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Intravascular Ultrasound Predictors of Major Adverse Cardiac Events in Patients with Unstable Angina

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Summary

Background: Intravascular ultrasound (IVUS) predictors of native culprit lesion morphology for occurrence of major adverse cardiac events (MACE) have not been reported. Moreover, the published data on IVUS predictors of restenosis include patients with stable and unstable angina, although the development and progression of atherosclerosis related to unstable coronary syndrome is different from that of stable angina.

Hypothesis: This study investigated whether IVUS-derived qualitative and quantitative parameters of native (preangioplastic) plaque morphologic features can predict major adverse cardiac events in patients with unstable angina.

Methods: Clinical (age, gender, coronary risk factors), qualitative and quantitative angiographic (lesion localization, morphology, pre- and postangioplastic minimal lumen diameter, reference diameter, and percent diameter stenosis), and IVUS variables (soft/fibrocalcific plaque, calcification, presence of thrombus or plaque disruption, different types of arterial remodeling, pre- or postangioplastic minimal lumen, external elastic membrane and plaque cross-sectional area, and plaque burden of the target lesion and reference segments) were analyzed by regression analyses using the Cox model, assuming proportional hazards.

Results: Of 60 consecutively enrolled patients, 21 suffered from MACE, while 39 remained event-free during the follow-up period. Multivariate regression analyses revealed that the presence of adaptive remodeling [p = 0.0177, risk ratio (RR) = 3.108, with 95% confidence interval (CI) = 1.371–8.289] and the preangioplastic lumen cross-sectional area (p = 0.0130, RR = 0.869, with 95% CI = 0.667–0.913) are independent predictors of MACE during follow-up, as is postangioplastic angiographic minimal lumen diameter (p = 0.0330, RR = 0.715 with 95% CI = 0.678–0.812).

Conclusions: Adaptive remodeling and preangioplastic lumen cross-sectional area determined by IVUS and postangioplastic minimal lumen diameter calculated by quantitative angiography are significant independent predictors of time-dependent MACE in patients with unstable angina.

Key words: coronary artery disease, unstable coronary syndrome, coronary angiography, intravascular ultrasound, remodeling, angina pectoris

Introduction

In spite of several advantages of catheter-based interventional therapy of coronary artery disease, restenosis remains the crucial problem. Several studies have been undertaken during recent years to define qualitative and quantitative culprit lesion characteristics as predictors of restenosis after coronary angioplasty, and have related these data to clinical,[1,2] laboratory,[3] angiographic,[4–7] and intravascular ultrasound (IVUS) data.[8–14] A variety of clinical and angiographic variables, such as coronary risk factors, angiographic morphology of the target lesion, postprocedural minimal lumen diameter, stenosis length, the presence of either calcification or major dissection after coronary intervention determined by coronary angiography, biochemical changes after angioplasty, and the type of conservative and invasive therapy have been correlated with restenosis and major adverse cardiac events (MACE) at follow-up.[4–7, 15, 16] These numerous variations of the factors influencing the outcome of the patients after angioplasty reveal the difficulty of estimating the exact risk of MACE, although the outcome of the patients also depends on the native morphology of the culprit lesion.

Few angiographic data have been reported on the predictive value of the native culprit lesion morphology (eccentricity, stenosis location at a bend point) and lesion severity before angioplasty with regard to subsequent restenosis,[12, 17, 18] and few IVUS-derived morphologic predictors have been published (absence of plaque fracture, presence of major dissection, and greater plaque burden).[9] Up to the date of submission of this manuscript, only one abstract had been published about the higher degree of restenosis severity being related to preexisting compensatory vessel enlargement.[19] Moreover, IVUS pre-

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dictors of native culprit lesion morphology for occurrence of MACE have not been reported. The published data on IVUS predictors of restenosis include patients with stable and unstable angina. Emerging evidence suggests that the development and progression of the atherosclerotic coronary artery lesion related to unstable coronary syndrome is different from that of stable angina.

Therefore, the purpose of the present study was to investigate whether IVUS-derived parameters of native (before coronary intervention) plaque morphologic features, luminal dimensions, together with demographic variables, coronary risk factors, and angiographic variables can predict major adverse cardiac events in patients with unstable angina pectoris.

Methods

Patients

Between September 1995 and March 1997, 95 consecutive patients with unstable angina (70 men and 25 women, mean age 62 ± 12 years) and no history of previous ischemic heart disease were included in a prospective IVUS study. Unstable angina was defined as a new onset of severe or accelerated angina (< 2 months of duration, Braunwald Class 1B), angina at rest (Braunwald Class 2B), or angina within 2 weeks of acute myocardial infarction (Braunwald Class 3C).[20] All patients were admitted to the Department of Emergency Medicine, University of Vienna, and were treated with the same antianginal therapy, including intravenous nitroglycerin and heparin. The medical history, including the coronary risk factors diabetes (medication-dependent only), hypertension (medication-dependent only), hypercholesterolemia (medication-dependent or serum cholesterol >240 mg/dl), and smoking, was recorded for each patient.

All patients underwent coronary angiography. Culprit lesions were localized according to the angiographic vessel morphology and the echocardiographic (ECG) pattern. In patients with single-vessel disease, the diseased artery was considered to be the ischemia-related artery. In patients with multivessel disease, the localization of the ECG changes during anginal episodes was used to identify the culprit lesion. The angiographic evidence of thrombus, the most severe stenosis or complex lesion morphology, and the regional wall motion abnormalities in contrast ventriculography were additional factors used for identification of the culprit lesion. If, for any reason, no clear culprit lesion could be reliably identified (normal or nearly normal coronary angiographic and/or IVUS findings or multivessel disease), the patient was excluded from the study.

Of 95 patients initially enrolled in the study, a culprit lesion could not be determined in 17 patients because of the presence of multivessel disease in 9 patients and a normal coronary angiogram in 8 patients. In another 12 patients, IVUS could not be performed because of severe main stem stenosis (4 patients) or total vessel occlusion (8 patients). Furthermore, in six patients quantitative IVUS measurements were not available because of extensive calcification (two patients) or the presence of a side branch at the site of the culprit lesion (four patients), making it impossible to delineate the vessel wall boundaries. Thus, qualitative and quantitative data on the culprit lesion and the proximal and distal reference segments could be determined in 60 of the 95 patients (41 men and 19 women, mean age 61 ± 8 years).

Balloon angioplasty of the target lesion was performed in 30 patients, stent implantation in 25, and aortocoronary bypass grafting in 4 patients. All patients, even if asymptomatic, were requested to return for follow-up angiography, which was performed at 6 months or earlier in the presence of recurrent symptoms. All 60 patients were followed 1 to 30 months (mean 8.2 ± 6.2 months) after the study inclusion. Medication at hospital discharge generally included platelet-aggregation inhibitor and beta blocker, with or without nitrate. Control coronary angiography was performed whenever indicated by the recurrence of symptoms or a positive exercise stress test. Angiographic restenosis was defined as >50% diameter narrowing at the site of angioplasty. Major adverse cardiac events were defined as death, nonfatal acute myocardial infarction, target lesion revascularization (TLR) by coronary artery bypass graft (CABG) or percutaneous transluminal coronary angioplasty (PTCA) for angiographically proven restenosis of the treated lesion.

The study protocol was approved by the local Ethical Committee, and written informed consent was obtained from all patients. All investigations were in accordance with the Declaration of Helsinki.

Coronary Angiography and IVUS Procedures

After completion of diagnostic coronary angiography and identification of the culprit lesion, IVUS imaging was performed. Before each IVUS procedure, intracoronary (0.1–0.2 mg) nitroglycerin was administered to prevent vasospasm. Intravascular ultrasound images were obtained with 2.9 or 3.2 F mechanical (CVIS, Sunnyvale, Calif., USA) or 3.0 F electronic (EndoSonics, Rancho Cordova, Calif., USA) imaging catheters. The imaging catheter was placed distally to the culprit lesion and was subsequently withdrawn manually. Correct assessment of the IVUS catheter position and the site of the culprit lesion were achieved by fluoroscopic control and/or angiographic documentation of the tip of the catheter. All IVUS images were obtained at 30 frames/s and recorded on VHS videotapes for subsequent off-line analysis. Selected images from the videotape were digitized (MediaGrabber, Rasterops) and stored in computer-based patient data files.

Qualitative and Quantitative Angiography

Cineangiograms were analyzed in two different sessions by two experienced observers blinded to the ultrasound results, using a computer-assisted quantitative coronary arteriographic edge-detection algorithm (Medis, The Netherlands). Calibration was performed on catheters filled with contrast medium. Minimal lumen diameter (MLD) and reference diameters,

lengths of stenoses, and percent diameter stenoses were measured at end-diastolic frames to minimize the variation caused by the cardiac motion and to maximize the contrast filling of the coronary vessel. Lesion length was measured as the distance (in mm) from the proximal to the distal shoulder of the lesion. Acute lumen gain was calculated as the difference between post- and preangioplastic MLD. Lesion localization [left anterior descending (LAD)- or non-LAD lesion] and lesion morphology (Type A, B, or C lesion) were determined for all patients.

Qualitative and Quantitative IVUS

Intravascular ultrasound images were analyzed in off-line mode with a computer-assisted IVUS analysis system (Tape Measure™; Indec System Inc., Sunnyvale, Calif., USA) by two experienced observers. The culprit lesions and the proximal and distal reference segments adjacent to the culprit lesion sites were analyzed. The proximal and distal reference segments were selected on the basis of the segment morphology determined by IVUS (normal or less diseased vessel segment with <50% area stenoses and without active plaques proximally or distally adjacent to the culprit lesion). Consensus between the two independent observers with regard to the qualitative features of the culprit lesion and reference segments was reached in all cases.

The qualitative IVUS analysis included assessment of plaque composition (soft or fibrocalcific plaque, presence of thrombus, plaque disruption, and calcification) and eccentricity. Plaque tissue less dense than the reference adventitia was classified as soft. Tissue producing echoes that were as bright as or brighter than the reference adventitia was classified as fibrocalcific. Bright echoes with acoustic shadowing were regarded as calcification. Calcified or mixed (soft and fibrocalcific) plaques were considered to be fibrocalcific plaque. Plaque was considered eccentric if the ratio of plaque thickness on opposite sides of the lumen was < 0.5, or if there was an arc of disease-free vessel wall. Plaque disruptions or thrombi were identified visually. Plaque disruption was defined as an abrupt, focal, superficial break in the linear continuity of the plaque surface that extended in only a radial direction. Vascular thrombi were considered present upon the typical appearance of speckled echoes softer than the dense atheroma echo signal within a soft plaque.

The site of the minimum lumen cross-sectional area (CSA) was identified by carefully scrolling the tape forward and back: if there were multiple image slices with the same minimum lumen CSA, then the image slice with the largest plaque burden was selected. For each lesion site, the lumen CSA and external elastic membrane (EEM) CSA (defined as the area encompassed by the adventitia) were measured at the point of maximal lumen narrowing and in adjacent proximally and distally located segments (reference segments). For each lesion, the lumen CSA [area within the lumen-intima border (mm^2)] and the EEM CSA were manually delineated. The plaque CSA was defined as the intima + media area, calculated as EEM CSA − lumen CSA (mm^2). The plaque burden was expressed as a percentage and calculated as (plaque CSA/EEM CSA) × 100 (%).

Compensatory vessel enlargement (adaptive remodeling) was assumed when the EEM CSA at the lesion site was larger than the proximal reference EEM CSA. Coronary shrinkage (constrictive remodeling) was considered present when the EEM CSA at the lesion site was smaller than that at the distal reference site EEM CSA. The definitions of different remodeling types are the same as those previously published from our laboratory[21, 22] and from other centers[23, 24] (Figs. 1, 2, 3).

Statistics

The statistical analyses included descriptive statistics, uni- and multivariate regression analyses, and analysis assuming the Cox proportional hazards model. Descriptive statistics were used to determine the mean ± standard deviation (SD) for continuous variables, frequencies, and percentages of categoric variables, regression analysis to assess the interobserver variability, and one-way analysis of variance (ANOVA) with repeated measurement for assessment of the reproducibility and intraobserver variability for all IVUS measurements. The exact method for the determination of intra- and interobserver variability of IVUS measurements used by our laboratory has been described in detail elsewhere.[21] Briefly, the coefficient of correlation of the interobserver variability was $r = 0.956$ ($p < 0.001$). The coefficient of variation of the repeated measurements of the lumen and EEM diameter was 3%, while that of the lumen and EEM CSA was 1.7%. The methodologic error of the measurement of the lumen and EEM diameter was therefore 0.19 mm, and that of the lumen and EEM CSA was 0.38 mm^2. Since the twofold coefficient of variation (0.76 mm^2) was 5.52% of the mean target lesion vessel size of 451 patients in our IVUS database, a difference of at least 6% between the target lesion and reference segment vessel size was considered to be significant.

The Cox proportional hazards model was run using univariate and multivariate regression approaches. The MACE (primary endpoint of the study) and TLR (secondary endpoint) and their relation to time were chosen as dependent variables. First, clinical variables (age, gender, and coronary risk factors), qualitative IVUS parameters (soft or fibrocalcific plaque, the presence of thrombus, plaque disruption, calcification, plaque eccentricity, adaptive and constrictive remodeling), and quantitative IVUS variables (proximal and distal reference pre- and target lesion pre- and postangioplastic lumen CSA, plaque and EEM CSA, and the plaque burden), qualitative angiographic variables (LAD and type C lesion) and quantitative angiographic parameters [stenosis length, pre- and postangioplastic MLD, reference diameter and % diameter stenosis (%DS)] were analyzed by univariate regression analyses. In the second step, all variables showing a p value < 0.1 in the univariate regression models were entered in stepwise fashion into the multivariate regression model. The adjusted risk ratio (RR) and its 95% confidence interval (CI) for significant independent variables in multivariate analysis were calculated. The corresponding event-free survival function (Kaplan-Meier curve) was estimated and supplemented with log-rank test.

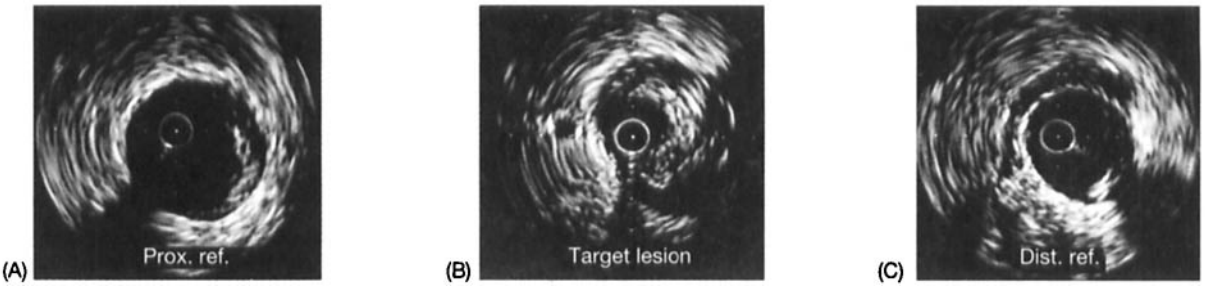

FIG. 1 Adaptive remodeling. The target lesion vessel size is larger than that of the proximal reference segment. Proximal reference segment (A) lumen cross-sectional area (CSA) = 11.7 mm^2, external elastic membrane (EEM) CSA = 16.8 mm^2, plaque CSA = 5.1 mm^2, plaque burden = 30.4%; target lesion (B) lumen CSA = 3.4 mm^2, EEM CSA = 18.8 mm^2, plaque CSA = 15.4 mm^2, plaque burden = 81.8%; distal reference segment (C) lumen CSA = 6.7 mm^2, EEM CSA = 10.6 mm^2, plaque CSA = 3.9 mm^2, plaque burden = 37.1%.

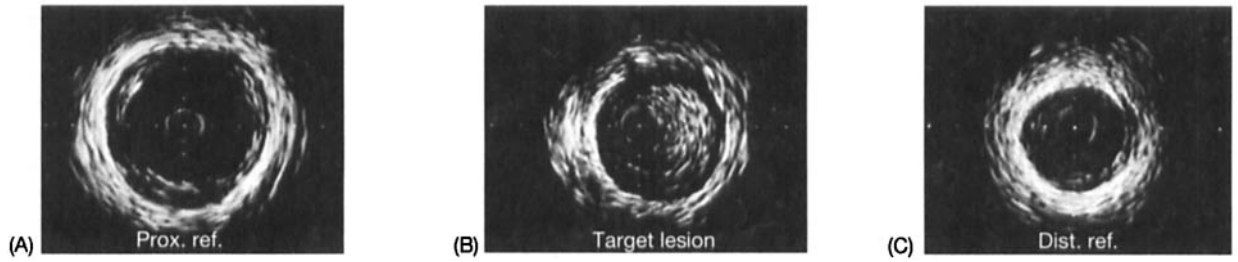

FIG. 2 No remodeling. The target lesion vessel size is between the proximal and distal reference vessel sizes. Proximal reference segment (A) lumen cross-sectional area (CSA) = 17.0 mm^2, external elastic membrane (EEM) CSA = 26.3 mm^2, plaque CSA = 9.3 mm^2, plaque burden = 35.4%; target lesion (B) lumen CSA = 1.3 mm^2, EEM CSA = 15.6 mm^2, plaque CSA = 14.3 mm^2, plaque burden = 91.4%; distal reference segment (C) lumen CSA = 8.4 mm^2, EEM CSA = 10.9 mm^2, plaque CSA = 2.5 mm^2, plaque burden = 22.2%.

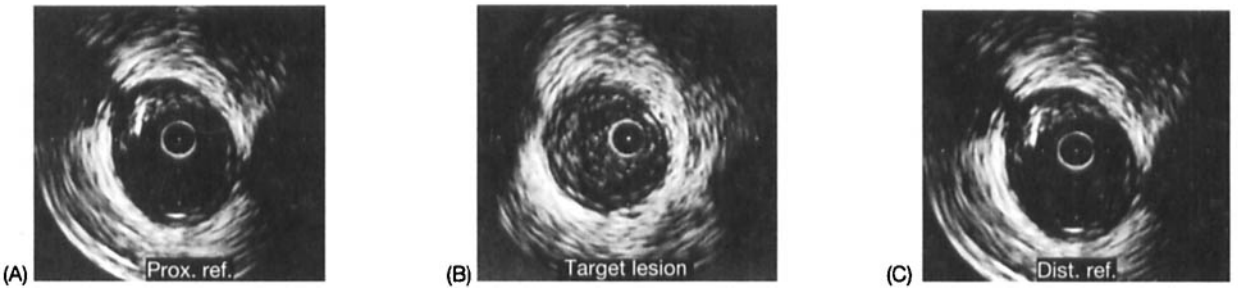

FIG. 3 Constrictive remodeling. The target lesion vessel size is smaller than that of the distal reference segment. Proximal reference segment (A) lumen cross-sectional area (CSA) = 10.1 mm^2, external elastic membrane (EEM) CSA = 15.8 mm^2, plaque CSA = 4.7 mm^2, plaque burden = 32.3%; target lesion (B) lumen CSA = 1.6 mm^2, EEM CSA = 12.9 mm^2, plaque CSA = 11.3 mm^2, plaque burden = 88.4%; distal reference segment (C) lumen CSA = 10.9 mm^2, EEM CSA = 14.0 mm^2, plaque CSA = 3.1 mm^2, plaque burden = 22%.

Results

Clinical Follow-Up

Clinical follow-up data were available for all 60 patients, and angiographic follow-up was performed in 52 (86.7%) patients. Of the 60 patients 21 (35%), experienced MACE (Group 1, 15 men, 60 ± 11 years), while 39 patients (65%) were event-free at follow-up (Group 2, 26 men, 60 ± 11 years). There were no differences between the two groups with regard to the type of invasive therapy of the target lesion; in Group 1, 11 stents [3 Palmaz-Schatz, 4 Arterial Vascular Engineering (AVE) and 4 Wiktor stents] (52.4%), and in Group 2, 15 stents (6 Palmaz-Schatz, 6 AVE, 2 Wiktor stents) (38.5%) were implanted. The average diameter and length of the implanted stents were similar in the two groups (data not shown). The coronary lesions were dilated by balloon in 8 patients (38.1%) in Group 1 and in 22 patients (56.4%) in Group 2.

In Group 1, follow-up angiography revealed restenosis in 17 patients; 1 patient had an uncomplicated acute myocardial infarction, 2 patients suffered sudden cardiac death with unsuccessful resuscitation, and 1 patient died during the postoperative phase of an aortocoronary bypass intervention due to therapy-resistant cardiogenic shock.

Patients in Group 2 had no MACE, follow-up clinical examination revealed no suspicion of coronary restenosis, and control angiography at follow-up in 35 of the 39 patients showed no significant restenosis of the target lesion.

TABLE I Baseline clinical data on patients with unstable angina with (Group 1) and without (Group 2) major adverse cardiac events

	Group 1 (n = 21)	Group 2 (n = 39)	p Value (univariate)	p Value (multivariate)
Male (%)	16 (76.2)	25 (64.1)	1.3161	
Age (years)	60.5 ± 10.6	61.3 ± 12.4	0.2911	—
LAD (%)	14 (66.7)	26 (66.7)	0.1011	—
Type C lesion (%)	6 (28.6)	13 (33.3)	0.2866	
Risk factors				—
Hypertension (%)	12 (57.1)	18 (47.4)	0.2503	—
Diabetes mellitus (%)	6 (28.6)	7 (18.4)	0.1100	—
Hypercholesterolemia (%)	15 (71.4)	22 (57.9)	0.5816	
Smoking (%)	13 (61.9)	20 (51.3)	0.0663	0.0852

Abbreviation: LAD = left anterior descending coronary artery.

TABLE II Quantitative coronary angiographic characteristics of the patients with unstable angina with (Group 1) and without (Group 2) major adverse cardiac events

	Group 1 (n = 21)	Group 2 (n = 39)	p Value (univariate)	p Value (multivariate)
Before angioplasty				
MLD (mm)	1.49 ± 0.63	1.59 ± 0.66	0.2658	—
Reference diameter (mm)	2.76 ± 0.82	2.82 ± 0.65	0.2222	—
% Diameter stenosis (%)	56.0 ± 19.2	53.4 ± 20.6	0.3633	—
Stenosis length (mm)	9.96 ± 5.51	7.43 ± 3.28	0.1467	—
After angioplasty				
MLD (mm)	2.84 ± 1.28	3.22 ± 0.75	0.0469	0.0330
Reference diameter (mm)	3.23 ± 1.93	3.87 ± 1.08	0.2315	—
% Diameter stenosis (%)	26.9 ± 9.1	25.7 ± 8.4	0.6258	—
Acute lumen gain	1.44 ± 0.65	1.78 ± 0.72	0.2172	—

Abbreviation: MLD= minimal lumen diameter.

Predictors of Major Adverse Cardiac Events (Primary Endpoint)

Clinical and angiographic predictors: Tables I and II list the clinical and qualitative and quantitative angiographic data in patients with or without MACE. Univariate analyses revealed postangiographic MLD as independent predictors for time-dependent MACE (p = 0.0469). Including the smoking (p = 0.0663) and postangiographic MLD into the multivariate regression analysis, MLD after angioplasty proved to be a significant (p = 0.0330) predictor for time-dependent MACE with an RR of $\sqrt{0.715}$ with 95% CI = 0.678–0.812.

Qualitative and quantitative IVUS predictors: Tables III, IV, and V list the IVUS characteristics of the patients with or without MACE. In the univariate regression models containing qualitative and quantitative IVUS variables, the presence of intracoronary thrombus (p = 0.0252), adaptive remodeling (p = 0.043), preangioplastic lumen CSA (p = 0.0115), and postangioplastic residual plaque CSA (p = 0.0455) exhibited an influence on MACE (dependent variable). Including the independent variables with univariate $p < 0.1$ into the multivariate regression analysis, presence of adaptive remodeling of the native lesion (p = 0.0177, RR = 3.108 with 95% CI = 1.371–8.289) and preangioplastic lumen CSA (p = 0.0130, RR = 0.869 with 95% CI = 0.667–0.913) predicted the time-related occurrence of MACE (Figs. 4 and 5).

Clinical, Angiographic, and IVUS Predictors of Target Lesion Revascularization (Secondary Endpoint)

When the TLR was chosen as endpoint, the results on predictive factors were similar to those for MACE. Among the clinical, angiographic, and IVUS parameters of 52 patients with control angiography (17 restenosis), adaptive remodeling, smoking, presence of thrombus, preangioplastic lumen area, and the postangioplastic plaque burden determined by IVUS and postangioplastic MLD measured by quantitative coronary angiography (QCA) proved to be significant predictors for time-dependent TLR. Data on the statistical significance of uni- and multivariate analyses, adjusted RR, and its 95% CI are tabulated in Table VI. The Kaplan-Meier curve showed a significantly better TLR-free survival rate in patients without preexisting adaptive remodeling (p = 0.0315), similar to the event (MACE)-free survival curve.

TABLE III Baseline qualitative intravascular ultrasound data of patients with unstable angina with (Group 1) and without (Group 2) major adverse cardiac events

	Group 1 (n = 21)	Group 2 (n = 39)	p Value (univariate)	p Value (multivariate)
Plaque compositions				
Soft plaque (%)	13 (61.9)	22 (56.4)	0.7168	—
Fibrocalcific plaque (%)	8 (38.1)	17 (43.6)	0.7168	
Thrombus (%)	16 (76.2)	27 (69.2)	0.0252	0.2998
Plaque disruption (%)	10 (47.6)	16 (41.0)	0.6409	—
Calcification (%)	7 (33.3)	12 (30.8)	0.7493	—
Plaque eccentricity				
Concentric (%)	7 (33.3)	15 (38.5)	0.1500	—
Eccentric (%)	14 (66.6)	24 (61.5)	0.1500	—
Remodeling				
Adaptive (%)	10 (47.6)	12 (30.8)	0.043	0.0177
Constrictive (%)	4 (19.0)	10 (25.6)	0.2298	—

TABLE IV Baseline quantitative intravascular ultrasound characteristics on target lesion of patients with unstable angina with (Group 1) and without (Group 2) major adverse cardiac events

	Group 1 (n = 21)	Group 2 (n = 39)	p Value (univariate)	p Value (multivariate)
Before angioplasty				
Lumen CSA (mm^2)	3.75 ± 1.64	4.22 ± 2.26	0.0115	0.0130
EEM CSA (mm^2)	15.82 ± 5.28	14.19 ± 5.19	0.3486	—
Plaque CSA (mm^2)	12.14 ± 5.54	10.10 ± 4.50	0.9677	—
Plaque burden (%)	70.6 ± 20.9	69.1 ± 16.2	0.5165	—
After angioplasty				
Lumen CSA (mm^2)	7.95 ± 3.57	8.54 ± 3.35	0.8844	—
EEM CSA (mm^2)	15.73 ± 5.14	14.89 ± 5.25	0.7816	—
Plaque CSA (mm^2)	9.81 ± 4.53	6.43 ± 2.90	0.0455	0.0678
Plaque burden (%)	38.1 ± 13.7	32.2 ± 12.9	0.5036	—

Abbreviations: CSA = cross-sectional area, EEM = external elastic membrane.

TABLE V Baseline quantitative intravascular ultrasound characteristics on proximal and distal reference segments of patients with unstable angina with (Group 1) and without (Group 2) major adverse cardiac events

	Group 1 (n = 21)	Group 2 (n = 39)	p Value (univariate)	p Value (multivariate)
Proximal reference				
Lumen CSA (mm^2)	9.73 ± 3.00	9.36 ± 3.13	0.1971	
EEM CSA (mm^2)	15.95 ± 4.25	15.30 ± 5.56	0.7355	—
Plaque CSA (mm^2)	7.03 ± 2.76	5.93 ± 2.93	0.0953	0.2155
Plaque burden (%)	37.2 ± 12.8	36.7 ± 13.5	0.5926	—
Distal reference				
Lumen CSA (mm^2)	8.27 ± 3.88	7.97 ± 3.11	0.1258	—
EEM CSA (mm^2)	11.89 ± 6.07	12.71 ± 5.29	0.1453	—
Plaque CSA (mm^2)	4.11 ± 3.10	4.91 ± 3.49	0.9838	
Plaque burden (%)	28.0 ± 12.8	35.1 ± 13.8	0.4069	—

Abbreviations as in Table IV.

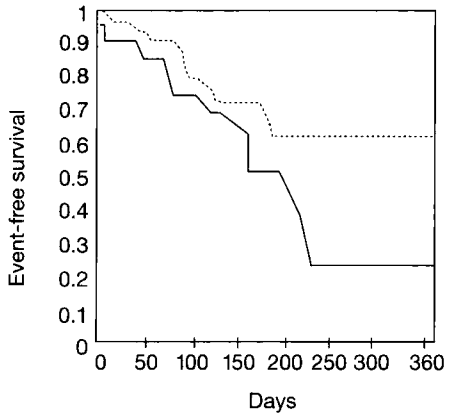

FIG. 4 Kaplan-Meier curve for relation between adaptive remodeling determined by intravascular ultrasound and major adverse cardiac events. P = 0.0442 between groups with or without adaptive remodeling. - - - = Adaptive remodeling no, — = adaptive remodeling yes.

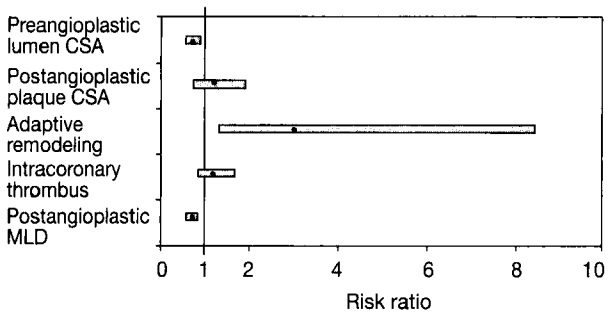

FIG. 5 Risk ratio and 95% confidence interval for adjusted risk ratio of the parameters as significant predictors of major adverse cardiac events in the uni- and multivariate regression analysis. CSA = cross-sectional area, MLD = minimal lumen diameter.

Discussion

The present study demonstrates that adaptive remodeling of the native culprit lesion, preangioplastic lumen CSA determined by IVUS, and postangioplastic MLD measured by QCA predict MACE and TLR in patients with unstable angina. The presence of intracoronary thrombi and the postangioplastic plaque burden assessed by IVUS (as independent predictors in univariate regression analyses) may also be regarded as possibly influencing factors for time-dependent MACE.

In the study by Mintz *et al.*, the preintervention angiographic assessment of the coronary lesion severity and the postintervention IVUS cross-sectional measurements, and in particular the postangiographic plaque burden, predicted restenosis.[12] Jain *et al.* found that a combination of high plaque burden, major dissection, and more elastic recoil after angioplasty predisposes to subsequent restenosis.[9] Tenaglia *et al.* showed that, among the postangioplastic IVUS parameters, the dissection (probably as a consequence of PTCA) was the only significant predictor for MACE.[8] In our study, none of the postangioplastic quantitative IVUS parameters predicted MACE significantly; however, we included in our study only patients with unstable angina. We did not determine the qualitative IVUS parameters after angioplasty, because 26 lesions (43.3%) were stented and four patients (6.7%) were admitted for acute CABG. Thus, the determination of the postangioplastic IVUS parameter would have been delusive in 50% of the patients. In our study, after invasive treatment, the only significant predictor was the postangioplastic MLD in QCA, which is concordant with the findings of most studies.[25–28] The preangioplastic lumen CSA also proved to be a significant independent predictor for MACE; this parameter could be regarded as an analogous parameter to the preangioplastic minimal lumen diameter, which has likewise been shown to correlate with the likelihood of restenosis.[25–28]

The definition of adaptive and constrictive remodeling is not unique in the literature. Glagov *et al.* and Gerber *et al.* used the phrase remodeling for the relation of plaque to vessel area of the target lesion, leaving the proximal and distal reference vessel areas out of consideration.[29,30] Pasterkamp *et al.* classified the lesions into three groups on the basis of their relative vessel areas (vessel area at lesion site/vessel area at reference site) ≥ 105, 95–105, and ≤ 95%; a relative vessel area ≥ 105% indicated a compensatory enlargement, while ≤ 95% was defined as shrinkage.[23] Gussenhoven *et al.* recommended a cut-off point of 10% of the vessel area at the target site as a significant change.[31] Mintz *et al.* defined the inadequate remodeling as a lesion/reference EEM CSA that exceeded the upper limit of normal arterial tapering (lesion/reference EEM CSA ≤ 0.78) or a 21% reduction in EEM CSA per 100 mm length.[32]

TABLE VI Results of uni- and multivariate analysis on significant predictors of target lesion revascularization in patients with unstable angina

	p Value (univariate)	p Value (multivariate)	Adjusted risk (univariate)	95% CI (multivariate)
Adaptive remodeling	0.0043	0.0038	2.724	1.380–5.361
Smoking	0.0332	0.1017	1.669	0.915–3.165
Thrombus of target lesion	0.0153	0.0660	1.506	0.730–3.361
Preangioplastic LA CSA (mm^2)	0.0338	0.0438	0.842	0.720–0.995
Postangioplastic MLD (mm)	0.0218	0.0422	0.923	0.868–0.988
Postangioplastic Pl CSA (mm^2)	0.0525	0.0745	1.327	0.911–2.526

Abbreviations: LA = lumen area, Pl = plaque, CSA = cross-sectional area, EEM = external elastic membrane, CI = confidence interval.

Moreover, Mintz *et al.*, Kimura *et al.*, and Lim *et al.* defined the arterial remodeling on the basis of serial IVUS studies.[33–35] We have tested several different methods by defining the remodeling types: (1) the vessel size of the target lesion is larger/smaller than that of the proximal/distal reference segment, (2) the vessel size of the target lesion is 6% larger/smaller than that of the proximal/distal reference segment, (3) the vessel size of the target lesion is larger/smaller than the mean of the proximal and distal reference segments, (4) the remodeling index after Pasterkamp, and (5) the remodeling index after Gussenhoven. Since the assessment in 451 target lesions in 451 patients of our IVUS database revealed a mean 1.77% difference between the above-mentioned five remodeling methods, a maximum of only 11 patients had to be reclassified into other remodeling groups, and we therefore used the remodeling classification as mentioned in this manuscript in all of our IVUS studies.[21,22]

Adaptive arterial remodeling can delay the development of coronary artery stenoses and prevent restenosis, whereas constrictive remodeling can contribute to de novo lesion formation and has been shown to be one of the dominant mechanisms of restenosis following coronary intervention.[29,36] Serial IVUS studies have been carried out to study the natural history of restenosis process; adaptive remodeling occurs early in native atherosclerotic lesions (within 1 month) and constrictive remodeling occurs late (between 1 and 6 months) after intervention. The residual plaque burden after coronary intervention acts as an amplifier in this process.[14,37,38] Surprisingly, in our study, the preexisting adaptive remodeling predicted the occurrence of MACE and TLR. Up to the date of submission of this manuscript, only one abstract had been published about the unfavorable effect of the preexisting adaptive remodeling during the follow-up in patients treated with directional atherectomy; nevertheless, the type of invasive therapy may also modify the outcome of the patients.[19] Although the exact mechanism by which MACE and TLR occur significantly more frequently in patients with preexisting adaptive remodeling is not clear, some factors may be related to this phenomenon. Our previous work has revealed that adaptive remodeling in unstable coronary syndrome is associated with a higher incidence of intracoronary thrombi, plaque disruption, and a larger plaque and EEM CSA in comparison with patients with constrictive or no remodeling.[22] Both thrombi and plaque rupture may trigger the biochemical cascade of atherosclerosis progression, and the preexisting larger plaque area in adaptive remodeling may also serve as a greater risk for restenosis and occurrence of MACE during follow-up.[39] Unfortunately, IVUS follow-up studies are not available in our patients (but this was not the purpose of our study), and the further explanation of the restenosis mechanism and occurrence of MACE in association with the preexisting adaptive remodeling therefore remains unclear.

There are preliminary data suggesting that the plaque burden in the reference segment correlates directly and strongly with the likelihood of restenosis after PTCA.[40] In contrast, Tenaglia *et al.* found no association between the reference segment disease determined by IVUS and MACE.[8] Similarly, the proximal and distal reference segment plaque burden did not differ between our patient groups with or without MACE.

Study Limitations

Our findings are based on the observation of 60 primary coronary lesions that excluded ostial lesions and also coronary lesions with severe calcification. Therefore, our findings might not be applicable to heavily calcified and ostial lesions. The number of patients is relatively small (although they originated from 95 consecutively admitted patients with unstable angina). For determination of the IVUS features in patients with unstable angina, we used only a "snapshot-like view" of the culprit lesion. Different amounts of vascular tone (spasm from the catheter at the lesion site or vasodilation due to nitroglycerin) could produce an artificial narrowing or enlargement of the lumen and vessel area measured by IVUS. However, all patients received the same basic antianginal therapy before and during the interventional procedure.

Conclusions

Multivariate regression analyses demonstrated that adaptive remodeling of the native culprit lesion, preangioplastic lumen CSA determined by IVUS, and postangioplastic MLD measured by QCA predicted MACE and TLR in patients with unstable angina. The presence of intracoronary thrombi and the postangioplastic plaque burden assessed by IVUS (as independent predictors in univariate regression analyses) may also be regarded as possibly influencing factors for time-dependent MACE.

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