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Value of a new post-procedural intravascular ultrasound score in predicting target vessel revascularization after coronary drug-eluting stents implantation*

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Abstract: Objective: There is no simple or feasible post-procedural intravascular ultrasound (IVUS) score to predict major adverse cardiac events (MACE) in patients undergoing drug-eluting stents (DES) implantation. The aim of this study is to validate a new IVUS score for predicting MACE. Methods: A total of 295 patients (with 322 lesions) were enrolled. IVUS score was calculated in each lesion based on five IVUS morphological characteristics: inflow/outflow disease, malapposition, underexpansion, tissue protrusion, and edge dissection (iMUTE score). We assigned two points to an underexpansion and one point for each presence of other factors. Patients were divided into low score (iMUTE score<2, n=137) and high score (iMUTE score≥2, n=158) groups. Results: At one year follow-up, a trend was seen in favor of the low iMUTE score group in MACE (3.65% vs. 10.10%; P=0.052), and there was more target vessel revascularization (TVR) in the high iMUTE score group compared with low score group (6.96% vs. 1.46%; P=0.044). Low iMUTE score was an independent predictor of freedom from TVR at one year (adjusted hazard ratio (HR) 0.5, 95% confidence interval (CI) 0.1–0.8; P=0.02). Conclusions: Post-procedural IVUS iMUTE scoring was simple and feasible in clinical practice, and can provide independent prognostic value for TVR in patients undergoing DES implantation.

Key words: Intravascular ultrasound, Drug eluting stents, Scoring schemes, percutaneous coronary intervention
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1 Introduction

Large randomized clinical trials have demonstrated that drug-eluting stents (DES) are safe and efficient compared with bare-mental stents (BMS) in treatment of patients with stenosis in de novo coronary lesions (Morice *et al*., 2002; Moses *et al*., 2003; Schofer *et al*., 2003). Despite this significant advance in the percutaneous treatment of coronary artery disease, DES are not free of restenosis and are limited by risks of late stent thrombosis and major adverse cardiac events (MACE) (Pfisterer *et al*., 2006; Daemen *et al*., 2007). Intravascular ultrasound (IVUS) is able to assess the morphology and composition of coronary lesions and is helpful in determining an appropriate interventional strategy, and thus has the potential to reduce both the need for repeat revascularization and DES thrombosis (Roy *et al*., 2008). A number of technical issues are associated with IVUS use in DES implantation, including stent expansion (Sonoda *et al*., 2004), residual stenosis (Fujii *et al*., 2005), edge dissection (Moses *et al*., 2008), malapposition (Lee *et al*., 2010), and tissue protrusion (Cheneau *et al*., 2003). However, there is no simple or feasible post-procedural IVUS scoring scheme to

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predict risk of MACE in patients undergoing DES implantation. The aim of this study was to assess the predictive value of a new IVUS scoring schemes that estimate risk of MACE at long-term follow-up in patients undergoing DES implantation.

2 Subjects and methods

2.1 Study population and study design

The population in this study was identified from consecutive patients who underwent percutaneous coronary intervention (PCI) from January 2006 to August 2009 at Shenyang Northern Hospital, China. Criteria for selection included age >18 years and undergoing IVUS guidance to implantation of DES in native coronary lesions. Patients were excluded if they presented with any of following characteristics: age <18 years, bypass graft lesions, acute myocardial infarction (ST-segment elevation, <7 d), coronary no-flow phenomenon after stent implantation, in-stent restenosis lesions after DES or BMS implantation, and failure to perform final IVUS in DES-treated lesions.

2.2 Procedures and adjunctive medical therapy

PCI was performed using standard technique via the radial approach in most cases. Selection of DES types was at the discretion of operators, including sirolimus-eluting stents, paclitaxel-eluting stents, and other DES. All patients were treated with aspirin 300 mg prior to PCI and loaded with clopidogrel 300–600 mg if not already on a maintenance dose. Dual antiplatelet therapy was recommended to all study patients for a minimum duration of six months. During PCI, patients were anticoagulated with unfractionated heparin (a bolus of 100 U/kg and additional heparin to achieve an activated clotting time of 250–300 s). Use of platelet glycoprotein IIb/IIIa inhibitors was at the discretion of operators. IVUS was performed using standard technique either post-intervention or both pre- and post-intervention. IVUS systems included iLab and Galaxy (both with Atlantis SR Pro IVUS Imaging Catheter, Boston Scientific Corp, Minneapolis, MN, USA). IVUS images were recorded after administration of 100–200 mg of nitroglycerin. The ultrasound catheter was advanced at least 5 mm beyond the lesion/stent and was pulled back to the ostium of target vessels using either an automatic or manual transducer pullback. IVUS was performed and interpreted by the treating physicians. Offline measurements were performed and recorded.

2.3 IVUS definition and scoring schemes

IVUS score was calculated in each lesion based on five IVUS morphological characteristics: inflow/outflow disease, malapposition, underexpansion, tissue protrusion, and edge dissection (iMUTE score). Inflow/outflow disease is a significant residual disease in coronary segments outside of treated segment, with a minimal lumen cross-sectional area (CSA) <4 mm^2 and plaque burden >70%. Malapposition is a separation of at least one stent strut from luminal border, shown as blood speckle behind stent struts not overlying a sidebranch. Underexpension is inadequate stent expansion with a minimum stent area of <5.0 mm^2 at final IVUS pullbacks (for left main lesions, cutoff value is 9 mm^2). Tissue protrusion is visible tissue on the luminal side of stent struts. Edge dissection is classified into three categories: intimal, limited to the intima or atheroma, and not extending to the media; medial, extending into the media; adventitial, extending through the external elastic membrane (EEM). In the current study, only intimal dissection could be found in post-procedural IVUS pullbacks. We assigned two points to an underexpansion and one point for the presence of other factors (Table 1), because inadequate stent expansion increases the likelihood of restenosis commensurate to two other risk factors combined. Per patient, scores in all treated lesions would be summed and serve as a patient's iMUTE score. For example, a target vessel which had an underexpension (+2) and a malapposition (+1) would have an iMUTE score of 3. IVUS scorings of ten randomly selected cases by two observers and by one observer, respectively, at two separate scorings showed an interobserver correlation

Table 1 Formation of post-stenting IVUS adverse characteristic scoring (iMUTE score)

Morphological characteristics	Score
Inflow/outflow disease	1
Malapposition	1
Underexpansion	2
Tissue protrusion	1
Edge dissection	1

coefficient of 0.948 and an intraobserver coefficient of 0.960. Patients were divided into low score (iMUTE score<2) and high score (iMUTE score≥2) groups.

2.4 Clinical endpoints and follow-up

MACE are defined as a composite of cardiac death, myocardial infarction, and target vessel revascularization (TVR). Cardiac death included all deaths where a non-cardiac cause could not be demonstrated. Q-wave myocardial infarction (MI) was defined as an elevation in creatine kinase MB isoenzyme ≥2 times the upper normal value in the presence of new Q-waves on the electrocardiograph in ≥2 contiguous leads. TVR was defined as either percutaneous or surgical revascularization of the stented epicardial vessel. The definition of definite stent thrombosis required the presence of an acute coronary syndrome with angiographic or autopsy evidence of thrombus or occlusion. Probable stent thrombosis included all definite stent thrombosis, death of cardiac cause within one year of the index procedure, and Q-wave MI attributable to the target vessel.

Clinical follow-up was conducted one year post-DES implantation. Demographic, clinical, and procedural data, along with in-hospital outcomes, were collected and entered into a prospective database. These data were obtained from hospital case report forms reviewed by an independent physician blind to the study objectives. Clinical follow-up was performed at one year by trained quality assurance nurses, who worked exclusively with the database to determine post-PCI clinical events via telephone contact or office visit. Clinical follow-up was available on all patients in the study population.

2.5 Statistics

Categorical variables were summarized as frequencies or percentages and were compared using the chi-square test or Fisher exact test. Continuous variables were presented as mean±standard deviation (SD) and compared using two-tailed, unpaired *t*-tests. The log-rank test was used to assess the statistical significance of prognostic differences in event distribution. A Cox proportional model was used to relate iMUTE score to event-free survival. Statistical significance was set at $P<0.05$.

3 Results

3.1 Distribution of iMUTE scores

A total of 295 patients (with 322 lesions) were enrolled. Frequencies of five IVUS morphological characteristics in all IVUS pullbacks were shown in Fig. 1. Among those characteristics, inflow/outflow disease was detected least frequently, and tissue protrusion was detected most frequently. iMUTE score in each lesion varied between 0 and 4 (43 (13.3%), 133 (41.3%), 119 (37.0%), 21 (6.5%), and 6 (1.9%) lesions were with a score of 0, 1, 2, 3, and 4, respectively). Patients' iMUTE scores varied between 0 and 7 (33 (11.2%), 104 (35.3%), 88 (29.8%), 45 (15.3%), 14 (4.7%), 9 (3.1%), 0 (0.0%), and 2 (0.7%) patients were with a score of 0, 1, 2, 3, 4, 5, 6, and 7, respectively). There were 137 patients in the low score group (iMUTE score<2) and 158 patients in the high score group (iMUTE score≥2).

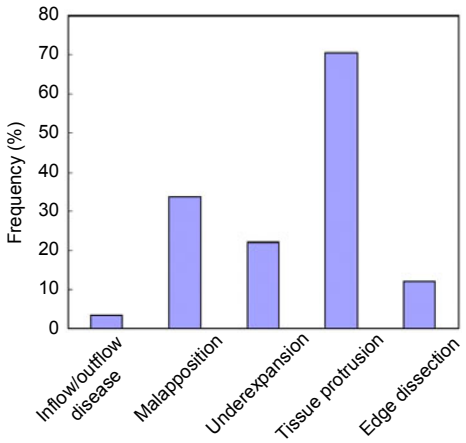

Fig. 1 Frequencies of five IVUS morphological characteristics in all IVUS pullbacks (322 lesions)

3.2 Baseline patient characteristics

Clinical, angiographic, and procedural characteristics are presented in Tables 2 and 3. There were no significant differences in baseline characteristics, angiographic and procedural details except that patients in low iMUTE score group were younger (58.6 years vs. 62.3 years; $P=0.006$). There was a trend that implanted stents in the low score group were longer than those in the high score group ((27.09±12.20) mm vs. (24.58±10.07) mm; $P=0.054$).

Table 2 Clinical characteristics of patients

Parameter	Value*		*P*-value
	iMUTE score<2 (*n*=137)	iMUTE score≥2 (*n*=158)	
Demographics and clinical history			
Male gender	110 (80.3%)	121 (76.6%)	0.481
Age (year)	58.6±11.9	62.3±11.1	0.006
Diabetes	17 (12.2%)	22 (13.9%)	0.733
Current smoker	63 (46.0%)	72 (45.6%)	1.000
Hypertension	75 (54.7%)	81 (51.3%)	0.561
Dyslipidaemia	53 (38.7%)	59 (37.3%)	0.904
Chronic renal insufficiency	18 (13.1%)	25 (15.8%)	0.620
Prior myocardial infarction	7 (5.1%)	17 (10.8%)	0.090
Prior coronary bypass surgery	5 (3.6%)	9 (5.7%)	0.585
Prior percutaneous coronary intervention	8 (5.8%)	14 (8.9%)	0.378
Clinical presentation			
Stable angina	15 (10.9%)	14 (8.9%)	0.563
Unstable angina	28 (20.4%)	38 (24.1%)	0.486
Acute myocardial infarction (non ST-segment elevation)	58 (42.3%)	78 (49.4%)	0.089
Acute myocardial infarction (ST-segment elevation, >7 d)	36 (26.3%)	28 (17.7%)	0.243
Left ventricular ejection fraction (%)	50±15	48±14	0.145

* Data are expressed as mean±SD or *n* (%)

Table 3 Angiographic and procedural details of patients

Parameter	Value*		*P*-value
	iMUTE score<2 (*n*=137)	iMUTE score≥2 (*n*=158)	
Target vessel			0.713
Left main coronary artery	5 (3.6%)	8 (5.1%)	
Left anterior descending artery	52 (38.0%)	68 (43.0%)	
Left circumflex	21 (15.3%)	22 (13.9%)	
Right coronary artery	59 (43.1%)	60 (38.0%)	
Lesion location			0.362
Ostial	2 (1.4%)	2 (1.3%)	
Proximal	53 (38.7%)	52 (32.9%)	
Mid	70 (51.1%)	80 (50.6%)	
Distal	12 (8.8%)	24 (15.2%)	
Lesion type (ACC/AHA classification)			0.314
Type A	9 (6.6%)	10 (6.3%)	
Type B	77 (56.2%)	102 (64.6%)	
Type C	51 (37.2%)	46 (29.1%)	
Procedural details			
Treated lesions	1.09±0.28	1.13±0.36	0.235
Stents implanted	1.04±0.19	1.06±0.23	0.411
Stent type (per patients)			0.614
Sirolimus-eluting stent	73 (53.3%)	92 (58.2%)	
Paclitaxel-eluting stent	24 (17.5%)	22 (13.9%)	
Others	40 (29.2%)	44 (27.8%)	
Maximal balloon diameter achieved during entire procedure (mm)	3.34±0.59	3.44±0.59	0.165
Stent length (mm)	27.09±12.20	24.58±10.07	0.054
Post-dilatation	69 (50.4%)	90 (57.0%)	0.292

* Data are expressed as mean±SD or *n* (%)

3.3 Clinical outcomes

Angiographic success was achieved in all patients. During hospitalization, only one patient in the high score group had a non-Q wave MI. At the one-year follow-up, there were no significant differences in cardiac death (0.73% vs. 1.27%; *P*=0.901) and MI (1.46% vs. 5.70%; *P*=0.108) between the low and high score groups. However, there was significantly more TVR in the high score group (1.46% vs. 6.96%; *P*=0.044). In addition, there was a trend that more MACE occurred in the high score group compared with the low score group (3.65% vs. 10.10%; *P*=0.052) (Table 4). Differences in the rate of freedom from TVR or stent thrombosis between groups over one year are illustrated in Figs. 2 and 3. Low iMUTE scores were an independent predictor of freedom from TVR at one year (adjusted hazard ratio (HR) 0.5, 95% confidence interval (CI) 0.1–0.8; *P*=0.02).

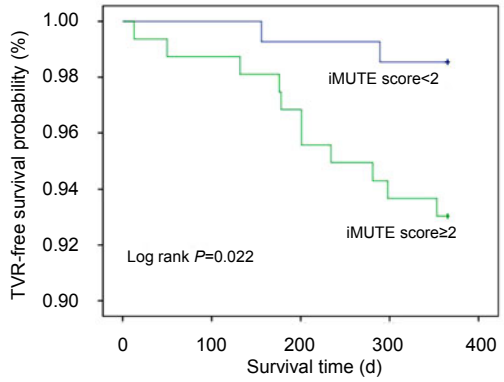

Fig. 2 Kaplan-Meier curves illustrating freedom from target vessel revascularization (TVR) in iMUTE score <2 and ≥2 groups over 12 months (Log rank *P*=0.022)

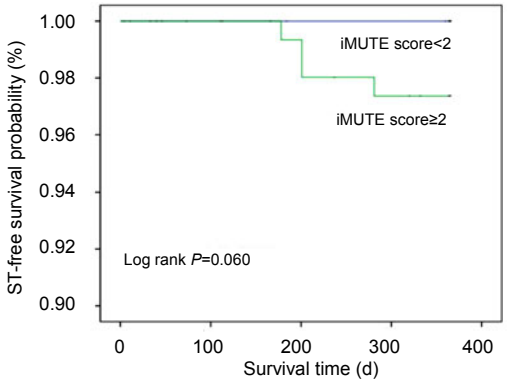

Fig. 3 Kaplan-Meier curves illustrating freedom from probable or definite stent thrombosis (ST) in iMUTE score <2 and ≥2 groups over 12 months (Log rank *P*=0.060)

Table 4 Major adverse cardiac events during hospitalization and one-year follow-up*

Parameter	Number of patients		*P*-value
	iMUTE score<2 (*n*=137)	iMUTE score≥2 (*n*=158)	
In-hospital MACE			
Cardiac death	0	0	–
Myocardial infarction	0	1 (0.63%)	0.943
Q-wave	0	0	
Non-Q wave	0	1 (0.63%)	
Target vessel revascularization	0	0	–
Surgical (CABG)	0	0	–
Percutaneous (re-PCI)	0	0	–
Composite MACE	0	1 (0.63%)	0.943
One-year MACE			
Cardiac death	1 (0.73%)	2 (1.27%)	0.901
Myocardial infarction	2 (1.46%)	9 (5.70%)	0.108
Q-wave	1 (0.73%)	4 (2.53%)	
Non-Q wave	1 (0.73%)	5 (3.16%)	
Target vessel revascularization	2 (1.46%)	11 (6.96%)	0.044
Surgical (CABG)	0	2 (1.27%)	
Percutaneous (re-PCI)	2 (1.46%)	9 (5.70%)	
Composite MACE	5 (3.65%)	16 (10.10%)	0.052

* If a patient had more than one event, only the highest-ranking (worst) event was counted. MACE: major adverse cardiac events, is defined as a composite of cardiac death, myocardial infarction, and target vessel revascularization; CABG: coronary artery bypass graft; PCI: percutaneous coronary intervention

4 Discussion

This study validated a new post-procedural IVUS scoring scheme, which had an independent prognostic value in predicting TVR at one year in patients undergoing DES implantation. Thus, this scheme could be an easy-to-use standard for IVUS optimized DES implantation.

In our scoring scheme, stents expansion was considered the most important component and was assigned two points. Many studies support our methodology. Serial IVUS analysis from the sirolimus-eluting stent (SES) in coronary lesions SIRIUS (SIRolImUS-coated Bx Velocity balloon-expandable stent in the treatment of patients with de novo coronary artery lesions) trial showed that a minimum stent area <5.0 mm^2 was responsible for the majority of SES restenosis in the trial (Sonoda *et al*., 2004). A study of IVUS predictors of angiographic restenosis in a large series of Korean patients treated with SES implantation found that the minimum stent cross-sectional area that best separated restenosis from no restenosis was 5.5 mm^2 (Hong *et al*., 2006). In our study, stent underexpension is defined as an inadequate stent expansion with a minimum stent area <5.0 mm^2 at final IVUS pullbacks. Recently, a new standard for IVUS optimized DES implantation was defined as achieving a final stent CSA greater than 70% of the chosen balloon CSA used to post-dilate the stent (Gerber *et al*., 2009). However, such criteria are difficult to apply in long stents, and may not be clinically feasible. Further studies are required to determine if this gain in stent optimization could translate into any clinical benefit such as lowering restenosis and stent thrombosis rates.

Other parameters in our scoring included residual edge stenosis/dissection, and malapposition. We assigned one point for each presence of those factors. Residual plaque burden also is a predictor of MACE. In the retrospective study of SES implants noted above, Fujii *et al*. (2005) reported that the stent thrombosis group was significantly more likely than control patients to have residual edge stenosis (67% vs. 9%, $P<0.001$), which was defined as an edge lumen cross-sectional area <4 mm^2 and a plaque burden >70%. Most acute incomplete stent apposition is modest in size if IVUS is used and there are no good data linking isolated acute stent malapposition to adverse clinical events. However, stent malapposition may serve as a local nidus for late stent thrombosis by allowing fibrin and platelet deposition (Joner *et al*., 2006). Recently, a study compared IVUS findings at DES and BMS sites in patients with very late stent thrombosis, and found that stent malapposition played a key role in DES-related very late stent thrombosis (VLST) (Lee *et al*., 2010).

Calculating an iMUTE score may have several clinical applications. Because patients with high iMUTE scores were more likely to have an MACE, they should receive more strict antithrombotic therapy. Also, in those patients, angiographic follow-up should be strongly recommended. In addition, iMUTE score could aid in decision making for patients who are undergoing non-cardiac surgical procedure because perioperative management depends on their risk of hemorrhage from the procedure compared with the underlying cardiac-thrombotic risk.

Our study has several limitations. First, the patients included in our study were relatively high-risk (Table 2), and only less than 10% patients were with stable angina; therefore, iMUTE scores may be more useful in high-risk populations. Second, this was a single-center, non-randomized study, and therefore cannot exclude the potential for unaccounted variables to influence patient's outcome, e.g., dual antiplatelet therapy duration. Third, our sample size was relatively small. Large, randomized controlled trials are required in order to further validate the use of the iMUTE scoring model.

5 Conclusions

iMUTE is an easy-to-use scoring scheme that estimates the risk of TVR in patients undergoing coronary DES implantation. Physicians could use iMUTE to make decisions about medicine therapy and angiographic follow-up based on patient-specific risk of TVR.

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