Diagnostic accuracy of 64 multi-slice CT angiography in the assessment of coronary in-stent restenosis: A meta-analysis

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Abstract

Purpose: The aim of this study was to perform a meta-analysis of the diagnostic accuracy of 64-slice CT angiography for the detection of coronary in-stent restenosis in patients treated with coronary stents when compared to conventional coronary angiography.

Materials and Methods: A search of PUBMED/MEDLINE, ProQuest and Cochrane library databases for English literature was performed. Only studies comparing 64-slice CT angiography with conventional coronary angiography for the detection of coronary in-stent restenosis (more than 50% stenosis) were included for analysis. Sensitivity and specificity estimates pooled across studies were tested using a fixed effects model.

Results: Fourteen studies met selection criteria for inclusion in the analysis. The mean value of assessable stents was 89%. Prevalence of in-stent restenosis following coronary stenting was 20% among these studies. Pooled estimates of the sensitivity and specificity of overall 64-slice CT angiography for the detection of coronary in-stent restenosis was 90% (95% CI: 86%, 94%) and 91% (95% CI: 90%, 93%), respectively, based on the evaluation of assessable stents. Diagnostic value of 64-slice CT angiography was found to decrease significantly when the analysis was performed with inclusion of nonassessable segments in five studies, with pooled sensitivity and specificity being 79% (95% CI: 68%, 88%) and 81% (95% CI: 77%, 84%). Stent diameter is the main factor affecting the diagnostic value of MSCT angiography.

Conclusion: Our results showed that 64-slice CT angiography has high diagnostic value (both sensitivity and specificity) for detection of coronary in-stent restenosis based on assessable segments when compared to conventional coronary angiography.
Keywords: Multi-slice computed tomography, stent, restenosis, coronary artery disease
Introduction

In recent years, coronary artery disease has been increasingly treated by coronary stent placement. The placement of coronary artery stents has significantly reduced the development of restenosis when compared with percutaneous coronary angioplasty (1, 2). The introduction of drug eluting stents has been reported to further reduce this complication (3). The clinical incidence of in-stent restenosis after coronary stenting is 20 to 35% for bare metal stents, and 5 to 10% for drug eluting stents (3, 4). Conventional invasive coronary angiography is widely used in clinical practice to detect in-stent restenosis as it allows direct visualization of the vessel lumen with high spatial and temporal resolution (5). However, coronary angiography is an invasive procedure associated with complications. Moreover, with the increasing use of drug eluting stents, the incidence of restenosis is low, thus follow-up with conventional coronary angiography might not be necessary if a non-invasive alternative to conventional angiography with high diagnostic accuracy could be developed.

Currently multislice computed tomography (MSCT) angiography has been established as an effective method for detection of coronary artery disease (6, 7) and has recently been evaluated for assessment of coronary stent patency or restenosis (8-10). In comparison to conventional angiography, detection of coronary in-stent restenosis by early type of scanners such as 4- slice CT was difficult due to the stent diameter, stent material, and limited spatial and temporal resolution. While the accuracy of stent lumen analysis was low or moderate with 4-and 16-slice CT scanners, the recently developed 64-slice CT (single source and dual source) scanners allow for more accurate stent visualization and characterization due to increased spatial and temporal resolution (11-14). As 64-slice CT is becoming widely available in clinical practice,
and also is increasingly used for assessment of coronary stents, therefore, it is necessary to know whether the 64-slice CT angiography has reached the diagnostic accuracy as that of coronary angiography for the detection of in-stent restenosis. The purpose of this study was to investigate the diagnostic value of 64-slice CT for the detection of coronary in-stent restenosis when compared to conventional coronary angiography, based on a meta-analysis of the currently published results.

Materials and Methods

Criteria for data selection and literature screening

A search of Pubmed/Medline, ProQuest and Cochrane library databases for English literature was performed for articles describing the diagnostic value of 64-slice CT angiography in coronary artery stenting when compared to conventional coronary angiography. Inclusion criteria required that articles must be peer-reviewed and published in English language. The key words used in searching the references included: multislice CT angiography and coronary stents, multislice/multidetector row CT imaging in coronary in-stent restenosis, multislice/multidetector CT assessment of coronary stents, dual source CT and coronary stents. The search of literature ranged from 2004 to 2008 (September 2008), as 64-slice was first introduced into clinical practice in 2004. In addition, the reference lists of identified articles were checked to obtain additional relevant articles. Prospective and retrospective studies were included if they met all of the following criteria: (a) studies included at least 10 patients and must be performed using 64-slice CT as a diagnostic tool for assessment of in-stent restenosis, with >50% diameter stenosis defined as the cut-off criterion for significant stenosis, and used invasive coronary angiography as the standard of reference; (b) patients underwent both 64-slice CT angiography and conventional coronary angiography examinations; (c) assessment of coronary in-stent restenosis
and occlusion by 64-slice CT was addressed when compared to conventional angiography in terms of sensitivity, specificity (or reporting the numbers of true positive, true negative, false positive and false negative). Exclusion criteria were: review article or a comment to the editor; case reports; conference abstracts; in vitro or phantom studies; inability to provide or obtain original numbers of true positive, true negative, false positive and false negative. The reviewing process of the study selection is described in Fig 1.

Data extraction

Data were repeatedly extracted by two reviewers independently based on study design and procedure techniques. Each reviewer independently assessed the retrieved articles for possible inclusion according to the selection criteria. In the case of conflicting findings as to whether a paper should be included, a decision was reached by consensus. The reviewers looked for the following characteristics in each study: year of publication; number of participants in the study; mean age; mean heart rate; percentage of male patients affected; number of patients receiving β-blockage; type of imaging unit used for CT; scanning protocols; assessable stents in each study; location of stents implanted; diameter of the stents implanted, stent materials (number of bare metal stents and drug eluting stents) and diagnostic accuracy of multislice angiography when compared to conventional coronary angiography with regard to the sensitivity and specificity for the detection of in-stent restenosis and occlusion. The reviewers also assessed the quality of each study in terms of patient enrolment, image interpretation (blinded to the results of other modality), report of findings of all readers and interobserver agreement. Moreover, the reviewers looked for the postprocessing methods used in each study with the aim of decreasing stent-related artifacts and improving visualization of stent and vessel lumens.
Statistical analysis

All of the data was entered into SPSS 14.0 (SPSS Inc, Chicago, ILL) for analysis. The main focus of analysis was at the assessable stents, as most studies focused on this level of information. We also did an evaluation on a per patient basis. Sensitivity and specificity estimates for each study were independently combined across studies using a fixed effects model. Between-study heterogeneity of the sensitivity and specificity estimates was tested using the Mantel-Haenszel Chi-squared test with n-1 degree of freedom (n is the number of studies). Statistical hypotheses (2-tailed) were tested at the 5% level of significance.

Results

General information

Sixteen studies met selection criteria and 14 were included in the analysis (15-30). Two studies were further excluded from analysis as they either dealt with stent geometry and in-stent contrast attenuation or cumulative addition of previous cases (29, 30). Twelve of the 14 studies were performed with single source 64-slice CT scanners, while the remaining two were performed with a dual source 64-slice CT scanner (25, 27). The number of patients using the beta-blocking agents was available in only half of the studies, which ranged from 19 to 100%, and no beta-blocking agents were used in the two studies performed with a dual source CT scanner. Table 1 lists patients’ characteristics and scanning protocols in the studies reviewed.

The number of stents implanted in these studies ranged from 39 to 178 with a total number of 1398. A shown in table 1, all of the stents were evaluated without exclusion of any stent in only three studies, while in the remaining studies, the stents were excluded from the analysis to variable extents. The mean value of assessable
stents was 89% (95% CI: 82%, 96%), and the prevalence of more than 50% in-stent restenosis was 20% (95% CI: 13%, 26%).

Image analysis and assessment

Analysis of the diagnostic accuracy of 64-slice MSCT angiography for detection of coronary in-stent restenosis was performed qualitatively in all of the studies, which involves subjective evaluation and analysis of MSCT angiography images by visual inspection and classification of in-stent restenosis or occlusion according to the contrast attenuation within any portion of the coronary stent. In addition, quantitative analysis was used in one study and compared with qualitative analysis for diagnosis of coronary in-stent restenosis (22). The quantitative analysis was performed by comparing the contrast attenuation of the cross-sectional images arising from the straightened multiplanar reformatted images with that measured at pre-stent location for determination of the restenosis or occlusion. This method of assessment was found to be inferior to qualitative analysis according to the results reported in that study.

The stents were deployed in the four main coronary branches in all of the studies, as shown in table 2, and most of these stents were implanted in the left anterior descending and right coronary artery branches. Distribution of the implanted stents in these main coronary branches was available in 12 of the 14 studies, while in remaining two studies this was not provided (18, 26).

Diagnostic accuracy of 64-slice CT for detection of in-stent restenosis

Pooled estimates and 95% confidence interval (CI) of sensitivity and specificity for 64-slice CT angiography to detect the coronary in-stent restenosis were 90% (86%, 94%), 91% (90%, 93%) based on assessable stents, respectively (Figs 2, 3).

Diagnostic accuracy of 64-slice CT angiography with inclusion of non-assessable
stents was reported in 5 studies (15, 19, 20, 24, 26), an analysis was also performed with pooled sensitivity and specificity decreased to 79% (68%, 88%) and 81% (77%, 84%), respectively. Table 3 presents the pooled summary estimates of these studies based on assessable stents.

There was significant between-study heterogeneity in the sensitivity and specificity estimates in all analyses, with highly significant heterogeneity among the studies with regard to specificity (p<0.001). Therefore, we also performed a further analysis of these studies and ten of them fit into the criterion demonstrating between-study homogeneity (p>0.05, inconsistency, 0%) (15, 16, 19-25, 28). The pooled sensitivity and specificity of these ten studies were 89% (83%, 93%) and 89% (87%, 91%), which was not significantly different from those analyzed with inclusion of all of the 14 studies.

In addition, we analyzed the diagnostic value of 64-slice CT based on per patient assessment, which was available in 4 studies. The pooled estimates of sensitivity and specificity were 88% (95% CI: 76%, 95%) and 92% (95% CI: 86%, 96%), respectively, with no evidence of heterogeneity neither among the sensitivities nor the specificities (Fig 4, 5).

Quality assessment for all included studies was performed. Our results showed that all of the study findings were analyzed by 2-3 and 1-2 readers blindly for 64-slice CT and coronary angiography examinations, respectively, except in one study in which results were only interpreted by one reader (24). Although the majority of the 64-slice images were assessed by more than 2 readers, reports of findings of all readers or inter-observer agreement/reproducibility were only available in six studies, indicating the lack of adequate information in these reports.

Factors affecting diagnostic accuracy of 64-slice CT angiography
The most common factor that affects assessment of coronary stents is the stent diameter. This was addressed in six studies which compared the diagnostic accuracy of 64-slice CT angiography for detection of coronary in-stent restenosis based on different stent diameters (15, 19, 20, 23, 25, 28). However, a meta-analysis of the results arising from these studies could not be performed due to variable criteria used in each of the study. It is generally agreed from these studies that more stents were interpretable and better diagnostic performance was achieved for assessment of stents larger than 3 mm in diameter when compared to assessment of stents less than 3 mm (or less than <2.5 or 2.75 mm).

**Discussion**

Our study showed that 64-slice CT angiography has relatively high diagnostic value (>90% for sensitivity and specificity) and could be used as a reliable less invasive alternative to conventional coronary angiography for the detection of coronary in-stent restenosis, based on assessable stents. Our meta-analysis also confirmed that the diagnostic value of 64-slice CT angiography is significantly increased when compared to that acquired with 16-slice (90% vs 81%) as a result of the increased spatial and temporal resolution (12).

MSCT angiography in imaging of coronary stents is different from imaging of coronary artery tree as the diagnosis of coronary in-stent restenosis is not only influenced by the cardiac motion, but also by the metal component of the stent implanted. The presence of metal within the coronary stent can lead to high-density artifacts, commonly defined as blooming artifacts, subsequently obscuring of a considerable part of the stent lumen. This was confirmed by earlier MSCT scanners such as 4-slice CT, with the stent lumen being virtually invisible (7). With increased number of slice such as 16- and 64-slice scanners, improved visualization has been
reported to demonstrate improved diagnostic accuracy in imaging of coronary artery
disease and coronary stents and this has been confirmed in our study when compared
to earlier types of MSCT scanners.

Our previous study concluded that good diagnostic accuracy was achieved with a
combination of 16-and 64-slice CT angiography in the evaluation of coronary in-stent
restenosis (12). Two recently published studies involving the meta-analysis of
diagnostic accuracy of multislice CT angiography were based on a combination of 16-
and 64-slice imaging (31, 32). The results from these two analyses showed that the
sensitivity of multislice CT angiography was limited and insufficient to detect in-stent
restenosis when compared to conventional angiography. However, we need to point
out that these researchers only included 4 and 5 studies performed with 64-slice CT in
their analysis, therefore, their findings could be affected by including most of the
studies performed with 16-slice CT. In contrast, we specifically focused on the 64-
slice CT, which is the latest technical development in MSCT imaging, and it is
becoming widely available in clinical practice. Our analysis was comprehensive and
included 14 studies with 2 performed with dual source CT. We believe our analysis
represents the diagnostic trend of multislice CT angiography for detection of coronary
stents and evaluation of in-stent restenosis. Our results confirmed the theoretical
assumption that 64-slice angiography should be more accurate than 16-slice CT as it
showed improved diagnostic value in the detection of coronary in-stent restenosis
compared to that from 16-slice CT angiography.

While interpreting or comparing the results arising from 16- or 64-slice CT
angiography, attention must be paid with regard to the study design or method of
assessment of the coronary stents. This is mainly represented by the inclusion of
evaluable and nonevaluable stents in the data analysis. Of 14 studies analyzed,
inclusion of unevaluable stents was reported in 5 studies. When the unevaluable stents were taken into account, the pooled sensitivity and specificity of MSCT angiography was found to decrease significantly from 90% and 91% of inclusion of only evaluable stents to 79% and 81% with inclusion of both evaluable and unevaluable stents. The most common factor leading to unevaluable stents is the blooming artifacts caused by the metal component and severe calcification. Stent diameter also plays a significant role in determining the diagnostic accuracy of MSCT angiography for detection of coronary in-stent restenosis. Our analysis showed that even with improved MSCT scanning technique, evaluation of the coronary stents still remains challenging. Earlier studies performed by Gilard and Gaspar et al (33, 34) with 16-and 40-slice CT demonstrated a significant influence of stent diameter on evaluability, with 3.5 mm being a threshold below which rate of evaluable stents is very low. With dual source CT, the unevaluable rate is found to be only 5% as reported in one study (25), with a low rate of false negatives irrespective of stent diameter, while in the other study, all of the coronary stents were assessable (27). However, a significant reduction of the specificity of dual source CT was noticed when the stent diameter was less than 2.75 mm, indicating that it could not adequately predict the presence of in-stent restenosis. Therefore, the diagnostic value of 64-slice for evaluation of in-stent restenosis is still limited to larger stents (>3 mm). This is also confirmed by a recent study investigating the coronary stent assessability by 64-slice CT (35).

Another factor that affects visualization of coronary stents is the blooming effect which results from beam hardening and causes the stent struts to appear thicker than they are. The use of dedicated edge-enhancing convolution kernel allows a significant decrease in the severity of blooming artifacts at the edges of high-
attenuation structures (36). Of 14 studies we reviewed, sharp reconstruction/convolution kernel was applied in 11 studies, indicating the necessity for inclusion of it in the data postprocessing and analysis. Relatively higher sensitivity was achieved in most of the studies. A possible reason for quite low sensitivity in one study is most likely due to the inclusion of some small diameter stents (2.5 mm) in the study (16). While spatial resolution is increased with 64-slice CT and blooming artifacts are reduced by the application of edge-enhancing filters, an increase in image noise has to be accepted as a trade-off (36). Thus, the most appropriate postprocessing methods must be chosen so that diagnostic accuracy of MSCT angiography for detection of in-stent restenosis could be maximized while achieving a balance between the visualization of coronary stents and lumen and image noise.

Some limitations exist in our study. First, the publication bias exists and may affect the results as non-English publications were excluded. However, it is reported that language-restriction meta-analyses overestimated the treatment effect by only 2% on average compared with language-inclusive meta-analyses (37). Although it is apparent that more studies are being performed on 64-slice CT scanners (especially with dual source CT), it was difficult to include all of the potential studies in the analysis, especially those studies currently being undertaken or under review. Second, lack of uniform criteria of assessment is another limitation inherent in most of the studies. Not all of the studies provided complete data with regards to the type, diameter of the coronary stents implanted. Although we tried to contact some authors for obtaining additional information, this was not very successful. Third, a limitation of pooled sensitivities and specificities is that different positive criteria used in individual studies are not considered. Between-study heterogeneity is significant,
however, heterogeneity is not necessarily a limitation in meta-analysis (37), and it provides a key opportunity to show the consistent performance of the method. Finally, we did not analyze the possibility of publication bias in our meta-analysis. When there is publication bias, then, all other things being equal, the funnel plot will exhibit the ‘tell-tale’ wedge shape. However, other conditions will also give rise to this shape, so its presence does not necessarily demonstrate publication bias. Moreover, the publication bias issue becomes more important in the context of the meta-analysis of studies involving two independent groups, namely randomized controlled trials. This is not the case in our study, as our analysis involves comparison of 64-slice CT with conventional angiography in the same group of patients in each study.

In conclusion, our meta-analysis showed that 64-slice CT angiography has high diagnostic accuracy for the detection of coronary in-stent restenosis when compared to conventional coronary angiography. The diagnostic performance of MSCT angiography was mainly influenced by the diameter of the implanted coronary stents. With increased spatial and temporal resolution achieved with 64-slice CT and aid of appropriate edge-enhancing convolution kernel, 64-slice CT angiography could be used as a reliable alternative to conventional coronary angiography for the assessment of coronary stents larger than 3 mm. Future studies should focus on:

- studies based on a large cohort;
- inclusion of patients with low to moderate pretest probability of in-stent restenosis;
- more through and uniform investigation of modern stents with inclusion of variable stent sizes;
- uniform method of reports with inclusion of non-assessable stents;
• assessment of effect of strut thickness on the diagnostic performance of 64-slice.
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