ORIGINAL RESEARCH

High coronary calcium score and post-procedural CK-MB are noninvasive predictors of coronary stent restenosis

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Purpose: High coronary calcium score (CCS) and post-procedural cardiac enzyme may be related with poor outcomes in patients with coronary stent implantation.

Methods: A total of 1,072 patients (63.2% male, mean age: 61.7±10.3 years) who underwent coronary multi-detect computed tomography at index procedure and follow-up coronary angiography (CAG) after drug-eluting stent (DES) were divided into two groups: those with and without target lesion revascularization (TLR; >50% reduction in luminal stent diameter or angina symptoms on follow-up CAG). The CCSs for predicting stent revascularization were elucidated.

Results: There were no significant differences between the two groups with regard to risk factors. The initial CCS was significantly higher in the TLR group (1,102.4±743.7 vs 345.8±51.05, P=0.04). After adjustment of significant factors for TLR, only CCS and post-procedural creatine kinase MB form (CK-MB) elevation were significant predictors of coronary artery TLR. Receiver operation curve revealed that >800 in CCS had 69% in sensitivity and 88% in specificity about predicting the TLR.

Conclusion: High CCS with post-procedural CK-MB might be the useful predictors for TLR after DES implantation.

Keywords: coronary restenosis, drug-eluting stents, calcium, creatine kinase

Introduction

Noninvasive imaging for early detection of cardiovascular disease is actively investigated. Also, routine cardiovascular screening tests in diabetic and elderly patients are increasing. To detect coronary artery disease (CAD), various noninvasive techniques, such as the measurement of coronary calcium score (CCS), have quantitative correlation with the prevalence of CAD.[1–6] According to a recent meta-analysis, low-dose coronary computerized tomography (CT) showed that CCS values of 0, 1–99, 100–400, 400–999, and ≥1,000, had 1.0, 1.9, 4.3, 7.2, and 10.8 as relative risk ratio of cardiovascular disease, respectively.[1,2] The quantification of CCS has been reported to be a more reliable prognostic factor for cardiovascular disease.[7,8] Highly calcified lesion was closely related with poor clinical outcomes due to stent underexpansion and edge dissection. Recently developed coronary stents show thin stent strut and high capability of conformational change, which increases the deliverability to highly calcified and angulated lesions. This kind of mechanical property has also increased the concern about stent deformation and restenosis, especially in highly calcified lesions. It must be elucidated what, other than the severity of coronary calcification, predicts stent restenosis.

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We examined whether CCS was significantly correlated with target lesion revascularization (TLR) of the coronary artery after drug-eluting stent (DES) implantation.

Subjects and methods
Subjects
A total of 1,072 stable angina patients (mean age 61.7±10.3 years, 63.2% male) diagnosed with CAD on the basis of multidetector CT (MDCT) were enrolled in this study. All of them had DESs implantation of not less than 2.5 mm in diameter and had been assessed by follow-up coronary angiography (CAG). We excluded patients with acute coronary syndrome, coronary stent implantation in the setting of cardiogenic shock complicating acute myocardial infarction, patients with unsuccessful stenting (defined as failure to place the stent at the desired site or to achieve a satisfactory angiographic result), patients with stenting intended primarily as a bridge to coronary artery bypass, patients with any major cardiac event (including death, myocardial infarction, bypass, repeated percutaneous transluminal coronary angioplasty, or stent vessel occlusion) during the 30 days immediately after the procedure. Above exclusion criteria may have been related to procedural complications and a lot of confounding bias so patients were not suitable for inclusion in the study.

Patients were divided into two groups. Group I included those patients who had no TLR on a follow-up CAG (n=910). Group II consisted of those patients who had TLR on a follow-up CAG (n=162). The mean age in group II was 62.1±9.0 years, and the proportion of male patients was 58.6% (n=95). TLR was defined as those who need to be revascularized for the stent restenosis due to ischemic-driven symptoms or angiographic restenosis >50% in diameter on a follow-up CAG. For all patients, MDCT was performed within a month before the initial CAG. Indications of MDCT in group I were angina (n=564, 62%), dyspnea (n=209, 23%) and asymptomatic (n=137, 15%). Group II had angina (n=115, 71%), dyspnea (n=30, 19%) and asymptomatic (n=17, 10%) as indications.

All patients submitted written informed consent. All tests and other procedures were approved by the Institutional Review Board of The Catholic University of Korea, Seoul, Korea.

Methods
Clinical data were obtained from medical records and through interviews with all study patients. MDCT images were obtained by reconstructing the cross-sectional and multi-planar images via imaging work stations. For calcification

assessment, unenhanced electrocardiographically (ECG)-gated cardiac CT was performed by using a 64 detector row CT scanner (Light speed; General Electric Medical Systems, Milwaukee, WI, USA) with 2.5 mm section thickness (4×2.5 mm collimation), pitch of 0.16, 0.35-second rotation time, 100–120 kV, and 250 mA. In the CAG image of MDCT, iopromide (Ultravist®; Berlex Laboratories Inc, New Jersey, USA) was used as a contrast medium and was intravenously infused at a rate of 5 mL/sec. A total of 70 mL was intravenously infused. Subsequently, 20 mL of saline was infused at a rate of 5 mL/sec. A bolus tracking was performed for the ascending aorta. Thus, images were obtained extending from the time point of 100 house field unit (HU) to 6 sec. The cross-sectional thickness was increased from 0.625 mm by degrees of 0.3 mm. Then, images were obtained using an ECG-gated half-scan algorithm. All the patients were given oral beta blocker if they had high baseline heart rate (>85 beat per minute). None of the study patients need to be given additional intravenous injections of β-blockers.

CAG and intervention
Patients were given aspirin (100 mg) and clopidogrel (600 mg) prior to the percutaneous coronary intervention (PCI). CAG was performed via a femoral or radial artery, for which major epicardial coronary arteries >2.5 mm in length were evaluated. In the lesions, where a stenosis was observed at a magnitude of >70% on the CAG, the PCI was performed using various DESs: Cypher® (sirolimus-eluting stent), Taxus® (paclitaxel-eluting stent), Xience®/Promus® (everolimus-eluting stent) and Endeavor resolute® (zotarolimus-eluting stent). Dual or triple antiplatelet therapy was continued for at least 1 year. A follow-up CAG after a mean period of 11.2±1.01 month was performed in 1,072 patients. DESs were classified according to the stent-coating drugs and polymers. Post-procedural creatine kinase MB form (CK-MB) was measured 6 and 9 hours after the procedure. More than two times elevation from upper normal limit was defined as post-procedural CK-MB elevation. High sensitivity C reactive protein (hs-CRP), lipid profiles and cardiovascular risk factors were also compared.

Statistical analysis
In the comparison of the groups with and without TLR, the continuous variables were subjected to an independent t-test and the categorical variables were subjected to a Pearson's chi-square test or Fisher's exact test. All the data after confirmation of normal distribution were expressed as mean ± standard deviation and the frequency (%). In all cases, a value of

$P<0.05$ was considered statistically significant. To analyze the factors affecting TLR, a binary logistic regression analysis was performed. Univariate variables with $P<0.20$ or known risk factor of TLR as proved in other studies were entered into the multivariate logistic models.[9] A value of $P<0.05$ in the multivariate logistic analysis was considered statistically significant. To predict the occurrence of TLR based on CCS, statistical analysis was performed using the receiver operating characteristic curve. The association between CK-MB elevation and CCS was compared by chi-square test. Statistical analysis was performed using SPSS Software, Ver. 15.

Results
Clinical characteristics
In the baseline characteristics of 1,072 stable angina patients, the mean age was 63.1 ± 10.1 years and the number of males was 687 (64.0%). The non-TLR group comprised 910 patients, where the male-to-female ratio was 592 (56.2%):318 (35.8%), and their mean age was 63.4 ± 10.1 years. In the TLR group, there were 162 patients with a male-to-female ratio of 95 (58.6%):77 (41.4%) and the mean age was 62.1 ± 9.0 years. A comparison between the groups with and without TLR showed no significant differences in sex, age, body mass index, diabetes mellitus (DM), smoking, fasting blood sugar, hypertension, HbA1c, creatinine, CRP, total cholesterol, triglyceride, low-density lipoprotein, high-density lipoprotein, or NT-pro-BNP between the two groups (Table 1).

Angiographic data showed no significant difference in stent diameter and length between the TLR group and the non-TLR group (Table 2). Coronary stent type was significantly different between both groups. But this significance had disappeared after regression analysis (Table 2).

The mean CCS was 345.8 ± 51.05 in the non-TLR group and $1,102.4\pm743.7$ in the TLR group. This difference was statistically significant ($P=0.04$; Table 1).

In univariate logistic regression analysis, parameters shown to differ significantly between the TLR and non-TLR groups included body mass index, hypertension, stent type, follow-up duration, post-procedural CK-MB elevation and calcium score. In a multivariate logistic regression analysis of these variables, the calcium score ($P=0.006$, odds ratio [OR] 1.30 [95% CI: 1.19–1.48]) and post-procedural CK-MB elevation ($P=0.02$, OR 1.45 [95% CI: 1.28–1.51]) were found to be independent predictors for TLR (Table 2). To analyze the prognostic value of the CCS for the occurrence of TLR, the receiver operating curve was used. The CCS was a more significant predictor of TLR. According to our results, at a CCS value of 800, TLR could be predicted with a sensitivity

Table 1 Baseline clinical characteristics in groups with and without TLR

	Group 1: non-TLR (n=910)	Group 2: TLR patients (n=162)	P-value
Male sex	592 (56.2)	95 (58.6)	0.13
Age (years)	63.4±10.1	62.1±9.0	0.07
BMI (kg/m²)	25.41±4.00	24.5±3.2	0.06
DM	202 (22.1)	34 (39.0)	0.11
HBP	402 (44.1)	86 (72.8)	0.12
Smoking	167 (18.3)	43 (26.5)	0.40
FBG (mg/dL)	123.7±43.9	121.6±40.2	0.40
HbA1c (%)	6.4±1.1	6.4±1.2	0.53
Creatinine (mg/dL)	1.07±0.6	1.1±0.3	0.20
CRP (IU)	8.6±11.8	9.3±17.4	0.57
TC (mg/dL)	170.3±43.1	165.5±44.2	0.91
TG (mg/dL)	136.48±80.07	144.3±97.0	0.12
HDL (mg/dL)	41.9±11.6	42.3±10.3	0.41
LDL (mg/dL)	101.9±39.2	95.3±32.5	0.60
Pro-BNP (pg/mL)	424.9±1.6	423.7±1.2	0.83
Calcium score	345.8±51.05	1,102.4±743.7	0.04*
Post-procedural CK-MB elevation[a]	157 (17.2)	135 (83.3)	0.02*
Stent type (lesion)			
PES	322 (35.3)	82 (37.3)	0.04*
SES	816 (69.6)	114 (51.8)	0.09
EES	68 (5.2)	9 (4.1)	0.23
ZES	91 (7.1)	15 (6.8)	0.45
Stent diameter (mm)	3.20±0.6	3.18±1.9	0.84
Stent length (mm)	32.4±11.4	34.8±17.2	0.07
True bifurcation	270 (29.6)	42 (25.9)	0.24
AHA/ACC lesion B2/C	188 (20.6)	32 (19.8)	0.81
Side branch occlusion (≥2.5 mm)	19 (2.1)	4 (2.2)	0.20

Notes: *$P<0.05$. [a]Patient number (>2 times elevation of the upper normal limit). Data presented as mean ± standard deviation or n (%).
Abbreviations: BMI, body mass index; CK-MB, creatine kinase MB form; CRP, C-reactive protein; DM, diabetes mellitus; EES, everolimus eluting stent; FBG, fasting blood glucose; HBP, hypertension; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PES, paclitaxel eluting stent; pro-BNP, pro B-type natriuretic peptide; SES, sirolimus eluting stent; stent type, coronary stent type; TC, total cholesterol; TG, triglyceride; TLR, target lesion revascularization; ZES, zotarolimus eluting stent; AHA, American College of Cardiology; ACC, American Heart Association.

of 69% and a specificity of 88% (Figure 1). The association with calcium score and CK-MB elevation was analyzed. The post-procedural CK-MB elevated patients (patients with high calcium score over 800), had a significantly high incidence of TLR rate (Table 3).

Discussion
The occurrence of TLR in the DES era has been markedly decreased as compared with cases of bare-metal stents.[10] But TLR still remains one of the most important clinical problems related to coronary interventions. TLR mainly occurs as a result of geometric remodeling and neointima hyperplasia based on vascular pathology.[11] These phenomena are also presumed to be a mechanism by which atherosclerosis occurs.[12,13]

Table 2 Logistic regression analysis of the influencing factors for prediction of TLR in lesions

Factor	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*-valve	OR (95% CI)	*P*-value
Sex	0.89 (0.67–1.19)	0.37	–	–
Age	1.18 (0.99–1.32)	0.37	1.13 (0.94–1.19)	0.49
BMI	0.95 (0.90–0.99)	0.02*	0.92 (0.35–1.24)	0.48
DM	1.27 (0.87–1.69)	0.13	0.84 (0.18–2.22)	0.39
HBP	1.42 (1.03–2.06)	0.02*	2.11 (0.78–11.9)	0.16
Smoking	0.83 (0.59–1.19)	0.24	–	–
FBG	0.99 (0.99–1.00)	0.47		
HbA1c	1.10 (0.89–1.12)	0.91	–	–
Creatinine	1.20 (0.90–1.30)	0.32	–	–
hs-CRP	1.45 (0.49–1.95)	0.88	–	–
TC	1.10 (0.99–1.20)	0.75	–	–
TG	1.23 (0.79–1.24)	0.21	–	–
HDL	0.99 (0.98–1.01)	0.60	–	–
LDL	0.99 (0.99–1.02)	0.50	–	–
Stent type		0.04*	–	0.73
PES	0.54 (0.40–0.70)	<0.01*	0.65 (0.19–2.17)	0.41
SES	0.23 (0.05–0.61)	0.06	1.00 (0.98–1.13)	0.91
EES	0.71 (0.38–1.21)	0.24	2.04 (0.42–10.09)	0.36
ZES	0.97 (0.12–1.28)	0.13	3.06 (0.14–67.11)	0.49
Stent diameter	1.017 (0.86–1.19)	0.84	–	–
Stent length	1.028 (1.01–1.03)	0.11	1.05 (1.02–1.09)	0.22
Calcium score	1.41 (1.20–1.51)	0.01*	1.30 (1.19–1.48)	0.01*
CK-MB elevation[a] (post-procedure)	1.60 (1.33–1.70)	0.02*	1.45 (1.28–1.51)	0.02*

Notes: *$P<0.05$. [a]More than two times elevation of the upper normal limit.
Abbreviations: BMI, body mass index; CK-MB, creatine kinase MB; CI, confidence interval; DM, diabetes mellitus; EES, everolimus eluting stent; FBG, fasting blood glucose; HBP, hypertension; HDL, high-density lipoprotein; hs-CRP, high sensitive C-reactive protein; LDL, low-density lipoprotein; OR, odds ratio; PES, paclitaxel eluting stent; SES, sirolimus eluting stent; stent type, coronary stent type; TC, total cholesterol; TG, triglyceride; TLR, target lesion revascularization; ZES, zotarolimus eluting stent.

Coronary calcification has been examined in many studies as a noninvasive surrogate by which atherosclerosis can be diagnosed and its severity can be assessed.[2–7] In addition, other studies have reported that CCS is helpful for the early detection of asymptomatic atherosclerosis.[11,14] Many studies have reported that the CCS measured on CT is a significantly

Figure 1 On the receiver operating curve, the calcium score was a significant predictor for TLR. A calcium score of 800 has a sensitivity of 60% and specificity of 85%.
Abbreviations: AUC, area under curve; TLR, target lesion revascularization.

predictive factor for the occurrence of asymptomatic and symptomatic CAD.[15–18] Furthermore, the progression of coronary calcification has also been reported to be a useful indicator for treatment effects on CAD.[19,20] The success rate of PCI is lower in calcified lesions of moderate or greater severity. Highly calcified lesions have a higher frequency of restenosis following PCI[21,22] due to stent failure of apposition or the poor attachment of arterial wall during the PCI.[23–25] Our study showed that TLR patients had a significantly higher CCS than non-TLR patients. Post-procedural CK-MB elevation with high calcium score might be related with incomplete PCI, such as incomplete apposition, small branch jail and small emboli of calcified plaque. These results suggest that the CCS can be used as a predictor of TLR in patients after DES implantation.

It has been alluded that CCS is a more reliable indicator for the prediction of cardiovascular diseases than CRP.[16] As MDCT has become common in clinical settings, CCS has been widely used as a noninvasive test to examine CAD. In this way, coronary artery calcification can be quantified more accurately and easily than with electron beam computerized tomography (EBCT).[26]

Parameters, such as DM, multiple stents, small final minimal luminal diameter, stent type, small coronary artery, and CRP have been reported as risk factors of TLR following DES
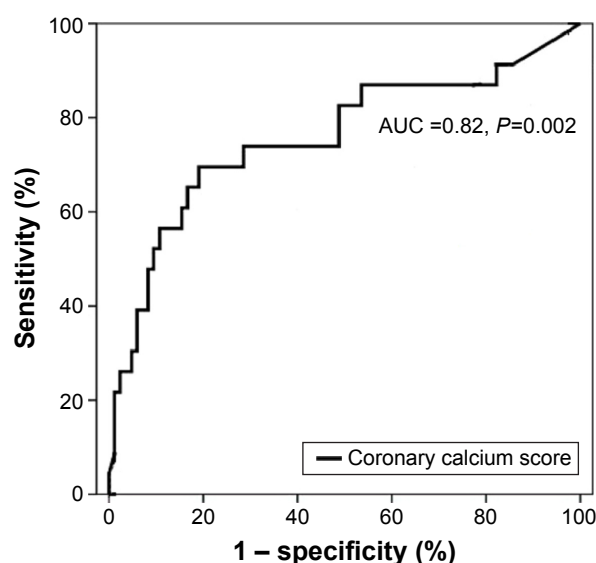
Table 3 Incidence of target lesion revascularization according to coronary calcium score and post-procedural CK-MB elevation

CK-MB elevation[a] (%)	Group I, CCS <300		Group II, 300≤ CCS ≤800		Group III, CCS >800	
	TLR (−), (n=396)	TLR (+), (n=7)	TLR (−), (n=270)	TLR (+), (n=45)	TLR (−), (n=244)	TLR (+), (n=110)
(−)	356 (85.8)	5 (1.2)	224 (68.9)	10 (3.0)	173 (51.3)	12 (3.5)
(+)	40 (9.6)	2 (0.4)	46 (14.1)	35 (10.7)	71 (21.0)	98 (29.0)*

Notes: *P<0.05 compared to Groups I and II. [a]Patient number (>2 times elevation of the upper normal limit). Data presented as n (%).
Abbreviations: CCS, coronary calcium score; CK-MB, creatine kinase MB form; TLR, target lesion revascularization.

implantation.[27–29] Also, DM, renal failure on hemodialysis, lesion length, reference vessel diameter, and post-interventional intravascular ultrasound (IVUS) lumen area had been reported as predictors for angiographic restenosis.[27–29]

Conclusion

In this study, post-procedural CK-MB and calcium score were significant predictors of TLR. This means that the CCS, as measured on MDCT prior to PCI, could be used as a noninvasive technique to predict TLR. High coronary calcium score does not directly indicate that the target lesion is heavily calcified. But it seems that the coronary lesion with high coronary calcium score should be thoroughly prepared for stent deployment. After the procedure, post-procedural CK-MB evaluation might be useful in patients with high calcium score. We suggest that the CCS reflects the multiple factors involved in TLR (the mechanical properties such as incomplete stent expansion), incomplete coverage of lesion for calcified lesions during stent deployment and the severity of coronary atherosclerosis. MDCT has broad clinical utility such as a screening tool, assessment of abnormal coronary anatomy in chronic total occlusion and cost benefit replacing the invasive angiography. However, it has concerns with radiation hazard. This study does have some limitations. No analysis was performed for the PCI through quantitative coronary anatomy or IVUS. Although many variables such as lesion characteristics, balloon inflation time, coadministrative medications are involved in the pathophysiology of TLR after DES implantation, these variables were not included in the retrospective data analysis. Calcium score measured by MDCT seems to be over-estimated.[30] The current study was a retrospective, cross-sectional study at a single center. Also, there were a lot of biases to influence the clinical outcomes. Enrolled patients, in this study, were stable angina patients who took planned CAG. This meant that they had mild symptoms and severity. So, we could not say for sure that our conclusion could be applied in acute coronary syndrome patients. In this study, the frequencies of TLR and periprocedural CK elevation seem to be higher than in other studies. This might be because we enrolled patients who received follow-up angiography without exception. So asymptomatic restenosed patients were included, which was unique and different from other studies. Considering these limitations, further studies will need to verify the noninvasive surrogates to predict the stent restenosis.

Disclosure

The authors report no conflicts of interest in this work.

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