Adding Coronary Computed Tomography Angiography to Invasive Coronary Angiography Improves Prediction of Cardiac Events

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Background: The additive value of plaque characteristics determined by computed tomography angiography (CTA) in patients undergoing invasive coronary angiography (ICA) has not been established.

Methods and Results: We studied 676 patients undergoing ICA and CTA within 3 months. The luminal diameter narrowing based on ICA and the presence of high risk plaque (HRP) based on CTA were assessed in all coronary artery segments except for those after or before scheduled treatment. We followed their cardiac events including cardiac death, acute coronary syndrome (ACS), and revascularization for de novo lesions ≥3 months after ICA. The incidence of coronary events was higher in the segments including >25% luminal narrowing than in those without (2.94% vs. 0.31%, P<0.0001), and higher in the segments containing HRP than in those without (12.6 vs. 0.46%, P<0.0001). Greater than 25% residual luminal narrowing and the presence of HRP were identified as independent predictors of cardiac events after risk adjustment for age, gender, and history of ACS (hazard ratio [HR], 3.22; 95% confidence interval [CI]: 1.29–10.76; P=0.0092, HR, 2.64; 95% CI: 1.59–4.35; P=0.0002, respectively). Adding the presence of HRP to a model including age, gender, ACS history, and >25% residual stenosis improved the prediction of cardiac events.

Conclusions: Assessment of coronary plaque characteristics on CTA improves the prediction of cardiac events in patients undergoing ICA. (Circ J 2014; 78: 2735–2740)

Key Words: Coronary computed tomography angiography; High-risk plaque; Invasive coronary angiography

Invasive coronary angiography (ICA), established as an invasive diagnostic tool for coronary artery disease (CAD), has contributed to improvement of the prognosis of CAD patients through percutaneous coronary intervention (PCI) and pharmacologic therapies. On the other hand, ICA has been demonstrated to have limitations in predicting future coronary events by several retrospective studies, since progression of coronary arterial atherosclerosis including acute coronary syndrome (ACS) can occur from not only severely but also mildly to moderately obstructive lesions. 

Meanwhile, the Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT) Study showed that the lesions responsible for future coronary events were characterized by not only plaque instability but also by large plaque burden and small luminal area on the basis of intravascular ultrasound (IVUS). It was suggested that clinical and angiographic characteristics had poor predictive accuracy in identifying patients with untreated high-risk plaque (HRP) related to future adverse events. 

Previously we reported that HRP (positive remodeling and/or low-attenuation) on computed tomography angiography (CTA) was associated with a high risk of ACS. The purpose of the present study was to confirm that detection of HRP on CTA in patients undergoing ICA improves the prediction of cardiac events.

Methods

Patients
We retrospectively studied 690 serial patients undergoing ICA...
and CTA within 3 months from November 2007 to May 2012, after excluding patients undergoing coronary artery bypass grafting before or in the 3 months after ICA. ICA was performed at Fujita Health University and Nagoya Memorial Hospital, and CTA at Fujita Health University, Nagoya Memorial Hospital, and Imai Clinic. The study was approved by the Institutional Review Board and the ethics committee at each participating center.

**CTA**

We used 320-slice CT in 392 patients (Fujita Health University) and 64-slice CT in 284 (150 in Nagoya Memorial Hospital and 134 in Imai clinic). The 320-slice CT (Aquilion ONE, Toshiba Medical Systems, Otawara, Japan) was performed with a 0.5-mm detector elements, rotation speed of 350, 375, and 400 ms, scanner settings of 350–450 mA and 100–135 kV. For the contrast-enhanced scan, 20.4 ml kg⁻¹ s⁻¹ of contrast medium was injected for 12 s followed by 20 ml saline at 3.0 ml/s. Axial scan was performed with prospective gated scan for 1 heart beat at a heart rate of <65 beats/min for half reconstruction, and in 2 or 3 heart beats for heart rate ≥265 beats/min for segment reconstruction. On the other hand, Aquilion 64 (Toshiba Medical Systems, Otawara Japan) was used in 150 patients with a collimation of 64×0.5 mm, detector pitch of 9.8–11.2, rotation speed of 350, 375, or 400 ms, scanner settings of 400–450 mA and 100–135 kV. For the contrast-enhanced scan, 60 ml of contrast medium was injected at 4.0 ml/s followed by 20 ml saline at 2.0 ml/s. Similarly, Brilliance CT 64 (Philips, Eindhoven, Netherlands) was used in 134 patients with a collimation of 64×0.625 mm, detector pitch of 12.8, rotation speed of 420 ms, and scanner settings of 300–450 mA and 120 kV. For the contrast-enhanced scanning, 1 ml/kg of contrast medium (body weight <60 kg: 60 ml) was injected for 15 s followed by 20 ml saline at 2.0 ml/s. The raw CT data were reconstructed using algorithms optimized for retrospective electrocardiogram (ECG)-gated segment reconstruction. The reconstructed CT image data were transferred to a computer workstation for post-processing (ZIOSTATION System 1000 or ZIO M900, Amin/ZIO, Tokyo, Japan).

HRP was defined as plaque manifesting positive remodeling and/or low attenuation. Low attenuation was defined as plaque with minimum CT density, namely <30 Hounsfield units (HU). Coronary arterial remodeling was defined as a change in the vessel area at the plaque site in comparison to the reference segment set proximal to the lesion in a normal-appearing vessel segment (reference area). Manual inspection of the cross-section was used for defining the remodeling index (lesion area/reference area). The remodeling index was reported as positive when the area at the plaque site was at least 20% larger than the reference segment. CTA interpretation was performed by consensus between 2 cardiologists who were unaware of both the ICA findings and outcome data.

**ICA**

We studied a group of patients undergoing ICA because of a suspicion of CAD. The indication for ICA was determined according to the guidelines. Coronary arteries were divided into 15 segments on the basis of the recommendations of the American Heart Association. We evaluated luminal diameter narrowing of the coronary artery segments with a diameter >2 mm visually, as in the PROSPECT study. The interpretation was performed by 4 cardiologists who were unaware of the CTA findings and the outcome data.

**Outcomes**

The endpoint was defined as cardiac events including cardiac death, ACS from de novo lesion, and revascularization required for de novo lesion ≥3 months after ICA due to stable angina pectoris. Deaths were considered as cardiac when the primary cause of death was related to myocardial ischemia/infarction, heart failure or arrhythmia, and when a non-cardiac cause of death could not be identified. ACS included non-fatal acute myocardial infarction (AMI) and unstable angina requiring revascularization. Non-fatal myocardial infarction (MI) was defined as typical acute chest pain due to myocardial ischemia resulting in abnormal cardiac biomarkers (>99th centile of the upper normal limit) with or without persistent ST-segment elevation on ECG. Unstable angina was defined as acute chest pain with or without the presence of ECG abnormalities and negative cardiac enzyme levels. Revascularization was performed for patients suffering from progressive chest symptoms due to coronary artery severe stenoses or with evidence of myocardial ischemia on stress tests.

The research coordinator and physicians recorded baseline data for all patients at CTA and ICA. Patient follow-up data were gathered by observers blinded to the CTA and ICA findings, at the time of clinical visits or standardized telephone interviews.

**Statistical Analysis**

All data were presented as mean±SD for continuous variables and frequency (percentage) for categorical variables. The means for the 2 groups were compared using chi-squared test for categorical and Student’s t-test for continuous variables.

On segment-based analysis, the incidence of coronary events including ACS and revascularization ≥3 months after ICA for de novo lesions was assessed in a univariate model. Receiver-operating characteristics (ROC) analysis was performed to determine cut-offs of luminal diameter narrowing for coronary events.

Risk-adjusted analysis was performed with Cox proportional hazard models to determine the independent prognostic value for cardiac events. Cumulative event rates were estimated with the Kaplan-Meier method and compared using the log-rank test.

The increased discriminative value after the addition of CTA identification of HRP to the established models including age, gender, ACS history, and >25% residual luminal narrowing on ICA was estimated using the C-index, net reclassification improvement (NRI), and integrated discrimination improvement (IDI). The C-index is defined as the area under the ROC curve (AUC) between individual predicted probabilities and incidence of cardiac events. NRI indicates relatively how many patients show a decrease in their predicted probabilities for

| Table 1. Baseline Clinical Characteristics | Variables | n (%) or mean ± SD |
|------------------------------------------|-----------|-------------------|
| Age (years)                              | 66.8±10.3 |
| Male                                     | 500 (74.0) |
| Hypertension                             | 501 (74.1) |
| Dyslipidemia                             | 418 (61.8) |
| Diabetes mellitus                        | 215 (31.8) |
| Current smoking                          | 188 (27.8) |
| Prior or current ACS                     | 308 (45.6) |
| Prior PCI                                | 216 (32.0) |

ACS, acute coronary syndrome; PCI, percutaneous coronary intervention.
events, while IDI represents the average decrease in predicted probabilities for events after adding the presence of HRP into the baseline model. Analysis was carried out using JMP version 10 (SAS Institute, Cary, NC, USA) and P<0.05 was considered as statistically significant.

**Results**

We examined 676 patients (74.0% male, aged 66.8±10.3 years) after excluding 14 who were lost to follow-up because of lack of follow-up hospital visits or moving away. Of these, 216 patients had a history of PCI, and 308 a history of ACS (Table 1).

**Segment-Based Analysis**

In 676 patients, 8,632 segments were analyzed after excluding 283 previously subjected to PCI and 499 containing target lesions for scheduled PCI.

On ICA, 832, 371, and 261 segments were classified according to luminal narrowing 26–50%, 51–75%, and 76–100%, respectively, while the remaining 7,168 segments did not have luminal narrowing >25%. On the basis of ROC analysis, the cut-off level of luminal narrowing associated with coronary events was determined as 15% (AUC, 0.82; sensitivity, 0.923; specificity, 0.724). We applied residual luminal narrowing >25% as a risk factor for future coronary events.

On CTA, HRP was observed in 198 segments (2.2%). Of the 198 segments containing HRP, 25 were associated with coronary events (12.6%), in contrast to only 40 of 8,434 segments without HRP (0.47%). Figure 1 shows a representative case.

**Patient-Based Analysis**

During the mean follow-up of 27.7±15.4 months, cardiac events occurred in 66 patients (cardiac death, n=9; ACS, n=17; late revascularization due to stable angina pectoris, n=40).

In the univariate Cox analysis, history of ACS, >25% residual luminal narrowing, and the presence of HRP were significant predictors of cardiac events. Greater than 25% residual luminal narrowing, and the presence of HRP were independent risk factors of cardiac events after adjustment for gender, age, and history of ACS (hazard ratio [HR], 3.22; 95% confidence interval [CI]: 1.29–10.76; P=0.0092; HR, 2.64; 95% CI: 1.59–4.35; P=0.0002, respectively; Table 2).

Figure 2 shows Kaplan-Meier estimated survival in the incidence of cardiac events in all studied patients. After assessing the luminal narrowing of the coronary arteries on ICA, we added the CTA result for the patients with >25% residual stenosis. The cumulative rate of cardiac events in patients with HRP adding on >25% residual luminal narrowing was higher than in those without HRP (log-rank P<0.0009).

**Discrimination of Cox Regression Models in Predicting Cardiac Events**

The addition of HRP to a model including clinical characteristics (age, gender, and history of ACS) and >25% residual...
On the other hand, several studies have reported that CTA is not only a diagnostic tool for the patients with suspected CAD, but also helps to predict the patient prognosis by delineating the severity of any coronary artery stenoses. Additionally we previously reported that the patients with positively remodeled coronary segments with low-attenuation plaque characterized on CTA were at high risk of ACS development. In this way, prognostic stratification determined non-invasively on CTA is becoming possible.

In the present study, we assessed the contention that reviewing the presence of HRP in individuals after ICA evaluation significantly improved NRI (P<0.0001), and IDI (P=0.0011). The C-index obviously increased, but did not reach statistical significance (0.704 vs. 0.654, P=0.0521; Table 3).

**Discussion**

The current study has shown that adding the CTA plaque characteristics to the ICA findings regarding luminal narrowing improves the prediction of cardiac events.

The CONFIRM study showed that CTA, a non-invasive modality that can reveal the severity of stenotic atherosclerotic lesions, may be used effectively as a gatekeeper to ICA. On the other hand, several studies have reported that CTA is not only a diagnostic tool for the patients with suspected CAD, but also helps to predict the patient prognosis by delineating the severity of any coronary artery stenoses. Additionally we previously reported that the patients with positively remodeled coronary segments with low-attenuation plaque characterized on CTA were at high risk of ACS development. In this way, prognostic stratification determined non-invasively on CTA is becoming possible.

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### Table 2. Patient Clinical Profile vs. Presence of Cardiac Events

|                          | Cardiac event (+) | Cardiac event (-) | Unadjusted HR (95% CI) | P-value | Adjusted HR (95% CI) | P-value |
|--------------------------|-------------------|-------------------|------------------------|---------|----------------------|---------|
| Male                     | 52 (78.8)         | 448 (73.4)        | 1.24 (0.71–2.33)       | 0.465   | 1.03 (0.58–1.97)     | 0.860   |
| Age (years)              | 65.6±11.3         | 66.9±10.2         | 0.99 (0.97–1.01)       | 0.408   | 0.99 (0.97–1.02)     | 0.548   |
| Hypertension             | 51 (77.3)         | 450 (73.8)        | 1.12 (0.65–2.07)       | 0.689   |                      |         |
| Dyslipidemia             | 38 (57.6)         | 380 (62.3)        | 0.75 (0.46–1.23)       | 0.250   |                      |         |
| Diabetes mellitus        | 23 (34.9)         | 192 (31.5)        | 1.11 (0.66–1.82)       | 0.698   |                      |         |
| Current smoking          | 19 (28.8)         | 169 (27.7)        | 1.09 (0.62–1.82)       | 0.760   |                      |         |
| Prior ACS                | 40 (60.6)         | 268 (43.9)        | 1.78 (1.09–2.96)       | 0.021   | 1.58 (0.95–2.66)     | 0.0763  |
| Prior PCI                | 22 (33.3)         | 194 (31.9)        | 1.05 (0.62–1.73)       | 0.850   |                      |         |
| Residual luminal narrowing >25% | 62 (93.9) | 478 (78.4)        | 3.97 (1.64–13.09)      | 0.001   | 3.22 (1.29–10.76)    | 0.0092  |
| HRP                      | 30 (45.5)         | 116 (19.0)        | 3.22 (1.97–5.23)       | 0.0001  | 2.64 (1.59–4.35)     | 0.0002  |

Data given as mean±SD or n (%). CI, confidence interval; HR, hazard ratio; HRP, high-risk plaque. Other abbreviations as in Table 1.

**Figure 2.** Kaplan-Meier curves for cardiac events on invasive coronary angiography (ICA) and computed tomography angiography (CTA). CAD, coronary artery disease; HRP, high-risk plaque on coronary CTA; residual stenosis, residual luminal narrowing >25% on ICA.
and invasive interventions for any obstructive stenoses improves the prediction of cardiac events. To our knowledge, this is the first study to prove the additive prognostic value of CTA above ICA data. This study focusing on the role of CTA in patients undergoing ICA expands our previous studies about the plaque characteristics predicting a high risk of ACS development in the future.5

### Luminal Narrowing

The question of whether coronary events evolve from atherosclerotic lesions with mild-moderate stenosis as well as those with severe stenosis has been controversial.21–23 In the late 1980s, retrospective angiographic studies suggested that in more than two-thirds of patients, AMI arises from mild-moderate stenosis.24 In contrast, the pathologic studies of patients recently dying after AMI or sudden cardiac death suggested that the mean percent vascular area involvement at sites of coronary thrombus almost always exceeds 50%.25,26 The PROSPECT study, which relied on IVUS rather than CTA, showed that the lesions responsible for future coronary events had a moderately or severely narrowed minimal luminal area on IVUS.27,28 ICA is a “luminogram” incapable of showing plaque, and is a 2-D representation of a complex 3-D structure, explaining why ICA can underestimate the real lesion severity.29 Stone et al concluded that the lesions responsible for future major adverse cardiac events are mild as seen on angiography but severe on IVUS, the latter more accurately reflecting the true situation.6,7,21

In the present study the incidence rate of coronary events was higher in the patients with >25% residual luminal narrowing on ICA than in those without, with 540 of 676 patients having >25% residual luminal narrowing. ICA has limitations in detecting the coronary artery lesions at high risk for future coronary events, although we determined the cut-off level of residual mild-moderate stenotic lesions. Additionally, it is possible that CTA assessment of plaque characteristics could be performed in high-risk patients with obstructive CAD for the prediction of future coronary events. In clinical practice, CTA has a pivotal role in identifying high-risk patients with remaining HRP, who require intensive pharmacologic intervention or cautious follow-up on imaging tests.10,29

### Plaque Instability

Pathological studies have shown that thrombotic coronary occlusion after rupture of a lipid-rich atheroma with only a thin fibrous layer of intimal tissue covering the necrotic core (thin-cap fibroatheroma) is the most common cause of MI and death from cardiac causes.22,24 Although actual histologic assessment of the coronary arteries in vivo is not feasible, the development of IVUS has made it possible to characterize the vessel wall with an imaging technique that correlates reasonably well with the histologic findings. Previously we found that the non-calcified plaque with <30 HU density on CTA correlate closely with IVUS-verified low attenuation in coronary atherosclerotic plaques.25 We revealed that the CT characteristics of culprit lesions in ACS include positive remodeling and low-attenuation plaque.8 On the basis of this result, we reported that the plaque characterized by positive remodeling and/or low attenuation on CTA was associated with a high risk of ACS.8

### Clinical Implications

The present study proves the prognostic additive value of CTA in the patients undergoing ICA. The CTA detection of HRP enhances the predictive accuracy of the clinical and angiographic characteristics for coronary events.

In the PROSPECT study, IVUS was performed for 3 major coronary arteries after successful PCI for the culprit lesion in patients suffering ACS.3 This multicenter prospective observational study provided much information about the atherosclerotic imaging findings and frequency of recurrent coronary artery events, albeit at the expense of complications in 11 patients (1.6%). In clinical practice, it is not realistic to perform 3-vessel IVUS after PCI for the culprit lesion, because of its high cost and invasiveness. In the present study, we adopted the same endpoint as the PROSPECT, and showed that HRP on CTA enhances the identification of high-risk patients to a degree similar to a plaque burden ≥70%, minimal luminal area ≤5.0 mm², and thin-cap fibroatheromas on IVUS.

Several previous studies demonstrated that recurrent coronary events occur in patients with a history of ACS more frequently than in those without, with such events much more likely to be fatal in those with a history of ACS.8,26–28 The present study also showed that patients with a history of ACS have a high prevalence of HRP and are at a high risk of recurrent ACS. It is crucial to identify patients at a high risk of recurrent coronary events. CTA can identify patients at high risk of subsequent coronary events, non-invasively, although ICA, the gold standard for confirming the indication for invasive therapy, is not sufficient. Identification of HRP on CTA may be useful for secondary prevention in prior ACS patients with residual mild-moderate stenotic lesions. Additionally, it is possible that CTA assessment of plaque characteristics could be performed in high-risk patients with obstructive CAD for the prediction of future coronary events. In clinical practice, CTA has a pivotal role in identifying high-risk patients with remaining HRP, who require intensive pharmacologic intervention or cautious follow-up on imaging tests.10,29

### Study Limitations

The current study has several limitations. First, it was retrospective and observational in nature in a limited population. We did not study all patients undergoing ICA despite examining all patients undergoing both CTA and ICA during a 4.5-year period retrospectively. This may have introduced selection bias. Second, the cut-off value <30 HU for low attenuation was defined in our IVUS-CTA comparison study on the setting of 135-kV tube voltages.8,25 In the present multicenter study, however, a wide range of tube voltages was noted (100–135 kV). Obaid et al showed that the difference in CT density at volt-

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**Table 3. Discrimination of Cox Regression Models in Predicting Cardiac Events**

| Risk factors and imaging findings | C-index (95% CI) | P-value | NRI | P-value | IDI | P-value |
|----------------------------------|------------------|---------|-----|---------|-----|---------|
| Clinical characteristics plus residual stenosis | 0.654 (0.588–0.720) | Reference | Reference | 0.0521 | 0.509 | 0.00004 | 0.0247 | 0.00107 |
| Clinical characteristics plus residual stenosis plus HRP | 0.704 (0.644–0.765) | | | | | | | |

CI, confidence interval; HRP, high-risk plaque on coronary computed tomography angiography; IDI, integrated discrimination improvement; NRI, net reclassification improvement; residual stenosis, residual luminal narrowing >25% on invasive coronary angiography.
ages between 100 and 140 kV was smaller in necrotic core on Integrated Backscatter (IB)-IVUS than in fibrous plaque: median HU for necrotic core was 56 HU and 42 HU at 100 kV and 140 kV, respectively, whereas for fibrous plaque it was 150 HU and 82 HU, respectively. In a meta-analysis Kristanto et al showed that variations in reported CT attenuation for lipid-rich and fibrous plaque is so large that generalized values are unreliable for clinical use. The proposed hierarchical classification can be used to determine reference CT attenuation for lipid-rich and fibrous plaque for the local setting. Taking them into consideration, it may be clinically acceptable to identify lipid-rich plaque if the cut-off point is set at low CT density (ie, <30 HU) even though under different conditions in CTA. Third, we did not evaluate luminal narrowing at the plaque site on CTA. Last, we have to consider the cost-effectiveness of adding CTA for patients undergoing ICA, for which a prospective study will be needed to confirm the present findings.

Conclusions

Assessing coronary plaque characteristics by CTA improves the prediction of cardiac events in patients undergoing ICA.

Disclosures

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