to diagnose coronary in-stent restenosis by 64-multislice computed tomography. *J Cardiol*. 2015;65(1):57–62.
33. Li Y, Yu M, Li W, Lu Z, Wei M, Zhang J. Third generation dual-source CT enables accurate diagnosis of coronary restenosis in all size stents with low radiation dose and preserved image quality. *Eur Radiol*. 2018;28(6):2647–2654.
34. Andreini D, Pontone G, Mushtaq S, et al. Diagnostic accuracy of coronary CT angiography performed in 100 consecutive patients with coronary stents using a whole-organ high-definition CT scanner. *Int J Cardiol*. 2019;274:382–387.
35. Narula J, Chandrashekhar Y, Ahmadi A, et al. SCCT 2021 Expert consensus document on coronary computed tomographic angiography: a report of the society of cardiovascular computed tomography. *Journal of Cardiovascular Computed Tomography*. 2021;15(3):192–217.
36. Pelletier-Galarneau M, Vandenbroucke E, Lu M, Li O. Characteristics and key differences between patient populations receiving imaging modalities for coronary artery disease diagnosis in the US. *BMC Cardiovasc Disord*. 2023;23(1):251.
37. Driessen RS, van Diemen PA, Raijmakers PG, et al. Functional stress imaging to predict abnormal coronary fractional flow reserve: the PACIFIC 2 study. *Eur Heart J*. 2022;43(33):3118–3128.
38. Jukema RA, Dahdal J, Kooijman EM, et al. Diagnostic accuracy of non-invasive cardiac imaging modalities in patients with a history of coronary artery disease: a meta-analysis. *Heart*. 2024 Aug 23. https://doi.org/10.1136/heartjnl-2024-324248. heartjnl-2024-324248. Epub ahead of print. PMID: 39179368.
39. Grundeken MJ, Beijk MA. A narrative review of ultrathin-strut drug-eluting stents: the thinner the better? *Heart Int*. 2021;15(2):84–93.
40. Thakkar A, Dave B. Revolution of drug eluting coronary stents: an analysis of market leader. *European Medical Journal*. 2016;4:114–125.
41. Goldberg SL, Loussararian A, De Gregorio J, Di Mario C, Albiero R, Colombo A. Predictors of diffuse and aggressive intra-stent restenosis. *J Am Coll Cardiol*. 2001;37(4):1019–1025.
42. Solinas E, Dangas G, Kirtane AJ, et al. Angiographic patterns of drug-eluting stent restenosis and one-year outcomes after treatment with repeated percutaneous coronary intervention. *Am J Cardiol*. 2008;102(3):311–315.
43. Tang CX, Guo BJ, Schoepf JU, et al. Feasibility and prognostic role of machine learning-based FFRCT in patients with stent implantation. *Eur Radiol*. 2021;31(9):6592–6604.
44. Mergen V, Sartoretti T, Baer-Beck M, et al. Ultra-high-resolution coronary CT angiography with photon-counting detector CT: feasibility and image characterization. *Invest Radiol*. 2022;57(12):780–788.
45. Flohr T, Petersilka M, Henning A, Ulzheimer S, Ferda J, Schmidt B. Photon-counting CT review. *Phys Med*. 2020;79:126–136.
46. Si-Mohamed SA, Boccalini S, Lacombe H, et al. Coronary CT angiography with photon-counting CT: first-in-human results. *Radiology*. 2022;303(2):303–313.
47. Hagar MT, Soschynski M, Saffar R, et al. Accuracy of ultrahigh-resolution photon-counting CT for detecting coronary artery disease in a high-risk population. *Radiology*. 2023;307(5):e223305.
48. Danad I, Raijmakers PG, Driessen RS, et al. Comparison of coronary CT angiography, SPECT, PET, and hybrid imaging for diagnosis of ischemic heart disease determined by fractional flow reserve. *JAMA Cardiology*. 2017;2(10):1100–1107.
49. Rizvi A, Han D, Danad I, et al. Diagnostic performance of hybrid cardiac imaging methods for assessment of obstructive coronary artery disease compared with stand-alone coronary computed tomography angiography: a meta-analysis. *JACC Cardiovasc Imaging*. 2018;11(4):589–599.
50. Danad I, Szymonifka J, Twisk JWR, et al. Diagnostic performance of cardiac imaging methods to diagnose ischaemia-causing coronary artery disease when directly compared with fractional flow reserve as a reference standard: a meta-analysis. *Eur Heart J*. 2017;38(13):991–998.
51. Lopez-Palop R, Pinar E, Lozano I, Saura D, Picó F, Valdés M. Utility of the fractional flow reserve in the evaluation of angiographically moderate in-stent restenosis. *Eur Heart J*. 2004;25(22):2040–2047.
52. Nam C-W, Rha S-W, Koo B-K, et al. Usefulness of coronary pressure measurement for functional evaluation of drug-eluting stent restenosis. *Am J Cardiol*. 2011;107(12):1783–1786.