Usefulness of 64-Slice Multislice Computed Tomography Coronary Angiography to Assess In-Stent Restenosis

Filippo Cademartiri, MD, PhD,*† Joanne D. Schuijf, MSC;‡§ Francesca Pugliese, MD,* Nico R. Mollet, MD, PhD,*† J. Wouter Jukema, MD, PhD;‡§ Erica Maffei, MD,† Lucia J. Kroft, MD, PhD;‡ Alessandro Palumbo, MD,† Diego Ardissino, MD,† Patrick W. Serruys, MD, PhD,* Gabriel P. Krestin, MD, PhD,* Ernst E. Van der Wall, MD, PhD;‡§ Pim J. de Feyter, MD, PhD,* Jeroen J. Bax, MD, PhD‡

Rotterdam, Leiden, and Utrecht, the Netherlands; and Parma, Italy

Objectives

This study sought to evaluate the diagnostic accuracy of 64-slice multislice computed tomography (MSCT) coronary angiography in the follow-up of patients with previous coronary stent implantation.

Background

Recent investigations have shown increased image quality and diagnostic accuracy for noninvasive coronary angiography with 64-slice MSCT as compared with previous-generation MSCT scanners, but data on the evaluation of coronary stents are scarce.

Methods

In 182 patients (152 [84%] male, ages 58 ± 11 years) with previous stent implantation (n = 192), 64-slice MSCT angiography using either a Sensation 64 (Siemens, Forchheim, Germany) or Aquilion 64 (Toshiba, Otawara, Japan) was performed. At each center, coronary stents were evaluated by 2 experienced observers and evaluated for the presence of significant (≥50%) in-stent restenosis. Quantitative coronary angiography served as the standard of reference.

Results

A total of 14 (7.3%) stented segments were excluded because of poor image quality. In the interpretable stents, 20 of the 178 (11.2%) evaluated stents were significantly diseased, of which 19 were correctly detected by 64-slice MSCT. Accordingly, sensitivity, specificity, and positive and negative predictive value to identify in-stent restenosis in interpretable stents were 95.0% (95% confidence interval [CI] 85% to 100%), 93.0% (95% CI 90% to 97%), 63.3% (95% CI 46% to 81%), and 99.3% (95% CI 98% to 100%), respectively.

Conclusions

In-stent restenosis can be evaluated with 64-slice MSCT with good diagnostic accuracy. In particular, a high negative predictive value of 99% was observed, indicating that 64-slice MSCT may be most valuable as a noninvasive method of excluding in-stent restenosis. (J Am Coll Cardiol 2007;49:2204–10) © 2007 by the American College of Cardiology Foundation

Stent implantation is increasingly performed in the treatment of significant coronary artery disease and has significantly reduced the occurrence of restenosis as compared with balloon angioplasty (1,2). Moreover, with the recent introduction of drug-eluting stents, the occurrence of in-stent restenosis has further decreased (3–5). Nonetheless, a subset of patients still presents with recurrent chest pain with possible in-stent restenosis, and frequently evaluation with invasive coronary angiography is required.

A noninvasive alternative approach to evaluating these patients may be offered by 64-slice multislice computed tomography (MSCT). In native coronary arteries, sensitivities and specificities of approximately 90% and 96% (6–9) for detection of coronary artery disease have been reported, with a substantial gain in diagnostic accuracy over 4- and 16-slice MSCT. Also the evaluation of coronary stents, which posed still considerable problems with 4- and 16-slice MSCT (10), may have improved with 64-slice MSCT. However, few data are currently available and the routine use of MSCT in patients....
with a history of stent implantation is at present not recommended (11,12). The purpose of the present study was to evaluate the diagnostic performance of 64-slice MSCT to identify in-stent restenosis (and occlusion) in comparison with the gold standard, invasive coronary angiography.

Methods

Study population. The study population consisted of 182 patients who were referred for invasive coronary angiography after previous coronary stent (≥2.5 mm diameter) implantation. Referral of patients for invasive coronary angiography was partially part of an ongoing protocol and partially routine (based on the presence of symptoms, abnormal exercise electrocardiogram [ECG], and/or ischemia on myocardial perfusion imaging). In addition to invasive coronary angiography, 64-slice MSCT was performed. Exclusion criteria were the following: 1) atrial fibrillation, 2) renal insufficiency (serum creatinine >120 mmol/l), 3) known allergy to iodine contrast media, 4) pregnancy, and 5) coronary stent diameter <2.5 mm. The study was approved by the ethical committee of the different centers, and all participating patients gave informed consent.

Scan protocol and image reconstruction. The MSCT angiography was performed with 2 different 64-slice MSCT scanners (Sensation 64, Siemens, Germany n = 150, and Aquilion 64, Toshiba Medical Systems, Japan, n = 32). Thirty-four patients (19%) had a prescan heart rate >80 beats/min, and were given a single oral dose of 100 mg metoprolol 1 h before the examination in the absence of contraindications. A bolus of 100 ml iomeprol (400 mg iodine/ml; Iomeron, Bracco, Milan, Italy) was intravenously injected (4 to 5 ml/s) followed by 50 ml of saline at the same rate using a double-head injector (Stellant, MedRAD, Pittsburgh, Pennsylvania). To trigger the start of the scan, a real-time bolus tracking technique was used (13). During the scan, which was performed during an inspiratory breath hold of 8 to 12 s, the MSCT data and ECG trace were acquired. Scan parameters were (for Siemens and Toshiba, respectively): individual detector collimation 32 × 2 × 0.6 mm and 64 × 0.5 mm, tube voltage 120 kV for both, mAs 900 and 712, gantry rotation time 330 and 400 ms. No ECG pulsing was used.

Reconstruction parameters (for Siemens and Toshiba, respectively): effective slice width 0.75 and 0.5 mm, increment 0.4 and 0.3 mm, standard and sharp heart view convolution filters for both. For Siemens, B30f and B46f were used, whereas for Toshiba, Q04 was used in addition to Q05 to Q07.

Synchronized to the recorded ECG, axial slices were reconstructed from the acquired MSCT data with the use of segmented or half reconstruction algorithms.

Image data sets were reconstructed during the mid-to-end diastolic phase, during which coronary artery displacement is relatively small, with reconstruction window positions starting at 400 ms before the next R wave and/or at 75% of the R-to-R interval. If indicated, additional temporal window positions were explored, including the end-systolic phase to obtain images with least motion artefacts.

MSCT image interpretation. At each center, 2 observers, both blinded to angiographic and clinical findings but aware of previous cardiac history, evaluated the MSCT examinations using axial slices and multiplanar and curved reconstructions (P.J.F., F.C., J.W.J., and J.D.S.). Of note, different window settings, including 1,500/300 HU, were used for optimal stent assessment.

A stent was judged to be occluded when the lumen inside the stent was darker than the contrast-enhanced vessel before the stent and/or when no run-off could be visualized at the distal end of the stent (14,15).

Nonocclusive in-stent restenosis was considered when the lumen inside the stent showed a darker rim (eccentric or concentric) between the stent and the enhanced vessel lumen with a lumen reduction ≥50% (as compared with other portions of the stent). In addition, the presence of reduced run-off distal to the stent was taken into consideration; if reduced distal run-off was observed, this was found to be suggestive of in-stent restenosis. Importantly, the presence of distal run-off was not used as a criterion for the absence of significant in-stent restenosis, because collateral filling may occur (which cannot be detected adequately by MSCT). In Figures 1, 2, and 3, examples are provided of patent and diseased stents.

Invasive coronary angiography. Conventional selective coronary angiography was performed with standard techniques and evaluated by a reviewer blinded to the MSCT results with the use of quantitative coronary angiography systems (CAAS II, Pie Medical, Maastricht, the Netherlands, or QCA-CMS version 6.0, Medis, Leiden, the Netherlands). The diameter stenosis, as a percentage of the reference diameter, was determined in 2 orthogonal directions and the average between these 2 values determined the stenosis severity.

Statistical analysis. Sensitivity, specificity, positive and negative predictive values (including 95% confidence interval [CI]) for the detection of in-stent restenosis ≥50% using conventional angiography in combination with quantitative coronary angiography as the gold standard, were calculated. All statistical analyses were performed using SPSS software (version 12.0, SPSS Inc., Chicago, Illinois). A value of p < 0.05 was considered statistically significant.

Results

Patient characteristics. In total, 182 patients (152 male, ages 57.8 ± 10.6 years) with a total of 192 coronary stents were enrolled in the study. A total of 4 patients were not
enrolled because of the presence of stents with a diameter <2.5 mm. Also, 5 patients were not studied because of a high heart rate in combination with beta-blocker intolerance. Baseline characteristics of the study population are provided in Table 1. The average time interval between stent implantation and 64-slice MSCT coronary angiography was 6.2 ± 1.6 months; 64-slice MSCT and conventional angiography were performed within 1 month of each other (average 9 ± 8 days); MSCT was always performed first. The site of stent implantation was: right coronary artery in 55 (28.6%), left main coronary artery in 11 (5.7%), left anterior descending coronary artery in 113 (58.9%), and left circumflex coronary artery in 13 (6.8%). Average stent diameter was 3.1 ± 0.4 mm (range 2.5 to 4.5 mm), whereas stent length ranged from 8 to 33 mm (average 18 ± 7 mm). Eight different stent types were evaluated, the non–drug-eluting stents being Vision (Guidant, Santa Clara, California), Driver (Medtronic, Minneapolis, Minnesota), Ave S7 (Medtronic), Orbus (Orbus Technologies, Hoevelaken, the Netherlands), Bx Velocity (Cordis Corp., Johnson & Johnson, Miami, Florida), and Liberte (Boston Scientific, Boston, Massachusetts). Included drug-eluting stents were Cypher (Cordis Corp.) and Taxus (Boston Scientific). Average heart rate during MSCT data acquisition was 60 ± 7.9 beats/min.

Coronary stent analysis. In total, 178 stents were available for evaluation, whereas 14 stents (7.3%) were considered uninterpretable because of residual motion and high-density artefacts (Table 2). No significant differences were observed in interpretability between the different stent diameters; 3

**Figure 1** Example of a Patent Stent

Conventional coronary angiography (A) showed patency of a stent (Cypher, 3.0 × 18 mm) placed in the left circumflex coronary artery. (B and C) Two orthogonal curved multiplanar reconstructions obtained with 64-slice MSCT (Siemens Sensation, kernel B46f) are provided, also showing patency of the stent. MSCT = multislice computed tomography.

**Figure 2** Example of In-Stent Restenosis

Conventional coronary angiography (A) showed in-stent restenosis in a stent (Taxus, 2.5 × 20 mm) placed in the second marginal branch of the left circumflex coronary artery (arrowhead). (B) A curved multiplanar reconstruction obtained with 64-slice MSCT (Siemens Sensation, kernel B46f) is provided. In the proximal part of the stent (arrowhead), a hypodense area can be observed, indicating the presence of in-stent restenosis. Abbreviations as in Figure 1.
(5.8%) of 52 stents with a diameter <3 mm were uninterpretable, whereas 7 (10%) of 70 and 4 (5.7%) of 70 stents with diameters of respectively 3 mm or >3 mm were uninterpretable (Table 3).

The incidence of significant in-stent restenosis (nonocclusive in-stent restenosis and total stent occlusions) was 11.2% (20 of 178), as determined by conventional angiography. Examples of patent stents as well as stents with significant in-stent restenosis are provided in Figures 1, 2, and 3, respectively.

All 7 stent occlusions were correctly identified by 64-slice MSCT, whereas 1 stent (located in the second diagonal) of 13 stents with significant but nonocclusive in-stent restenosis remained undetected by MSCT. Of the 158 stents without significant in-stent restenosis, 147 were correctly evaluated by 64-slice MSCT, whereas 11 stents were incorrectly considered positive. Accordingly, the overall sensitivity, specificity, and positive and negative predictive value to detect significant in-stent restenosis were 95.0% (19 of 20, 95% CI 85% to 100%), 93.0% (147 of 158, 95% CI 90% to 97%), 63.3% (19 of 30, 95% CI 46% to 81%), and 99.3% (147 of 148, 95% CI 98% to 100%), respectively. More detailed information is listed in Table 2. In stents without significant stenosis on conventional angiography, average percentage stenosis as determined by quantitative coronary angiography was significantly higher in stents falsely classified as positive on MSCT as compared with stents correctly classified as negative (36% vs. 25%, p <
Similarly, average percentage stenosis was lower in stents false-negative on MSCT as compared with correct positive stents (65% vs. 73%, p = NS).

In a subanalysis, the rate of false diagnosis was evaluated according to stent diameter. In stents with a diameter <3.0 mm, 3 (6.1%) of 49 stents were incorrectly diagnosed. For stents with a diameter of 3.0 mm, this percentage was 1.6% (1 of 63), whereas in stents with a diameter >3.0 mm, incorrect diagnosis was obtained with MSCT in 8 of 66 (12.0%). More details on the rate of false positives and negatives are provided in Table 3. In Table 4, the results from the 2 scanners from the 2 centers are reported separately. At the Leiden center, relatively more stents were deemed uninterpretable as compared with the Rotterdam center (14.3% vs. 5.3%, p = NS). Diagnostic accuracy was slightly lower in the Rotterdam center (91.5% vs. 100%, p < 0.05). However, when all stents (including the uninterpretable stents) were included in the analysis, no significant differences were observed.

### Discussion

In the present study, a sensitivity and specificity of respectively 95% and 93% were observed for the noninvasive detection of coronary in-stent restenosis. In addition, a negative predictive value of 99% was observed, suggesting that 64-slice MSCT may allow reliable exclusion of in-stent restenosis before more invasive procedures such as conventional coronary angiography.

During MSCT imaging, visualization of stents is particularly challenging because of the metallic struts resulting in blooming artifacts (16). Accordingly, the stent wall appears enlarged on the MSCT images, which in turn affects the capability to visualize the in-stent lumen. The extent of this artefact depends on the material and design of the stent, with more severe artefacts in stents with high metal content. Although this effect is of minor or no importance in large vessels, such as the aorta and its abdominal branches, it can considerably impair the visualization of the lumen in smaller vessels such as the coronary arteries (16).

Not surprisingly, therefore, visualization of stent lumen could not be achieved in preliminary investigations using 4-slice MSCT scanners (10). In a more recent report, 16-slice MSCT was applied, resulting in a sensitivity and specificity of 78% and 100% (15). Nonetheless, 15 (23%) of the 65 included stents were uninterpretable, indicating still a limited value for MSCT coronary angiography in populations with previous stent implantation (15). More detailed analysis of these 15 uninterpretable stents revealed that stent assessability seems to be highly dependent on stent type and size in particular. These observations were further underlined by Gilard et al. (17), who showed, in 143 patients undergoing 16-slice MSCT, an increase of stent interpretability from 51% for stents ≤3.0 mm to 81% when only stents >3.0 mm were included. More recently, data on stent evaluation using more advanced MSCT technology were reported by Gaspar et al. (18), who evaluated 65 patients with 111 implanted coronary stents using 40-slice MSCT. A considerable improvement in image quality was witnessed in this study because only a small number of stents (n = 5, 5%) were of nondiagnostic image quality. Considering these

### Results From the 2 Scanners From the 2 Centers Separately

<table>
<thead>
<tr>
<th></th>
<th>Rotterdam, Siemens Sensation 64-Slice Stents (%)</th>
<th>Leiden, Toshiba Aquilion 64-Slice Stents (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assessable</td>
<td>142/150 (94.7%, 91%–99%)</td>
<td>36/42 (85.7%, 76%–96%)</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>15/16 (93.8%, 82%–100%)</td>
<td>4/4 (100%)</td>
</tr>
<tr>
<td>Specificity*</td>
<td>115/126 (91.3%, 86%–96%)</td>
<td>32/32 (100%)</td>
</tr>
<tr>
<td>Positive predict value*</td>
<td>15/26 (57.7%, 39%–77%)</td>
<td>4/4 (100%)</td>
</tr>
<tr>
<td>Negative predict value</td>
<td>115/116 (99.1%, 97%–100%)</td>
<td>32/32 (100%)</td>
</tr>
<tr>
<td>With uninterpretable stents included</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>15/17 (88.2%, 82%–100%)</td>
<td>4/4 (100%)</td>
</tr>
<tr>
<td>Specificity</td>
<td>115/133 (86.5%, 80%–92%)</td>
<td>32/38 (84.2%, 72%–96%)</td>
</tr>
<tr>
<td>Positive predict value</td>
<td>15/33 (45.5%, 28%–62%)</td>
<td>4/10 (40.0%, 10%–70%)</td>
</tr>
<tr>
<td>Negative predict value</td>
<td>115/117 (98.3%, 95%–100%)</td>
<td>32/32 (100%)</td>
</tr>
</tbody>
</table>

*p < 0.05 between 2 centers.
5 stents as having restenosis, the investigators reported a sensitivity and specificity for detection of in-stent restenosis of 89% and 81%, respectively.

These observations are further underlined by the first ex vivo reports on stent evaluation with 64-slice MSCT, suggesting further improvement in stent visibility as well a reduction of artificial lumen narrowing as compared with 16-slice MSCT (19,20). Also in vivo promising results were reported using 64-slice MSCT by Rist et al. (21), who could evaluate 45 (98%) of 46 stents with a sensitivity and specificity of 75% and 92%, respectively. Nonetheless, somewhat discouraging results were recently reported by Rixe et al. (22), who performed 64-slice MSCT in 64 patients with 102 previously implanted stents. Similar to our study, 64-slice MSCT was shown to be highly accurate, with reported sensitivity and specificity of 86% and 98%, respectively. However, evaluation could be performed in only 58% of stents, indicating a major limitation of the current technique. In contrast, only 7% of stents were deemed uninterpretable in our present study. To a large extent this discordance may be caused by differences in image interpretation. In our present study, evaluation was performed with the intention to diagnose to allow generalization of results as much as possible to daily clinical routine. Thus, only stents with severely degraded image quality were excluded. In contrast, a more stringent approach was performed by Rixe et al., and in their study, stents were deemed uninterpretable in the presence of any artifact, albeit small. Importantly, both in their study as well as ours, a high negative predictive value was obtained (98% and 99%, respectively), implying a potential role for MSCT to exclude in-stent restenosis in patients presenting with chest pain after stent implantation.

**Study limitations.** Several limitations should be addressed. First, only patients having stents with a diameter $\geq 2.5$ mm were included, whereas stents $< 2.5$ mm, which may be encountered in 3% to 5% of patients with previous stent placement, were excluded, because at present they cannot be evaluated accurately with MSCT. Accordingly, the results obtained in the present study may not be generalizable to other populations with different stent characteristics. Second, as previously reported with MSCT coronary angiography, only patients with stable and low heart rates were included in this study, and a high percentage received additional beta-blockers to further reduce heart rate. Accordingly, the results of the present study may not apply to the general population, because in addition to patients with smaller stents, also patients with atrial fibrillation and contraindications to beta-blocking medication were not studied. Third, in-stent restenosis was only present in a small number of stents (11%). However, the findings reflect the current clinical situation, with low in-stent restenosis rates (3–5). In addition, data acquisition was performed in 2 different centers using 2 different 64-slice MSCT systems, which may have influenced the results. Also, no data on interobserver variability were available. Finally, several disadvantages are inherent to the technique itself, including the high radiation exposure (15 to 20 mSv) (23,24) and use of iodinated contrast, which remain a matter of concern for routine use of this technique. Also, an important limitation of MSCT remains the fact that only anatomical information is obtained, whereas the presence or absence of ischemia cannot be established from the MSCT images. Accordingly, in patients with significant restenosis, functional testing remains mandatory to determine further management.

**Conclusions**

In-stent restenosis can be evaluated with 64-slice MSCT with good diagnostic accuracy. In particular, a high negative predictive value of 99% was observed, indicating that 64-slice MSCT may be most valuable to exclude in-stent restenosis.

**Reprint requests and correspondence:** Dr. Jeroen J. Bax, Department of Cardiology, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, the Netherlands. E-mail: jbbox@knwore.nl.

**REFERENCES**


