Assessment of In-Stent Restenosis Using High-Definition Computed Tomography With a New Gemstone Detector

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Background: Until now, there have been few reports on the accuracy of in-stent restenosis (ISR) detection using high-definition computed tomography (HDCT). The purpose of this study was to assess ISR using HDCT with a new gemstone detector and to examine the diagnostic accuracy compared with invasive coronary angiography.

Methods and Results: We evaluated 162 consecutive patients with 316 stents and the image quality (IQ) scores used to assess ISR, and analyzed whether stent strut thickness and diameter affected IQ score and assessability. In the 316 stents, 278 were diagnosed as assessable with HDCT (88.0%). IQ score for stent diameter $\geq$3 mm was significantly higher than that for stent diameter <3 mm, for stents with both thick struts $\geq$140 $\mu$m in thickness (mean IQ: 2.04±0.97 vs. 2.83±1.06, P=0.001) and thin struts <140 $\mu$m (mean IQ: 1.92±0.87 vs. 2.64±0.96, P=0.01). Assessability for stent diameter $\geq$3 mm was significantly higher than that for stent diameter <3 mm only for stents with thick struts (92.8% vs. 76.1%, P<0.001). Stent strut thickness, however, was not statistically significantly associated with either IQ score or assessability.

Conclusions: In-stent lumens have high HDCT assessability, and HDCT is useful to evaluate thick-strut stents with diameter <3 mm.

Key Words: Computed tomography; Diagnosis; Restenosis; Stent

Percutaneous coronary intervention with stent implantation reduces restenosis of culprit lesions compared with plain-old balloon angioplasty alone. Moreover, drug-eluting stents (DES) have remarkably improved results by preventing excessive neo-intimal hyperplasia of coronary arteries, so that they are now widely used for small vessels, long lesions, and those with bifurcations, for example. But even in the DES era, lesion complexity or patient comorbidities are related to restenosis. Recently, computed tomography coronary angiography (CTCA) has become established in the non-invasive assessment of coronary stents. Multi-slice computed tomography (MSCT) or multi-detector computed tomography (MDCT) with 64-slice technology has improved the spatial resolution with a sensitivity of 82–95% and a specificity of 82–98% for de novo lesions of the coronary artery. Reports so far have indicated that MSCT or MDCT have a sensitivity of 90–95%, and a specificity of 73–93% for detecting in-stent restenosis (ISR). It is sometimes difficult, however, to assess in-stent lumens due to stent strut artifacts. Moreover, stents with diameter <3 mm are reported to have lower assessability than those $\geq$3 mm. As an alternative method, stress tests could be used for non-invasive detection of ISR, but unfortunately the diagnostic accuracy is not so high. Although invasive coronary angiography (ICA) is the most reliable method for assessing ISR, there are disadvantages due to the possible serious complications during the procedure, and high cost. Thus, CTCA is the preferred modality to detect ISR in patients undergoing previous coronary stent implantation because it can visualize the in-stent lumen, non-invasively.

Discovery CT 750HD (GE Healthcare Technologies, WI, USA) is a high-definition CT (HDCT) machine with a new gemstone detector (GE Gemstone TM detector). Gemstone is a complex rare earth-based oxide that has a chemically replicated garnet crystal structure, and has a primary speed of only 30 ns (100-fold faster than existing detectors) and low afterglow (4 times lower), which is a key contributor to fast kVP switching acquisition through its scintillator and data acquisition.
The total amount of contrast medium was estimated according to the patient body weight, scan time and heart rate (21 mgI·kg⁻¹·s⁻¹). A test injection method was used; 12 ml of bolus contrast medium was given at the prior speed with 20 ml saline, then the region of interest was set within the ascending aorta. The scan was started approximately 3 s after the contrast medium reached the ascending aorta and was performed between the tracheal bifurcation and diaphragm with the following parameters: collimation width 64×0.625 mm, rotation time 350 ms, tube voltage 120 kV, effective tube current 600 mA, table feed 8 mm/rotation, and pitch 0.2.

Data Acquisition
Image reconstruction was retrospectively gated to an electrocardiogram, and the optimal cardiac phase showing the minimum motion artifact was determined. Depending on the heart rate during examination, a non-helical scan (heart rate ≤60 beats/min) or a helical scan (heart rate >60 beats/min) were selected for scanning and then axial slices were reconstructed according to an algorithm synchronized to the electrocardiogram. R-wave indicators were manually repositioned to improve the quality. Non-helical and helical methods scanned approximately 75%, and only 40–50% of the R-R time of the diastolic phase, respectively. The latter needed more cardiac cycle phases to scan the whole coronary segment for improvement of image.

The CTCA data generated were transferred to an offline workstation (Advantage Workstation Volume Share4.4, GE Healthcare Technologies) for image analysis. Cross-sectional multi-planar reconstruction (MPR) images of the stents and curved-planar reconstruction (CPR) images through the median of the stents were reconstructed for assessing in-stent lumen, and transferred to Wizard.
High-Definition CT Assessment of ISR

CTCA
CTCA image quality (IQ) of stented segments was visually classified into 5 groups using a 5-point grade scale on the basis of the MPR and CPR images: 1, excellent (stent and in-stent lumen were distinct, without any artifact); 2, good (stent and in-stent lumen were clear, with few artifacts, and assessable); 3, adequate (stent and in-stent lumens were partially clear, with moderate artifacts, and assessable); 4, insufficient (stent and in-stent lumens were indistinct, with obvious artifacts, and only partially assessable); and 5, non-assessable. Images with scores 1–3 were defined as diagnostic, and those with scores 4, 5 as non-diagnostic (Figure 1). The IQ was evaluated by 2 skilled observers. Moreover, inter- and intra-observer variability were assessed.

Contrast attenuation inside and at both edges of the stents compared with the vessel lumen was regarded as neointimal proliferation. Reconstructed CTCA images of stented segments were visually classified into 4 grades using the following criteria: grade 1, no or slight neointimal proliferation; grade 2, mild neointimal proliferation but no significant restenosis (<50% narrowing); grade 3, moderate neointimal prolifer-

eration with significant restenosis (≥50% narrowing); grade 4, neointimal proliferation with severe stenosis or total occlusion (≥75% narrowing or occlusion). Two skilled observers evaluated the grades of all images while blinded to ICA and each other’s data. Significant ISR was defined as grade 3 or 4.

ICA
The ICA was performed with standard techniques, and at least 4–6 different views were obtained for assessing each main vessel and major side branch. All stented segments, including 5 mm proximal and distal to stent edges, were evaluated by 2 skilled observers. Segments were classified into 4 groups according to percentage of diameter stenosis (%DS). Binary ISR was visually defined as %DS ≥50% in stented segments on ICA, and the accuracy of CTCA for detecting ISR was assessed in comparison with ICA results.

Table 1. Patient Characteristics

| Characteristic                        | Value          |
|--------------------------------------|----------------|
| Gender (M/F)                         | 119/43         |
| No. stents/patient                   | 2.0±1.0 (1–6)  |
| Age (years)                          | 68.1±8.4 (49–84)|
| BMI (kg/m²)                          | 23.8±3.2 (17.0–38.1)|
| Hypertension                         | 89 (54.9)      |
| Diabetes mellitus                    | 59 (36.4)      |
| Dyslipidemia                         | 63 (38.9)      |
| Old myocardial infarction            | 68 (56.7)      |
| History of CABG                      | 10 (6.2)       |

Table 2. Stent Characteristics

| Characteristic                        | Value          |
|--------------------------------------|----------------|
| Stent location                       |                |
| Right coronary artery                | 88 (27.8)      |
| Left anterior descending artery      | 167 (52.8)     |
| Left circumflex artery               | 61 (19.3)      |
| Stent characteristics                |                |
| Bare-metal                           | 89 (28.2)      |
| Drug-eluting                         | 227 (71.8)     |
| Cypher                               | 197            |
| Stent diameter (mm)                  | 3.00±0.46 (2.25–4.0) |
| Stent length (mm)                    | 18.3±5.6 (8–33) |
| Post-dilatation pressure (atm)       | 18.2±4.9 (8–30) |
| Post-dilatation diameter (mm)        | 3.32±0.59 (2.0–5.2) |

Figure 2. Flow chart for patient inclusion. HDCT, high-definition computed tomography; ICA, invasive coronary angiography.
was 68.1±8.4 years (range, 49–84 years). Ten patients experienced previous coronary artery bypass surgery, but no stents were implanted in the grafts (Table 1). In total, 316 stents (2.0 stents per patient) were assessed on HDCT, 88 located in the right coronary artery, 167 in the left anterior descending artery, and 61 in the left circumflex artery. Some 227 (71.8%) were DES, including 197 Cypher stents (62.3%; Cordis, Miami, FL, USA). Mean length and mean diameter were 3.00±0.46 mm and 18.3±5.6 mm, respectively, and 157 stents (49.7%) were <3.0 mm in diameter (Table 2). Mean heart rate during HDCT was 61.9±7.8 beats/min, and the percentage of patients with

### Statistical Analysis

All data were analyzed with SPSS statistics 22 (IBM, Armonk, NY, USA). Patient data and quantitative variables are expressed as mean±SD and range. P<0.05 was considered statistically significant.

### Results

#### Patient Characteristics

The flow chart for this study is given in Figure 2. Among 162 patients, 119 were male and 43 were female, and mean age was 68.1±8.4 years (range, 49–84 years). Ten patients experienced previous coronary artery bypass surgery, but no stents were implanted in the grafts (Table 1). In total, 316 stents (2.0 stents per patient) were assessed on HDCT, 88 located in the right coronary artery, 167 in the left anterior descending artery, and 61 in the left circumflex artery. Some 227 (71.8%) were DES, including 197 Cypher stents (62.3%; Cordis, Miami, FL, USA). Mean length and mean diameter were 3.00±0.46 mm and 18.3±5.6 mm, respectively, and 157 stents (49.7%) were <3.0 mm in diameter (Table 2). Mean heart rate during HDCT was 61.9±7.8 beats/min, and the percentage of patients with

#### Figure 3

Image quality score distribution: 1, excellent; 2, good; 3, adequate; 4, insufficient; 5, non-assessable.

### Table 3. Baseline Characteristics vs. Image Quality Score

| Image quality score | P-value† |
|---------------------|----------|
| 1–3                 | 4, 5     |
| Gender (M/F)        |          |
| 108/38              | 11/5     | 0.77 |
| No. stents/patient  |          |
| 1.86±1.12 (1–6)     | 2.64±1.34 (1–5) | 0.01 |
| Age (years)         |          |
| 68.2±8.46           | 66.8±7.34 | 0.53 |
| BMI (kg/m²)         |          |
| 23.8±3.24           | 23.7±3.29 | 0.90 |
| Hypertension        |          |
| 84 (57.1)           | 5 (35.7) | 0.12 |
| Diabetes mellitus   |          |
| 53 (36.1)           | 6 (42.9) | 0.77 |
| Dysplasia           |          |
| 59 (40.1)           | 4 (28.6) | 0.57 |
| Old myocardial infarction | 63 (42.9) | 5 (35.7) | 0.78 |
| History of CABG     |          |
| 8 (5.4)             | 2 (14.3) | 0.21 |
| Heart rate during HDCT (beats/min) | 61.5±7.6 | 65.0±9.2 | 0.16 |
| Stent location      |          |
| Right coronary artery | 77 (27.7) | 11 (29.0) | 0.87 |
| Left anterior descending artery | 141 (50.7) | 26 (68.4) | 0.06 |
| Left circumflex artery | 60 (21.6) | 1 (2.63) | 0.006 |
| Stent characteristics|          |
| Bare-metal          |          |
| 83 (29.9)           | 6 (15.8) | 0.08 |
| Drug-eluting        |          |
| 195 (70.1)          | 32 (84.2) | 0.07 |
| Cypher              |          |
| 168 (60.4)          | 29 (76.3) | 0.06 |
| Stent diameter (mm) |          |
| 3.05±0.46 (2.25–4)  | 2.70±0.30 (2.5–4) | <0.0001 |
| Stent length (mm)   |          |
| 18.3±5.6 (8–33)     | 18.3±5.8 (8–33) | 0.99 |
| Post-dilatation pressure (atm) | 18.2±4.9 (8–27) | 18.4±5.0 (8–30) | 0.84 |
| Post-dilatation diameter (mm) | 3.36±0.57 (2.33–5.2) | 3.00±0.62 (2–4.63) | 0.003 |

Data given as mean±SD (range) or n (%). †Chi-squared test. HDCT, high-definition computed tomography. Other abbreviations as in Table 1.
High-Definition CT Assessment of ISR

HDCT and ICA was also obtained (r=0.85, P=0.02). Of the 259 stents, 80 underwent ICA, with no ISR detected. In assessable stents, the assessability of the in-stent lumen on HDCT was 88.0%, with a sensitivity of 100%, specificity of 98.8%, positive predictive value of 94.4%, and negative predictive value of 100%.

IQ Score and HDCT Assessability

Moreover, all stents were divided into thick-strut stents with diameter ≥3 mm, thin-strut stents with diameter ≥3 mm, thick-strut stents with diameter <3 mm, and thin-strut stents with diameter <3 mm. Thick-strut stents were defined as having strut thickness ≥140 μm, which included only Cypher and Bx-VELOCITY stents (Cordis) in this study, and thin struts as <140 μm in thickness. Moreover, differences in IQ score and assessability among groups were also investigated, to determine whether stent strut thickness and stent diameter affected IQ score and assessability. IQ score for stent diameter ≥3 mm was significantly higher than that for stent diameter <3 mm for stents with both thick struts ≥140 μm (mean IQ: 2.04±0.97 vs. 2.83±1.06, P<0.001) and thin struts <140 μm (mean IQ:

| Image quality score | Thick-strut stent (no. stents=199) | Thin-strut stent (no. stents=117) |
|---------------------|-------------------------------------|-----------------------------------|
|                     | ≥3 mm (no. stents=111)               | <3 mm (no. stents=88)             |
|                     | ≥3 mm (no. stents=92)               | <3 mm (no. stents=25)             |
| 1                   | 36                                  | 8                                 |
| 2                   | 47                                  | 27                                |
| 3                   | 20                                  | 32                                |
| 4                   | 5                                   | 14                                |
| 5                   | 3                                   | 7                                 |

Image quality score (mean±SD) 2.04±0.97 2.83±1.06 1.92±0.87 2.64±0.96

P<0.001†  P=0.89†  P=0.01†  P=0.93†

†Chi-squared test.

Accuracy of HDCT ISR Detection

In the 316 stents, 38 (12.0%) could not be evaluated because of poor IQ, with HDCT IQ scores of 4 and 5. In 278 stents, 19 were diagnosed as having ISR, with IQ scores 1–3. Of these latter, 1 could not be assessed on ICA because informed consent was not able to be obtained from the patient who was symptom free, and the other 18 were also diagnosed as having ISR on ICA (1 was at a fracture site, 7 at overlap sites, 1 at bifurcation site, and 9 were simple ISR). Correlation between HDCT and ICA was also obtained (r=0.85, P=0.02). Of the 259 stents, 80 underwent ICA, with no ISR detected. In assessable stents, the assessability of the in-stent lumen on HDCT was 88.0%, with a sensitivity of 100%, specificity of 98.8%, positive predictive value of 94.4%, and negative predictive value of 100%.

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Moreover, all stents were divided into thick-strut stents with diameter ≥3 mm, thin-strut stents with diameter ≥3 mm, thick-strut stents with diameter <3 mm, and thin-strut stents with diameter <3 mm. Thick-strut stents were defined as having strut thickness ≥140 μm, which included only Cypher and Bx-VELOCITY stents (Cordis) in this study, and thin struts as <140 μm in thickness. Moreover, differences in IQ score and assessability among groups were also investigated, to determine whether stent strut thickness and stent diameter affected IQ score and assessability. IQ score for stent diameter ≥3 mm was significantly higher than that for stent diameter <3 mm for stents with both thick struts ≥140 μm (mean IQ: 2.04±0.97 vs. 2.83±1.06, P<0.001) and thin struts <140 μm (mean IQ:
1.92±0.87 vs. 2.64±0.96, P=0.01; Table 4). Assessability for stent diameter ≥ 3 mm was significantly higher than that for stent diameter < 3 mm only for stents with thick struts (92.8% vs. 76.1%, P<0.001; Figure 4). Stent strut thickness, however, was not statistically significantly associated with either IQ score or assessability.

**Discussion**

This study evaluated symptomatic or asymptomatic patients with clinical indications for potential ISR, using HDCT. Only 38 stents (12.0%) proved impassable because of motion or stent strut artifacts. In prior studies the clinical utility of 64-MDCT for assessing coronary stenosis was good, in that it had good sensitivity, specificity, and positive and negative predictive values. Few, however, have reported on the accuracy of HDCT for ISR detection.

Partial volume artifacts from stent materials lead to blooming and artificial lumen narrowing. Given that the stents are small, they may be less likely to be visualized or assessed on HDCT because they are within the shadow of the partial volume artifacts created by metal stent struts. Oncel et al showed good performance of 64-detector row CT for detection of ISR, but stents with diameter ≥ 2.5 mm were excluded from their study and the average stent diameter was 3.1±0.1 mm. A larger stent naturally provides fewer blooming artifacts and is more visible, which leads to more accurate ISR quantification. Stent strut thickness is also related to ISR detection. For example, thick-strut stents (>140 μm) are reported to have low sensitivity on MDCT as compared with thin-strut stents (<140 μm). Another report suggested that tantalum, gold or gold-coated stents, and covered stent grafts had reduced visualization of the lumen compared with stainless steel or cobalt stents.

The present study included both 2.25-mm and 2.5-mm stents (a total of 105/33.2%), classified as small stents, but Cypher stent was used at a high rate (62.3%), these being made of stainless steel, but with a strut thickness of 140 μm which provides severe artifacts on evaluation of the in-stent lumen.25,26

A previous study reported that the assessability of thick-strut stents with diameters ≥ 3 mm and < 3 mm on MDCT was 85% and 25%, respectively. In both the thick-strut and thin-strut groups, stents with diameter ≥ 3 mm had higher IQ score than those with diameter < 3 mm, but for the thick-strut stents this was not statistically significant. Moreover, in the thick-strut stents, those with diameter ≥ 3 mm had significantly higher assessability than their < 3-mm-diameter counterparts. We showed that the assessability of 92.8% for thick-strut stents with diameter ≥ 3 mm and that of 76.1% for < 3 mm, respectively, was evidence of good utility for evaluation of in-stent lumen, which was much more accurate in comparison with the previous study, in particular with regard to thick-strut stents with diameter ≥ 3 mm.

Recently, late catch-up phenomena or neo-atherosclerosis of the in-stent lumen have been reported for Cypher stents. Very late stent thrombosis in DES also remains an unresolved problem after incomplete healing, which leads to stent malapposition and incomplete re-endothelialization. Although the Cypher stent, a first-generation DES, is no longer implanted in new lesions, there are a considerable number of patients with this type, who need continued care. The high sensitivity, specificity, and negative predictive value of HDCT suggest that patients assessed as visible no-ISR can avoid ICA with its associated risks. ICA also may not be suitable to assess or follow-up ISR lesions on a regular basis, which is the same in the research field. Such invasive techniques, however, as intravascular ultrasonography or optical coherence tomography can provide more accurate information on lesion dimensions or other characteristics. HDCT evaluation for these assessable lesions could be useful for detecting changes in the long term.

**Study Limitations**

The limitations of this study were as follows: first, only a relatively small number of patients underwent HDCT. They were enrolled, however, for clinical indications, so this study can be considered as well-balanced because of the reasonable stent number and high rate of DES use, leading to less likelihood of ISR, similar to others. Overall, significant ISR was detected in only 18 stents (12.0%). If inassessable stents were included, overall sensitivity and specificity would obviously be decreased. And second, the radiation dose was comparatively high. Reduction of radiation is important because of the association with long-term cancer risk. Reduction of radiation exposure was greatest in patients with a heart rate ≤ 60 beats/min because they underwent non-helical shots, whereas the effective dose was significantly higher in those with heart rate > 60 beats/min because of the necessity for helical shots, which require acquisition of data over multiple cardiac cycles to improve temporal resolution, reconfirming the importance of β-blocker use. In this study, only 45% of patients received β-blockers to reduce heart rate, indicating that more effort is needed decrease the radiation dose. The relatively high radiation dose is one of the remaining problems of HDCT, but this may be expected to be reduced in the future, with the introduction of new technology.

**Conclusions**

HDCT has high assessability, as well as high sensitivity, specificity, and negative predictive value in the assessment of stents for ISR. But, given that HDCT cannot completely replace ICA, careful patient selection regarding stent type, including diameter and strut thickness, remains of importance to optimize the HDCT image, which has the potential to become an alternative to routine follow-up CAG after stent implantation, and would be a useful modality for the non-invasive, long-term assessment of patients in clinical practice.

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**Disclosures**

Conflict of Interest: The authors have no conflicts of interest to declare.

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