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Diagnostic performance of computed tomography angiography in the detection of coronary artery in-stent restenosis: evidence from an updated meta-analysis

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Abstract

Objectives To evaluate the performance of computed tomography angiography (CTA) ≥ 64 slices for detecting coronary in-stent restenosis (ISR) and determine the influence of separate characteristics on diagnostic accuracy.

Methods We searched the PubMed, EMBASE and Cochrane databases for studies of CTA \geq 64 slices in diagnosing ISR. We pooled data on bivariate modelling, and subgroup analysis was also performed.

Results A total of 35 studies involving 4131 stents were included. The pooled positive likelihood ratio $(LR⁺)$ and the negative likelihood ratio (LR–) were 14.0 and 0.10, for CTA in diagnosis-significant ISR \geq 50%. LR⁺ and LR⁻ were similar between CTA >64 slices versus 64 slices (both $P > 0.99$). LR⁻ (0.10) was good for ruling out suspected ISR for \leq 3-mm diameter. Time between CTA and stent implantation >6 months did not affect the ability of CTA for the high $LR^+(12.3)$ and the LR[–] (0.10). Thick-strut stents \geq 100 μm or bifurcation stenting demonstrated inferior accuracy, which was unfavourable for stent imaging.

Tao Dai and Jiang-rong Wang are authors contributed equally

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Conclusions With the high LR^+ and LR^- of CTA, patients with ISR may be appropriate for non-invasive angiographic follow-up. However, CTA imaging seems unsuitable for patients with characteristics unfavourable for stent imaging, such as thick-strut stents or bifurcation stenting.

Key points

- CTA may provide accurate information on characteristics of in-stent restenosis lesions.
- Using CTA, ISR patients may be appropriate for noninvasive angiographic follow-up.
- Stent diameter and the number of slices do not influence CTA.
- CTA seems unsuitable for patients with thick-strut stents or bifurcation stenting.

Keywords Computed tomography angiography \cdot Coronary heart disease . Meta-analysis . In-stent restenosis . Stents

Abbreviations

- CHD Coronary heart disease
- CTA Computed tomography angiography
- ICA Invasive coronary angiography
- ISR In-stent restenosis
- PCI Percutaneous coronary intervention

Introduction

Coronary heart disease (CHD) is the most common cause of death and disability worldwide. Each year, more than one million CHD patients are treated with stent implantation [\[1\]](#page-7-0). Unfortunately, it is not a permanently curative treatment; even with drug-eluting stents (DESs), in-stent restenosis (ISR) will occur in a certain proportion of patients [\[2](#page-7-0)]. ISR can occur in

20–35% of patients for bare-metal stents, and in 5–10% for DES, as demonstrated by intravascular ultrasound [\[3](#page-7-0)]. The underlying process of atherosclerosis in the coronary lumen may progress to coronary restenosis, and in patients presenting with recurrent chest pain following DES implantation, invasive coronary angiography (ICA) is still frequently indicated to evaluate the presence of ISR [\[4](#page-7-0)]. However, ICA has limitations due to its invasiveness and association with potential risks of morbidity and mortality; therefore, a non-invasive alternative approach for the assessment of stent patency is highly desirable.

Computed tomography angiography (CTA) may have some effect for a more precise visualisation of coronary arteries and the patency of the lumen after stent implantation [\[5,](#page-7-0) [6](#page-7-0)]. This modality has been developed significantly in recent years, effectively allowing non-invasive coronary arteriography. However, the imaging of stents by CT scanner is more difficult than the native coronary artery. This is due to the presence of the stent metal, which can cause artefacts to interfere with the interpretation of lumen patency. With an increasing number of detector rows, promising results of CTA in coronary artery disease have been reported with improved spatial and temporal resolution. Primary studies have been published that compared anatomic imaging by CTA with functional imaging by various methods [\[7\]](#page-7-0) and with standard care in the diagnosis of patients with suspected CHD [\[8\]](#page-7-0). However, currently, no major clinical trial has been conducted that relates to the use of CTA in the evaluation of stent patency. Current research uses different scanning protocols and scanner types, and the reported figures for ISR exhibit considerable variability. Furthermore, a multitude of stent sizes, stent types, strut thickness and other factors exist and have been evaluated with CTA, with varying results for diagnostic accuracy. Thus, the purpose of this study was to assess the pooled diagnostic accuracy of CTAwith 64 slices or higher for the detection of ISR, and to determine the influence of separate characteristics of the CTA scanner and stent on the diagnostic performance.

Methods

We did a meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [[9\]](#page-7-0) and the methods described in the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy.

We searched for the relevant studies in the EMBASE, PubMed and Cochrane databases for all published studies from the date of their inception until July 2016. We used the search terms and corresponding medical subject headings for 'computed tomography' and 'in-stent restenosis'. No language restriction was placed. The references in all the retrieved articles were also searched for any additional relevant studies. Two reviewers were asked to look through all this literature and assess their eligibility for analysis.

Eligible studies had to meet the following criteria: (i) they used ≥64-slice CTA as a diagnostic test for coronary luminal restenosis, and reported patients' baseline characteristics, and their sensitivity and specificity of modality; (ii) true positives (TPs), false positives (FPs), true negatives (TNs) and false negatives (FNs) were able to be calculated on the basis of sensitivity and specificity in respective publications; and (iii) substantial coronary artery restenosis was defined as $\geq 50\%$ reduction in diameter using ICA as reference. Systematic reviews and meta-analyses were identified and their reference lists were screened. The reference lists of the retrieved articles were also screened. Finally, 35 studies were finalised, and any disagreement between them was resolved by discussion with a third party.

Two reviewers independently extracted relevant data from the selected studies in a standard form. Any identified discrepancies were discussed and corrected. Two-by-two contingency tables were constructed based on the data published, summarising TP, FP, TN and FN on the basis of sensitivity and specificity in respective papers. For each report, we extracted the following items: author, publication years, country, number of restenosis patients and stents, description of the study population (age, sex), scanner type, number of slices, stent size, mean heart rate during scanning, average months between the scan and the stent placement, and days between the CTA scan and the ICA (Table [1\)](#page-2-0).

The quality of the selected studies and the potential bias were assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) guidelines, including additional items as recommended by the Cochrane Collaboration [\[10](#page-7-0)]. Discrepancies were resolved by consensus.

Analysis was performed at the per-stent level, and a random effects model was performed for the primary metaanalysis. The primary objective was to estimate the sensitivity and specificity, and the positive and negative likelihood ratios (LR⁺ and LR⁻, respectively) with 95% confidence intervals (CIs). We assumed bivariate normal distributions for sensitivity and specificity and presented a forest plot. LR^+ and LR^- are metrics derived from the summarised sensitivity and specificity for assessing the discriminating ability of the imaging modality. If the LR^+ is >10.0 and the LR^- is < 0.1 , then the test can both rule in and rule out the disease [[11\]](#page-7-0). Each data point of the summary receiver operator characteristic (SROC) graph comes from an individual study; then, the SROC curve is formed based on these points to form a smooth curve to reveal pooled accuracy. The sources of heterogeneity were explored at the stent level by using the bivariate generalised linear mixed model as previously described [\[12,](#page-7-0) [13\]](#page-7-0). We assessed the following covariates in meta-regression: sample size (divided by a median of 50 patients), average age of patients (divided by a median of 62 years), percentage of male subjects (divided by a median of 80%), number of slices (defined as either 64

Table 1 Baseline characteristics of the studies included

*= average number of months between scan and stent placement

**= average days between CT scan and invasive coronary

***= average stent diameter

CT/ICA = computed tomography/invasive coronary angiography; CT/PCI = computed tomography/percutaneous coronary intervention; GE = General Electric; ND = not documented

slices or >64 slices), and the average time between the CT scan and the stent placement. The Deeks' funnel plot was generated to assess the evidence of bias towards studies [\[14\]](#page-7-0). Significance testing was at the two-tailed 0.05 level. All analyses were performed using the software Stata SE version 14 (Stata Corp) and Meta Disc (Version 1.4).

Results

As illustrated in Fig. 1, 35 studies that constituted populations ranging between 15 and 231 patients were included in the final analysis [\[15](#page-7-0)–[48\]](#page-8-0). All studies defined significant luminal restenosis as a cut-off ≥50%. One of the studies consisted both of a 64-slice and a 320-slice CT in the diagnosis of ISR simultaneously, and raw data of the two methods were involved in the analysis, respectively [\[16\]](#page-7-0). Baseline characteristics of included studies are listed in Table [1](#page-2-0). The total included number of patients and atherosclerotic lesions was 2656 and 4131, respectively. The mean age of included patients was 62.2 years, and 80% of them were male. The mean peri-scan heart rate at the time of CTA was 62 beats/min (54–78 beats/min).

Of the 35 publications, 24 studies evaluating 1788 patients with a 64-slice CTA were used [\[16](#page-7-0), [18](#page-7-0), [21](#page-8-0)–[24,](#page-8-0) [26,](#page-8-0) [29](#page-8-0)–[34,](#page-8-0) [37](#page-8-0)–[40](#page-8-0), [42](#page-8-0)–[48](#page-8-0)]; whereas 11 studies analysed 128- or 320 slice or dual-detector CTA in a total of 961 patients [\[15](#page-7-0)–[17,](#page-7-0) [19,](#page-8-0) [20](#page-8-0), [25,](#page-8-0) [27,](#page-8-0) [28](#page-8-0), [35,](#page-8-0) [36,](#page-8-0) [41](#page-8-0)]. Six studies (482 patients) evaluated the effect of strut thickness on diagnostic performance [[19](#page-8-0), [22,](#page-8-0) [23](#page-8-0), [26,](#page-8-0) [29](#page-8-0), [34](#page-8-0)], whereas 11 studies (902 patients) analysed the effect of stent diameter [[19](#page-8-0), [22,](#page-8-0) [23](#page-8-0), [25](#page-8-0), [26,](#page-8-0)

[29,](#page-8-0) [33](#page-8-0), [34,](#page-8-0) [41](#page-8-0), [43,](#page-8-0) [44](#page-8-0)]. Furthermore, six studies (475 patients) analysed stenting methods [[19](#page-8-0), [25](#page-8-0), [34](#page-8-0), [41,](#page-8-0) [44,](#page-8-0) [48\]](#page-8-0).

Table S1 shows the results from the assessment of the methodological quality by QUADAS-2 tools. All the included studies exerted high quality in terms of applicability and satisfactory quality in terms of risk of bias. Risk of bias regarding flow and timing was unclear in 12 studies because the timing between the CTA scanning and the ICA was unknown.

The results were pooled from 35 studies with a total of 2656 patients and 4131 stents. Raw data (TP, FP, FN and TN) are depicted in Table S2. The coupled sensitivity and specificity values with a 95% CI are illustrated by the forest plot as shown in Fig. [2](#page-4-0). In the per-stent analysis, the pooled sensitivity and specificity for CTA on the diagnosis of ISR were 0.90 (95% CI, 0.85–0.94) and 0.94 (95% CI, 0.91– 0.96), respectively. LR^+ and LR^- were 14.0 (95% CI, 9.6– 20.3) and 0.10 (95% CI, 0.07–0.17). For a test to be helpful in diagnosis, it is generally accepted that LR^+ should be higher than 10 and LR[−] below 0.1 [[11](#page-7-0)]. The SROC curve was symmetric, and the area under the curve (AUC) value was 0.97 (95% CI, 0.95–0.98; Fig. [3\)](#page-5-0).

The ROC space did not illustrate a curvilinear trend of points, and there was no presence of threshold effect ($P =$

Fig. 2 Forest plots of sensitivity and specificity of computed tomography angiography (CTA) compared with invasive coronary angiography (ICA). Each solid square represents an eligible study (error bars represent 95% confidence intervals)

0.603). Statistical heterogeneity was found for sensitivity (l^2 = 82.5%; $P < 0.001$) and specificity ($l^2 = 93.2\%$; $P < 0.001$). According to meta-regression, all covariates [slice number, CT/percutaneous coronary intervention (PCI) interval (average number of months between scan and stent placement), sample size, male subjects and age] showed a significant effect on sensitivity and specificity. According to I^2 statistics, heterogeneity was present in the covariates of male subjects ($l^2 = 55.0\%$; $P = 0.11$) and age ($I^2 = 83.0\%$; $P < 0.001$). A publication bias existed in this study on the basis of Deeks' test ($P = 0.01$).

All covariates showed a significant effect on sensitivity and specificity; a subgroup analysis was performed to estimate the level of the effect by classifying studies in certain covariates (Table [2\)](#page-6-0). An analysis stratified according to the number of slices demonstrated a similar sensitivity (0.90) and specificity (0.94) for >64 slices compared with sensitivity (0.90) and specificity (0.94) for 64 slices ($P > 0.99$). Similarly, stratified according to the strut thickness, indicated a significantly favourable sensitivity (0.96) with thinner struts <100 μ m compared with sensitivity (0.84) with thicker struts \geq 100 μ m (P < 0.001), with equal specificity ($P = 0.231$). Sensitivity and specificity of the CT/PCI period ≤ 6 months were similar to those >6 months ($P = 0.399$ and $P = 0.085$, respectively).

Diagnostic performances in stents with a diameter of ≥3 mm were more sensitive than those with a diameter of \leq 3 mm ($P =$ 0.024) and specificity ($P = 0.073$), whereas adjusted LR⁻ (0.10) was good for ruling out ISR for a diameter of \leq 3 mm.

Sensitivity in the peri-scan heart rate <65 was significantly higher than the heart rate ≥ 65 ($P = 0.028$), but with equally high values of specificity in both groups ($P = 0.421$). Although LR^+ (15.0) was enough to rule in ISR for the heart rate ≥ 65 , the LR^{$-$} (0.17) was modest. Sensitivity and specificity of CTA were significantly higher in simple stenting than in bifurcation stenting ($P = 0.012$ and $P = 0.001$, respectively).

Discussion

This study was performed to test the accuracy of CTA ≥ 64 slices in the diagnosis of suspected ISR. Our main finding was that CTA, using currently available technology, can effectively rule in and rule out significant restenosis; therefore, it may serve as a gatekeeper before an invasive method is necessary. Using ICA as the reference standard, it exhibited an excellent pooled LR⁺ (14.0) and LR⁻ (0.10) for the inclusion and exclusion of ISR. ICA may not be suitable to assess or follow-up ISR lesions on a regular basis [[49](#page-8-0)].With the high accuracy of CTA, patients assessed as no visible ISR may partly avoid ICA with its non-negligible risks for several complications.

The assessment of restenosis is essential for risk stratification and determination if concomitant coronary revascularisation is necessitated. CTA has been noted as being useful for the prognosis of high-risk patients and the prediction of coronary events to discriminate unstable plaque [[50\]](#page-8-0). However, only a few

Fig. 3 Summary receiver operator characteristic (SROC) curve of computed tomography angiography (CTA) in the diagnosis of in-stent restenosis. Pooled diagnostic accuracy of CTA for the detection of instent restenosis (ISR). Hollow circles are individual studies; the full curved line is the SROC curve; and the solid diamond is the pooled accuracy measures surrounded by the 95% confidence interval ellipse

studies with limited sample sizes have tested the evaluation of ISR using CTA, and definitive evidence advocating the use of this scanner in ISR requires further validation.

This study differs in two key aspects from the previous studies. First, we enriched the influence of more characteristics of CTA and stents to have adjudicated diagnostic accuracy compared with previous studies [\[6](#page-7-0), [51](#page-8-0)–[55](#page-9-0)]. Second, our study had more global representation and a larger number of patients, whereas the largest sample size of a previous study was 895 [[52](#page-9-0)]. Six earlier meta-analyses explored the role of CTA with ≤64 slices in suspected restenosis [\[6](#page-7-0), [51](#page-8-0)–[55\]](#page-9-0). They concluded that the sensitivity was insufficient, and only in selected patients may CTA serve as alternative method to rule out ISR. However, they did not report CTA with >64 slices and adjudicated accuracy for some certain characteristics of the scanner and the stent. Accordingly, access to these data would have warranted further studies.

The present study indicated that the introduction of 128 and 320-slice and dual-detector armamentarium had similarly high diagnostic accuracy together with the 64-slice CTA. This result was clinically relevant because it indicated that CTA ≥64 slices could be effectively used to rule in and rule out ISR. A CT/PCI period >6 months did not affect the ability of CTA to reliably rule in and rule out significant ISR for the high LR^+ (12.3) and LR^- (0.10). A larger stent naturally provides fewer blooming artefacts and is more visible, which leads to more accurate ISR quantification, whereas stents with <3-mm in diameter were more likely to have ISR than those \geq 3 mm in diameter [\[56\]](#page-9-0). Although analysis stratified by stent

diameter demonstrated more favourable sensitivity and specificity for \geq 3 mm in diameter, adjusted LR[–] (0.10) was also good for ruling out suspected ISR. CTA was probably enough to use as a rule-out triage modality in stents <3 mm in diameter. Strut thickness is also related to ISR detection, and partial volume artefacts from the stent led to blooming and artefactual lumen narrowing. Given that the stents are thick, they may be less likely to be visualised on CTA as they are within the shadow of the artefacts created by stent struts. Based on the present work, thick-strut stents $(\geq 100 \,\mu\text{m})$ had lower diagnostic accuracy than thin-strut stents, which suggested that thickstrut stents may reduce visualisation of the lumen.

Besides thick struts, diagnostic performances tend to be lower with other characteristics that are unfavourable for stent imaging, such as bifurcation stenting and an elevated heart rate. However, Yue et al. [\[16](#page-7-0)] revealed that the motion artefacts caused by slice misalignment may be optimised in patients with elevated heart rates for the improved information of 320-slice CTA. Additional research may be warranted to better define the efficiency of 320-slice CTA.

In this study, we clarified that a post-processed iterative reconstruction (IR) algorithm was not adopted in any included paper. The IR algorithms technique was developed in an attempt to decrease the radiation dose or improve image quality, it can significantly reduce image noise without loss in the diagnostic performance and thus holds the potential for radiation dose reduction [\[57](#page-9-0)–[59\]](#page-9-0). In first-generation IR algorithms, a substantial noise reduction might be associated with the image, leading to a blotchy appearance of the IRreconstructed studies [\[60](#page-9-0), [61](#page-9-0)]. Second-generation IR algorithms allow for a more effective reduction of image noise without substantial effects on attenuation; this may have a role in reducing beam hardening and partial-volume artefacts associated with coronary artery stents and heavily calcified vessels [[62](#page-9-0), [63](#page-9-0)]. Reductions in stent volumes prompts less blooming artefacts and image noise along with improved instent visualisation and diagnostic accuracy [\[64](#page-9-0), [65](#page-9-0)].

However, it is important to note that all IR techniques are vendor-specific with limited applicability to other CT systems [AIDR (Toshiba), ASIR (GE), IRIS (Siemens), iDose (Philips), SAFIRE (Siemens)], the choice of the IR algorithm and its strength level influences the image impression and noise characteristics. Accordingly, the selection of the preferred IR technique is a specific clinical task germane to the individual preferences for image quality [[66\]](#page-9-0). In view of the fact that a large data base comparable to the one solely including filtered back-projection images is still lacking today, but that it would be very interesting to conduct a meta-analysis on whether performance of CTA for ruling in and ruling out of instent-restenosis could be further increased by using IR algorithms.

Some limitations exist in our study. First, there was heterogeneity between the results in our study, which is reflected in

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*= average month between scan and stent placement

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CT/PCI = computed tomography/percutaneous coronary intervention; DOR = diagnostic odds ratio; LR− = negative likelihood ratio; LR+ = positive likelihood ratio.

 $CTPCI = computed tomography/pecutaneous conary intervention; DOR = diagnostic odds ratio; LR = negative likelihood ratio; LR* = positive likelihood ratio.$

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the wide predictive intervals around each estimate. We did not find a threshold effect in this study, while meta-regression was conducted to seek potential heterogeneity, and covariates of male subjects and age may have affected the pooled results. Second, not all the reports provided details regarding technical issues in the sub-analysis, which cast caution on the interpretation of the estimates of the adjusted effects. Third, in statistics, meta-analysis comprises statistical methods for contrasting and combining results from different studies in the hope of identifying patterns among study results. Unlike many clinical researches that rely on self-reported data, the meta-analysis is based on indirect observation in the context of multiple papers, and some specific issues may not be included caused by time and skill. Fourth, the vendor-specific IR algorithms were not elucidated in all studies, so we cannot assess the efficiency and efficacy of this advanced techniques. Further overview of CTA-adapted IR algorithms is warranted to investigate the potential usage of IR algorithms.

Conclusion

CTA could provide accurate information on ISR lesions or other characteristics of stents, and evaluation of these assessable lesions could be useful for detecting changes in the long term. Using this modality, patients with ISR may be appropriate for non-invasive angiographic follow-up. However, CTA imaging seems unsuitable for patients with characteristics unfavourable for stent imaging, such as thick-strut stents or bifurcation stenting.

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Tao Dai.

Conflict of interest The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

Statistics and biometry The author Tao Dai has significant statistical expertise in diagnostic meta-analysis.

Informed consent All analyses were based on previous published studies; thus, no ethical approval and patient consent are required.

Ethical approval Institutional review board approval was not required because all analyses were based on previous published studies; thus, no ethical approval and patient consent are required.

Methodology This is a diagnostic meta-analysis performed at one medical institution.

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