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Role of Low Endothelial Shear Stress and Plaque Characteristics in the Prediction of Nonculprit Major Adverse Cardiac Events

The PROSPECT Study

Peter H. Stone, MD,[a] Akiko Maehara, MD,[b] Ahmet Umit Coskun, PhD,[a] Charles C. Maynard, PhD,[c] Marina Zaromitydou, MD, PhD,[a] Gerasimos Siasos, MD, PhD,[a] Ioannis Andreou, MD, PhD,[a] Dimitris Fotiadis, PhD,[d] Kostas Stefanou, PhD,[d] Michail Papafaklis, MD, PhD,[d] Lampros Michalis, MD, PhD,[d] Alexandra J. Lansky, MD,[e] Gary S. Mintz, MD,[b] Patrick W. Serruys, MD, PhD,[f] Charles L. Feldman, ScD,[a] Gregg W. Stone, MD[b]

ABSTRACT

OBJECTIVES This study sought to determine whether low endothelial shear stress (ESS) adds independent prognostication for future major adverse cardiac events (MACE) in coronary lesions in patients with high-risk acute coronary syndrome (ACS) from the United States and Europe.

BACKGROUND Low ESS is a proinflammatory, proatherogenic stimulus associated with coronary plaque development, progression, and destabilization in human-like animal models and in humans. Previous natural history studies including baseline ESS characterization investigated low-risk patients.

METHODS In the PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) study, 697 patients with ACS underwent 3-vessel intracoronary imaging. Independent predictors of MACE attributable to untreated nonculprit (nc) coronary lesions during 3.4-year follow-up were large plaque burden (PB), small minimum lumen area (MLA), and thin-cap fibroatheroma (TCFA) morphology. In this analysis, baseline ESS of nc lesions leading to new MACE (nc-MACE lesions) and randomly selected control nc lesions without MACE (nc-non-MACE lesions) were calculated. A propensity score for ESS was constructed for each lesion, and the relationship between ESS and subsequent nc-MACE was examined.

RESULTS A total of 145 lesions were analyzed in 97 patients: 23 nc-MACE lesions (13 TCFAs, 10 thick-cap fibroatheromas [ThCFAs]), and 122 nc-non-MACE lesions (63 TCFAs, 59 ThCFAs). Low local ESS (<1.3 Pa) was strongly associated with subsequent nc-MACE compared with physiological/high ESS (≥1.3 Pa) (23 of 101 [22.8%]) versus (0 of 44 [0%]). In propensity-adjusted Cox regression, low ESS was strongly associated with MACE (hazard ratio: 4.34; 95% confidence interval: 1.89 to 10.00; $p < 0.001$). Categorizing plaques by anatomic risk (high risk: ≥2 high-risk characteristics PB ≥70%, MLA ≤4 mm^2, or TCFA), high anatomic risk, and low ESS were prognostically synergistic: 3-year nc-MACE rates were 52.1% versus 14.4% versus 0.0% in high-anatomic risk/low-ESS, low-anatomic risk/low-ESS, and physiological/high-ESS lesions, respectively ($p < 0.0001$). No lesion without low ESS led to nc-MACE during follow-up, regardless of PB, MLA, or lesion phenotype at baseline.

CONCLUSIONS Local low ESS provides incremental risk stratification of untreated coronary lesions in high-risk patients, beyond measures of PB, MLA, and morphology. (J Am Coll Cardiol Img 2017;■:■–■)
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From the [a]Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School Boston, Massachusetts; [b]New York Presbyterian Hospital, Columbia University Medical Center, and the Cardiovascular Research Foundation, New York, New York; [c]Department of Health Services, University of Washington, Seattle, Washington; [d]Department of Materials Science and Engineering, University of Ioannina, Ioannina, Greece; [e]Section of Cardiology, Yale University School of Medicine, New Haven, Connecticut; and the [f]International Centre for Cardiovascular Health, Imperial College, London, United Kingdom. The authors acknowledge with grateful appreciation the support from the Schaubert Family, as well as support from the George D. Behrakis Cardiovascular Research Fellowship Program. Dr. Maehara has received research grants from Boston Scientific and St. Jude Medical; and is a consultant for OCT Medical Imaging. Dr. Mintz has received grant support from Volcano and Boston

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

CAD = coronary artery disease

CFD = computational fluid dynamics

ESS = endothelial shear stress

FA = fibroatheroma

IVUS = intravascular ultrasound

MACE = major adverse cardiac events

MLA = minimal lumen area

nc = nonculprit

PB = plaque burden

PCI = percutaneous coronary intervention

RF = radiofrequency

TCFA = thin-cap fibroatheroma

ThCFA = thick-cap fibroatheroma

Despite advances in preventive approaches and therapies, coronary artery disease (CAD) remains the major cause of morbidity and mortality in developed countries. Identifying high-risk patients and coronary artery lesions prone to future cardiac events may direct more potent systemic and local approaches for pre-emptive treatment. The demonstration that most acute coronary syndromes (ACS) arise from a pre-existing thin-cap fibroatheroma (TCFA) (1,2) led to the development of a variety of invasive imaging modalities including radiofrequency intravascular ultrasound (RF-IVUS), optical coherence tomography (OCT), and near-infrared spectroscopy to characterize the anatomy and structure of plaque. Several natural history studies identified that the baseline anatomic characteristics of large plaque burden (PB), small minimal lumen area (MLA), and TCFA morphology as determined by RF-IVUS are associated with the lesion-specific development of major adverse cardiac events (MACE) during follow-up (3-7). The prognostic value of risk assessment determined on the basis of plaque anatomy alone, however, has been disappointing, in part because of a low positive predictive value. Moreover, the morphology and underlying activity of individual coronary plaques are heterogeneous and dynamic, and the risk associated with an individual plaque may change over time (8,9). A single "snapshot" of plaque anatomy may therefore not provide sufficient predictive accuracy concerning that lesion's natural history.

Low wall or endothelial shear stress (ESS) is a potent proinflammatory and proatherogenic stimulus that is associated with the development and progression of coronary atherosclerosis in human-like animal models (8,10,11) and in humans (4,12). The ongoing presence of low local ESS has been correlated with a more inflamed and unstable plaque phenotype (8,10,11,13). The PREDICTION (Prediction of Progression of Coronary Artery Disease and Clinical Outcome Using Vascular Profiling of Shear Stress and Wall Morphology; NCT01316159) study demonstrated in 506 patients with ACS that the positive predictive value for CAD progression requiring percutaneous coronary intervention (PCI) during 1-year follow-up was 22% on the basis of plaque anatomy alone (large PB and small MLA), but it increased to 41% if low ESS was also present in that plaque (4). PREDICTION was conducted in low-risk patients in Japan, however, and the incidence of cardiac events during follow-up was low.

The purpose of this post hoc, pilot study was to explore whether low ESS has incremental prognostic value to predict future events in the higher-risk U.S. and European patients enrolled in the PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree; NCT00180466) study, in which patients with ACS underwent coronary angiography and 3-vessel intravascular imaging and were followed for >3 years.

METHODS

PROSPECT was a prospective natural history study of 697 patients presenting with an ACS at 37 sites in the United States and Europe. All patients underwent successful PCI of the culprit lesion or lesions, after which angiography and 3-vessel RF-IVUS were performed as previously described (4). Coronary arteries were characterized at baseline by independent angiographic and IVUS core laboratories, and patients were then followed for a median of 3.4 years for new MACE, defined as cardiac death, cardiac arrest, myocardial infarction, or unstable or progressive angina requiring hospitalization. Lesion-based analyses were performed identifying those nonculprit (nc) plaques at baseline from which new MACE arose during follow-up (nc-MACE lesions). The presence of TCFA morphology, PB ≥70%, and MLA ≤4 mm^2 were demonstrated to be independently predictive of nc-MACE (4), observations that were subsequently confirmed in additional studies (6-9). The study was approved by the Institutional Review Board at each institution, and each subject gave informed consent.

For this post hoc analysis, all nc-MACE lesions (n = 54) and an approximate 4-fold sample of randomly selected nc lesions not causing MACE (nc-non-MACE lesions) were identified from the PROSPECT dataset. Local plaque ESS was assessed using validated vascular profiling techniques using coronary angiography and IVUS to reconstruct the coronary artery lumen and perform computational fluid dynamics (CFD) calculations (4). Custom software was used for 3-dimensional (3D) reconstruction of coronary arteries by merging the coronary

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angiographic centerline with the IVUS centerline (14). Each reconstructed coronary artery was divided along its entire length into 3-mm segments for characterization of vascular characteristics (local ESS, plaque area, external elastic membrane [EEM] area, lumen area, and the derived variables of PB and arterial remodeling index, as described later). The site of the lowest and highest local ESS along the length of the lesion was determined in 90° arcs around the circumference of the vessel and was related to the MLA location (4,11).

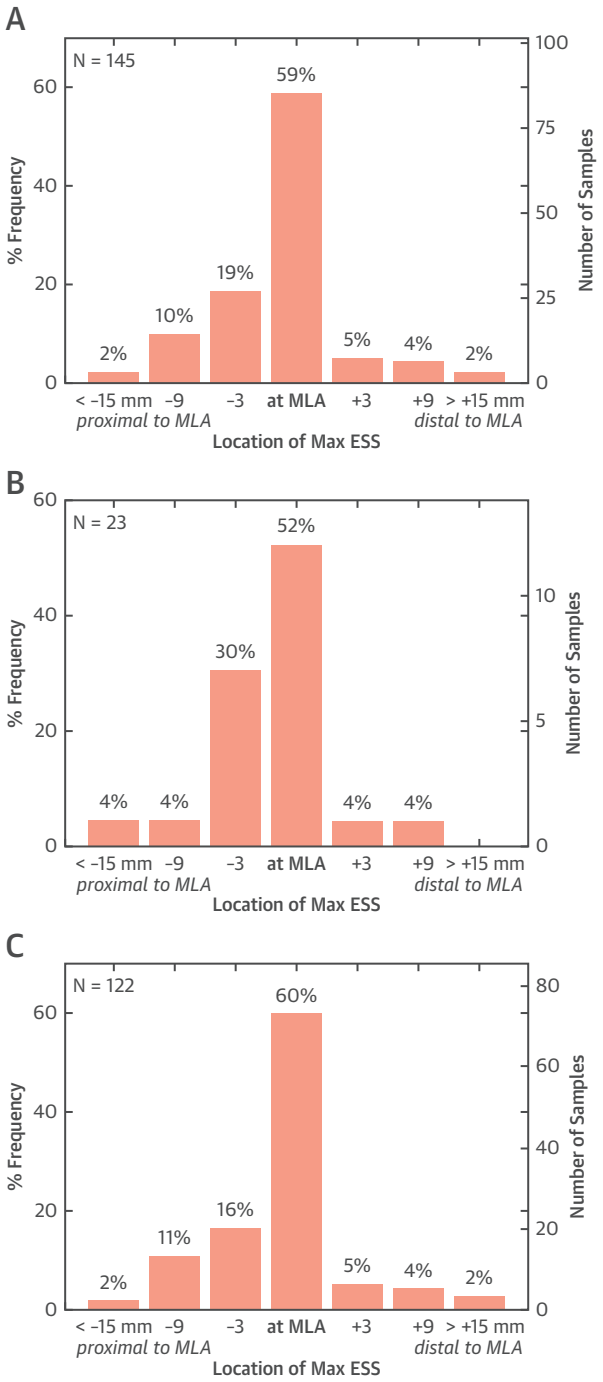
The rate of nc-MACE events during follow-up was analyzed according to baseline ESS, as well as the previously reported baseline PROSPECT anatomic characteristics of PB, MLA, and morphology (TCFA vs. thick-cap fibroatheroma [ThCFA], vs. nonfibroatheromas [non-FAs]) (3). We selected the value of <1.3 Pa to indicate low ESS for our primary analysis because that value is the lowest tertile of the baseline ESS values in this PROSPECT cohort. In a secondary analysis we also reanalyzed the study outcomes using a low ESS cutoff threshold of <1.0 Pa, a value used by others in different patient cohorts. ESS ≥1.3 Pa was considered physiological or high, as previously published (4).

As previously described (4), a remodeling index was computed along the course of each lesion. If the EEM area over a 3-mm segment was >10% different from the expected EEM given the normal distribution of the EEM along the entire artery length, that segment was defined as having either local expansive or constrictive remodeling depending on the direction of the difference. If the difference was ≤10% of the EEM trend along the entire artery length, then that segment was considered to have compensatory remodeling.

DEFINITIONS AND STATISTICAL METHODS. Plaque morphology was classified as described in PROSPECT (4). By RF-IVUS, FAs were defined by the presence of >10% confluent necrotic core. If more than 30° of the necrotic core abutted the lumen in ≥3 consecutive frames, the FA was classified as a TCFA; otherwise, it was categorized as a ThCFA. Non-FAs were classified as follows: 1) fibrotic plaques consisting mainly of fibrous tissue with <10% confluent necrotic core, <10% confluent dense calcium, and <15% fibrofatty tissue; 2) fibrocalcific plaques consisting mainly of fibrous tissue with >10% confluent dense calcium, with <10% confluent necrotic core; and 3) pathological intimal thickening consisting of ≥15% fibrofatty tissue, with <10% confluent necrotic core and <10% confluent dense calcium.

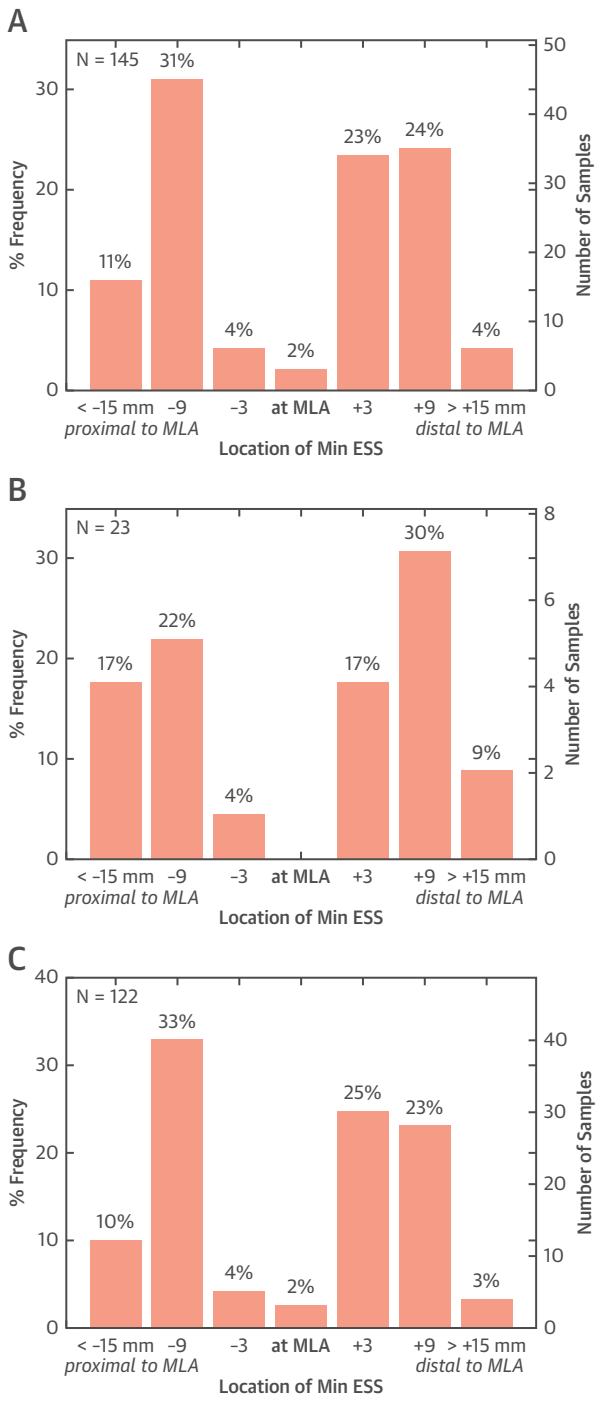
The 2-sample Student *t* test was used to compare continuous lesion characteristics, and the chi-square statistic was used for categorical variables.

FIGURE 1 Relationship Between the Lesion Location of Highest ESS and MLA



The distance upstream or downstream from the minimal lumen area (MLA) is indicated by a negative or positive number, respectively (in millimeters). **(A)** All lesions (N = 145). **(B)** Nonculprit major adverse cardiac event lesions (n = 23). **(C)** Nonculprit lesions not causing major adverse cardiac events (n = 122). ESS = endothelial shear stress; Max = maximum.

FIGURE 2 Relationship Between the Lesion Location of Lowest ESS and MLA



The distance from the minimal lumen area (MLA) as in Figure 1. **(A)** All lesions (N = 145). **(B)** Nonculprit major adverse cardiac event lesions (n = 23). **(C)** Nonculprit lesions not causing major adverse cardiac events (n = 122). ESS = endothelial shear stress; Min = minimum.

The Kaplan-Meier method was used to display time to event according to ESS category, compared by the log-rank statistic at the patient level and by Cox regression at the lesion level. For the patient-level analysis, the lesion with the lowest ESS was used. Logistic regression was used to construct a propensity score for low ESS, which included PB, MLA, plaque morphology (TCFA vs. ThCFA), the specific coronary artery in which the lesion was located (left anterior descending vs. left circumflex vs. right) and lesion location within the artery (proximal vs. middle vs. distal). Propensity-adjusted Cox regression analysis were then performed to assess the association between the continuous measure of ESS and lesion-specific nc-MACE. Standard errors of the regression coefficients were corrected for clustering of arterial segments within patients with the Huber-White sandwich estimator. Statistical significance was set at the 0.05 level. All statistical analyses were performed with STATA software version 14.1 (Stata Corportation, College Station, Texas) and SPSS software version 19 (IBM Corporation, Armonk, New York).

RESULTS

LESIONS AND BASELINE CHARACTERISTICS. In the entire PROSPECT population 54 nc-MACE lesions were identified from 53 patients, including 25 TCFAs, 18 ThCFAs, 7 non-FAs, and 4 unclassified lesions. The imaging acquisition was sufficient for ESS vascular profiling analyses in 30 of 51 (58.8%) nc-MACE lesions, including 13 TCFAs, 12 ThCFAs, and 5 non-FAs. Three lesions were too short (<9 mm) for meaningful ESS evaluation (2 ThCFAs and 1 non-FA). Given the small number of evaluable non-FAs with events (n = 4), subsequent analyses were confined to FAs (TCFAs and ThCFAs).

The control group consisted of 122 nc-non-MACE lesions from 84 patients who did not have nc-MACE, including 63 TCFAs and 59 ThCFAs. The final analytic dataset for the present study thus consisted of 145 lesions: 23 nc-MACE lesions (13 TCFAs, 10 ThCFAs) and 122 nc-non-MACE lesions (63 TCFAs and 59 ThCFAs). The specific MACE outcomes in these 23 patients during follow-up included acute myocardial infarction in 3 patients and unstable or progressive angina in 20 patients.

CHARACTERISTICS OF ESS PER LESION AND PER PATIENT. Low ESS was observed in 101 of 145 lesions (69.7%; mean low ESS 0.65 ± 0.32 Pa) and physiological/high ESS in 44 (30.3%; mean ESS 1.95 ± 0.69 Pa). Among the 76 TCFAs, 51 (67.1%) exhibited low ESS (mean 0.62 ± 0.30 Pa), and 25 (32.9%) exhibited physiological/high ESS (mean 1.87 ± 0.47 Pa).

Among the 69 ThCFAs, 50 (72.5%) exhibited low ESS (mean 0.68 ± 0.33 Pa), and 19 (27.5%) exhibited physiological/high ESS (2.06 ± 0.91 Pa). Low ESS values were similar in both TCFAs and ThCFAs (0.62 ± 0.30 Pa vs. 0.68 ± 0.33 Pa; p = 0.55), as were physiological/high ESS values (1.87 ± 0.47 vs. 2.06 ± 0.91 Pa; p = 0.52). Among the 97 patients, 81 (83.5%) had at least 1 lesion with low ESS: 61 patients (62.9%) had lesions only with low ESS, and 20 patients (20.6%) had both lesions with low ESS and lesions with physiological/high ESS; 16 patients (16.5%) had lesions only with physiological/high ESS. Lesions were similarly distributed in the left anterior descending, the left circumflex, and the right coronary artery (TCFA: 41.2%, 35.3%, and 23.5% respectively; ThCFA 31.9%, 31.9%, and 36.2% respectively). Lesions were primarily located in the proximal portion of each coronary artery compared with the midportion or distal portion of the artery (51.7% vs. 29.7% vs. 18.6%).

LESION LOCATION OF THE LOWEST AND HIGHEST ESS. The highest baseline ESS most commonly occurred at the site of MLA (85 of 145 [58.6%]), whether or not the lesion was responsible for nc-MACE during follow-up (12 of 23 [52.2%] vs. 73 of 122 [59.8%] respectively; p = 0.78) (Figures 1A to 1C). In contrast, the lowest baseline ESS occurred either proximal or distal to the MLA, but rarely at the MLA (Figures 2A to 2C). There was no difference in the lowest ESS distribution pattern between nc-MACE lesions and nc-non-MACE lesions (p = 0.87).

ASSOCIATION OF BASELINE LOW LOCAL ESS WITH MACE. The baseline characteristics of nc-MACE compared with nc-non-MACE lesions are presented in Table 1. nc-MACE lesions were significantly longer and had larger PB, smaller MLA, and lower local ESS values. There were no significant differences in the EEM area, coronary vessel or lesion location, proportion of TCFA versus ThCFA, or highest local ESS measurement.

The cumulative distribution of local ESS values for all lesions, and for TCFAs and ThCFAs individually, and the relationship of ESS with subsequent nc-MACE are shown in Figures 3A to 3C and 4A and 4B. Low baseline local ESS (<1.3 Pa) was strongly associated with the development of nc-MACE during follow-up compared with lesions with physiological or high ESS (≥1.3 Pa) (23 of 101 [22.8%] vs. 0 of 44 [0.0%]). In the propensity-adjusted Cox regression analysis, coronary lesions with baseline lower ESS, as a continuous variable, had a substantially higher likelihood of leading to nc-MACE during follow-up (hazard ratio: 4.34; 95% confidence interval: 1.89 to 10.00; p < 0.001) (Figure 4A).

TABLE 1 Baseline Characteristics of Lesions Responsible for Future Major Adverse Cardiac Events Compared With Lesions Without Subsequent Events

	nc-MACE Lesions (n = 23)	nc-non-MACE Lesions (n = 122)	p Value
Lesion length, mm	33.0 ± 21.0	21.0 ± 12.0	0.02
Plaque burden, %	67.7 ± 8.0	59.0 ± 8.6	<0.001
Minimal lumen area, mm^2	4.2 ± 1.0	5.4 ± 2.0	<0.0001
Lowest local ESS, Pa	0.61 ± 0.34	1.13 ± 0.79	<0.0001
Highest local ESS, Pa	6.02 ± 2.95	4.69 ± 2.44	0.12
EEM area, mm^2	14.44 ± 3.50	14.11 ± 4.47	0.78
Lumen area, mm^2	6.66 ± 1.52	7.20 ± 2.41	0.31
Plaque area, mm^2	7.78 ± 2.29	6.91 ± 2.49	0.22
Arterial remodeling at the MLA			0.003
Constrictive	14 (60.9)	35 (28.7)	
Compensatory	9 (39.1)	87 (71.3)	
Expansive	0 (0.0)	0 (0.0)	
Artery-specific coronary blood flow, ml/s	1.27 ± 0.50	1.30 ± 1.30	0.81
Thin-cap fibroatheroma	13 (56.5)	63 (51.6)	0.67
Thick-cap fibroatheroma	10 (43.5)	59 (48.4)	0.67
Coronary artery			0.97
Left anterior descending	8 (34.8)	42 (34.4)	
Left circumflex	8 (34.8)	40 (32.8)	
Right	7 (30.4)	40 (32.8)	
Location in artery			0.25
Proximal	15 (65.2)	59 (48.4)	
Middle	6 (26.0)	37 (30.3)	
Distal	2 (8.7)	26 (21.3)	

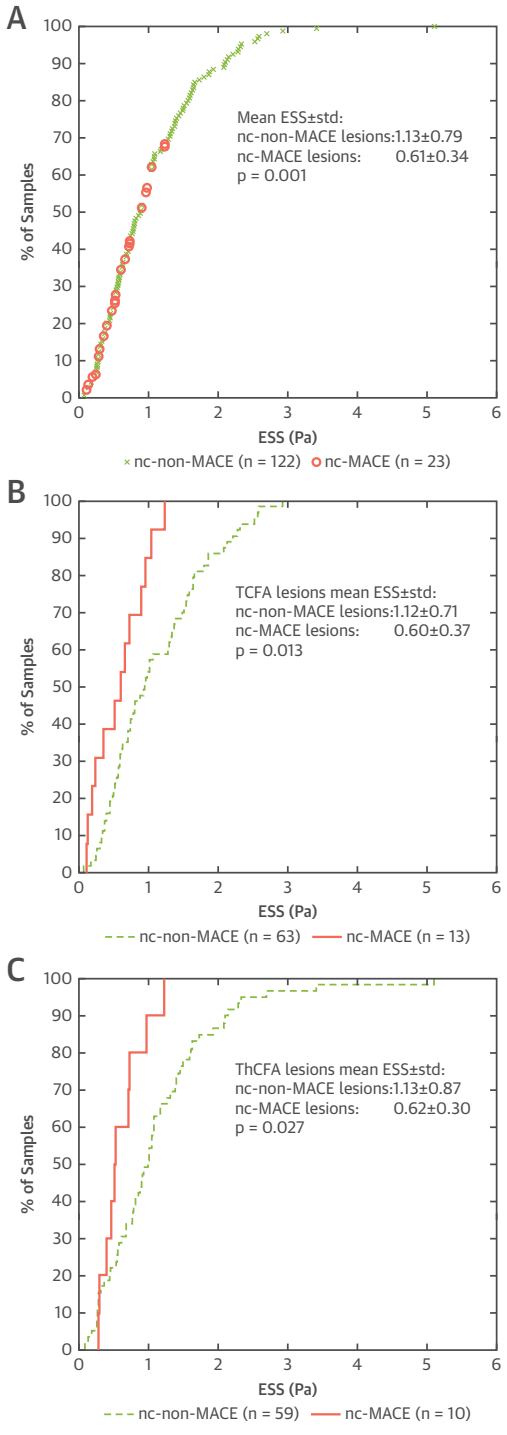
Values are mean ± SD or n (%).

EEM = external elastic membrane; ESS = endothelial shear stress; MACE = major adverse cardiac events; MLA = minimal lumen area; nc = nonculprit.

Lesions were further categorized at baseline on the basis of anatomic characteristics as high risk (the presence of ≥2 characteristics of PB ≥70%, MLA ≤4.0 mm^2, TCFA morphology) versus low risk (≤1 risk characteristic) and the presence of low ESS versus physiological/high ESS. Nc-MACE occurred only in the presence of low ESS; there were no nc-MACE events in the presence of physiological/high ESS regardless of anatomic risk (Figure 4B). However, among low-ESS lesions, the presence of ≥2 high-risk anatomic characteristics further risk stratified the likelihood of developing nc-MACE at 3 years (52.1% in lesions with high anatomic risk vs. 14.4% in lesions with low anatomic risk; p < 0.0001) (Figure 4B).

Patients with ≥1 nc lesion with baseline low ESS were significantly more likely to develop nc-MACE in follow-up compared with those patients with nc lesions with physiological/high ESS (Figure 5A). No nc-MACE occurred if the patient did not have a lesion with baseline low ESS. Among patients with ≥1 nc lesion with baseline low ESS, the 3-year nc-MACE rate was substantially higher if 1 or more of these lesions also had ≥2 high-risk anatomic characteristics (54.9% vs. 19.5%; p = 0.004) (Figure 5B).

FIGURE 3 Cumulative Distribution of Low Local ESS Within Lesions According to the Development of nc-MACE (nc-MACE Lesions) or No nc-MACE (nc-Non-MACE Lesions) During Follow-Up



(A) All lesions. **(B)** Thin-cap fibroatheromas (TCFAs). **(C)** Thick-cap fibroatheromas (ThCFAs). ESS = endothelial shear stress; MACE = major adverse cardiac event; nc = nonculprit; nc-MACE lesions = nonculprit major adverse cardiac event lesions; nc-non-MACE lesions = nonculprit lesions not causing major adverse cardiac events.

When the categorical analyses were re-run with a low ESS cutoff of <1.0 Pa, the number of low ESS lesions was reduced from 101 (70%) to 83 (57%). The association between dichotomous ESS <1.0 Pa and outcome at the lesion level remained statistically significant ($p = 0.006$), as was the association between the combined lesion anatomic risk and ESS risk ($p < 0.0001$). Changing the cutoff value to ESS <1.0 Pa reduced the number of patients with a low ESS lesion from 81 (84%) to 70 (72%). The nc-MACE rate was higher in patients with a lesion categorized by low ESS <1.0 Pa alone, although the association was of borderline significance ($p = 0.12$). When lesions were categorized using the combined lesion anatomic risk and low ESS risk, however, the association between patient risk and nc-MACE remained statistically significant ($p = 0.008$), similar to the results using the <1.3 Pa cutoff. In general, changing the low ESS cutpoint from <1.3 to <1.0 Pa did not noticeably alter the association between ESS and nc-MACE at either the lesion or patient level.

DISCUSSION

This post hoc, hypothesis-driven pilot study explored the prognostic significance of the presence of baseline low local ESS when added to the known anatomic prognostic indicators of large PB, small MLA, and TCFA phenotype in high-risk U.S. and European patients presenting with ACS. The results suggest that the presence of proinflammatory low ESS within a lesion, as a continuous or a categorical variable, may provide substantial prognostic utility for future nc-MACE on a per-lesion and per-patient basis when added to the other known anatomic risk factors. Notably, no lesion without low ESS led to nc-MACE during a median follow-up time of 3.4 years, regardless of PB, MLA, or lesion phenotype at baseline. Moreover, the presence of low ESS and high-risk anatomic characteristics appeared to be synergistic in identifying lesions and patients likely to develop nc-MACE during long-term follow-up.

Despite the systemic nature of atherosclerosis, its phenotypic manifestations are highly focal. As a potent proinflammatory and proatherogenic stimulus, low ESS is a major factor responsible for the development and progression of atherosclerosis (15-17). Through mechanotransduction of local blood flow forces along the microenvironment of the arterial wall, low ESS stimulates local endothelial cells to down-regulate atheroprotective genes and switch to an atherogenic phenotype, including activation of nuclear factor-κB, a nuclear transcription factor that up-regulates a broad constellation of

proinflammatory and proatherogenic mediators (15). In the diabetic hypercholesterolemic pig model, low ESS is an independent predictor of the development of high-risk TCFAs, and the magnitude of the atherogenic phenotype is inversely related to the magnitude of preceding local ESS (10,11,13).

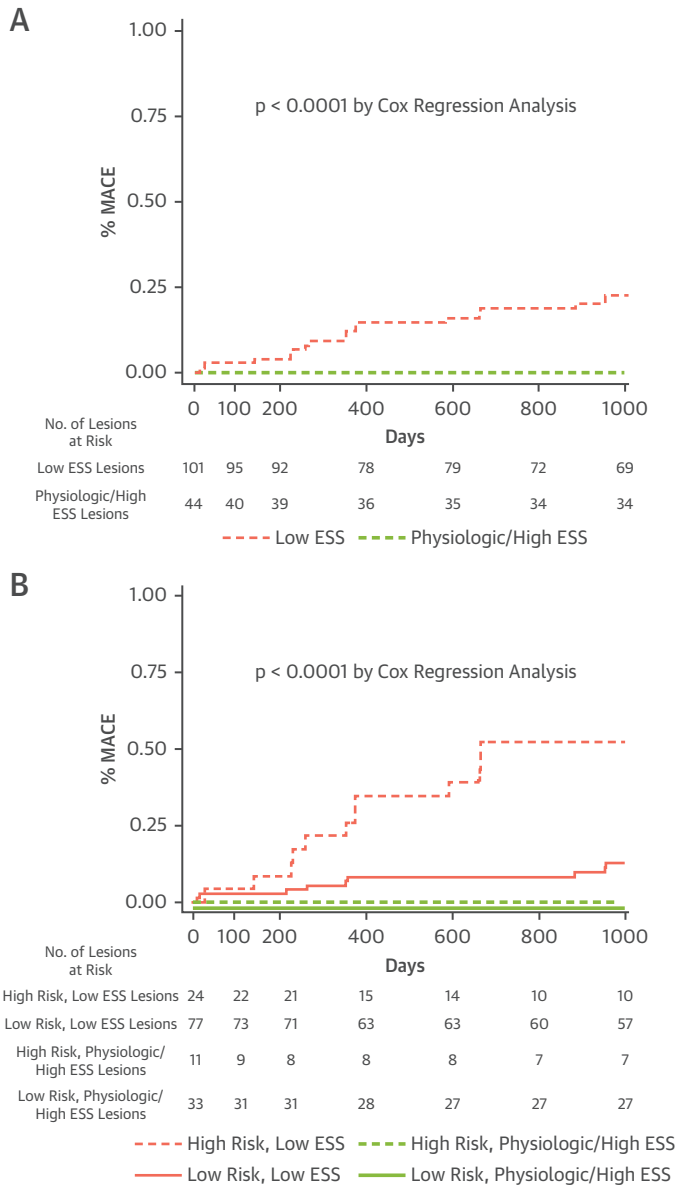
In this pilot, limited study we used an unbiased determination of low ESS for our primary categorical analysis on the basis of the lowest tertile of ESS values within the PROSPECT cohort, which was <1.3 Pa. Most of the previous determinations of low ESS have been made in severely hypercholesterolemic and diabetic swine models, which are not germane to humans. Some human studies, such as PREDICTION, have also used unbiased determinations of low ESS on the basis of the lowest tertile within the study cohort to categorize low ESS, which was <1.0 Pa in that low-risk cohort. In a secondary analysis we also reanalyzed the results using the low ESS cutpoint of <1.0 Pa and observed similar associations between ESS and nc-MACE at either the lesion or patient level. Future large-scale studies are needed to provide more data to guide optimal selection of low ESS cutoff in patients with different characteristics.

The cutoff values to determine the most proinflammatory low ESS value likely depend on a variety of systemic risk factors and demographic characteristics, such as ethnicity, sex, body mass index, and so forth. In the Yorkshire pig model, for example, the absolute low ESS value that is proatherogenic is higher in pigs with a higher cholesterol level, and lower in pigs with a lower cholesterol level (16). Preliminary data from the PREDICTION study also indicate that high C-reactive protein values synergistically exacerbate the proatherogenic effect of low ESS (18). More data are needed from human investigations to enhance the understanding of the specific low ESS values that are most proinflammatory in individual patients.

The observation that the highest local ESS within a coronary lesion occurs at the MLA but that low ESS locates either upstream or downstream from the MLA suggests important implications for understanding the vascular biology of atherosclerosis along the length of a lesion. Plaque morphology consists of a heterogeneous structure along its longitudinal course, and there may be multiple areas of different vessel dimensions, PB, composition, remodeling, and local ESS within individual coronary plaques (19,20). Our hypothesis-generating results reinforce the prognostic role of high-risk anatomic lesion features, but they also suggest that an ongoing proinflammatory stimulus of local low ESS may also contribute to the process of plaque destabilization and triggering of nc-MACE. There may be multiple areas of low ESS along the course of a coronary lesion, both upstream and downstream from the MLA (**Figure 2**), although it is not clear which specific low-ESS area will be responsible for triggering MACE.

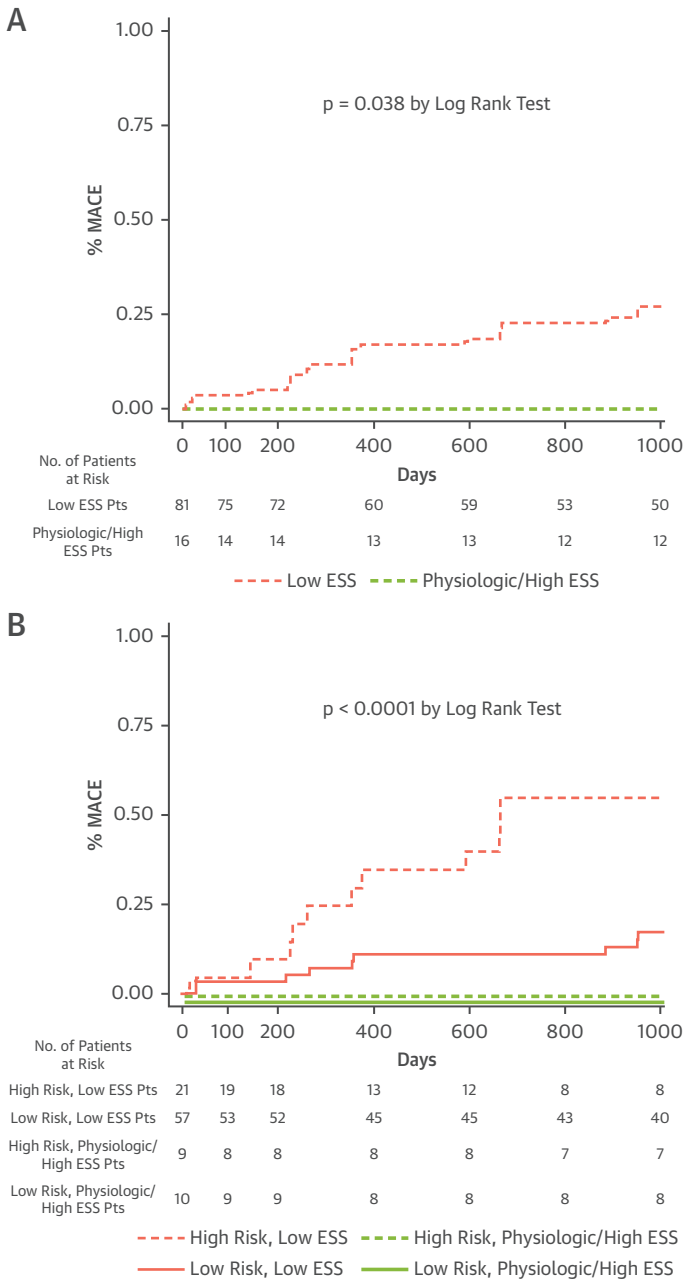
The natural history of atherosclerosis is also variable; although some plaques evolve to rupture and

FIGURE 4 Kaplan-Meier Curves of Lesion-Level nc-MACE According to Baseline ESS



(A) All lesions. **(B)** Lesions categorized by high-risk anatomic features and by local endothelial shear stress (ESS). The number at risk refers to the number of lesions at risk. Low endothelial shear stress is <1.3 Pa. Physiologic or high endothelial shear stress is ≥1.3 Pa. MACE = major adverse cardiac events.

FIGURE 5 Kaplan-Meier Curves of Patient-Level MACE According to Baseline ESS



(A) All patients. **(B)** Patients with lesions categorized by high-risk anatomic features as well as local endothelial shear stress (ESS). The number at risk refers to the number of patients at risk. Endothelial shear stress classification as in Figure 4. MACE = major adverse cardiac events.

thrombosis, most remain quiescent over time (8,9). The observation in PROSPECT that <20% of plaques with all 3 high-risk anatomic criteria (large PB, small MLA, and TCFA composition by RF-IVUS) were associated with new nc-MACE over 3 years demonstrates the relatively low positive predictive value of morphological imaging (3). In contrast, an nc lesion that remains in a low-ESS microenvironment will likely continue to progress (4,8,17), whether it is a TCFA or a ThCFA at the time of the baseline anatomic imaging "snapshot." Thus ESS profiling is complementary to anatomic lesion assessment, and it substantially improves the positive predictive value of lesion characterization without sacrificing sensitivity. In this regard, accurate risk assessment requires careful evaluation of the entire lesion because the highest-risk portion of the plaque may be distinct from the MLA.

As suggested from this study, the presence of low ESS at any point along the course of a lesion may be a particularly ominous indicator for future plaque instability. Nonetheless, not all plaques with low local ESS resulted in nc-MACE during 3-year follow-up. Those plaques with low ESS and ≥2 high-risk anatomic characteristics (large PB, small MLA, or TCFA morphology) had a particularly high rate of causing nc-MACE during 3.4-year follow-up, whereas the prognosis of low-ESS lesions with ≤1 high-risk anatomic characteristic was reasonably benign (although not as favorable as for lesions with physiological/high ESS, in which no nc-MACE developed during follow-up, regardless of morphology). The dynamic and variable remodeling process of each lesion may be the critical driver determining whether an individual plaque remains expansively remodeled with proinflammatory low local ESS and consequent proclivity to plaque disruption (10,11,17) versus compensatory remodeling developing (8) with resolution of the low ESS stimulus and consequent plaque quiescence. Heterogeneous morphology, ESS, and variable dynamic remodeling along the course of individual plaques contribute to the difficulty of determining whether a particular lesion is in jeopardy of further progression and has the potential for disruption (21).

We emphasize that risk stratification of individual coronary lesions and possible pre-emptive selective intervention, even if proven efficacious, would only supplement systemic secondary prevention therapies, such as statin agents, antiplatelet drugs, and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and would never supplant them.

We underscore that these results are speculative and hypothesis generating. It will be critical to pursue larger-scale prospective studies with imaging sufficient to address the prognostic significance of low ESS in a more robust manner.

STUDY LIMITATIONS. Several important limitations of this post hoc, hypothesis-generating study deserve mention. Only 59% of the nc-MACE lesions in PROSPECT were suitable for calculation of local ESS, thus introducing the possibility of sampling error and selection bias. Many statistical analyses, including receiver-operating characteristic analyses to calculate the threshold low ESS value associated with nc-MACE, as well as positive and negative predictive values, could not be reliably assessed because of the small sample size. There were also too few events to allow construction of a comprehensive multivariable model predicting outcomes. Although the results suggest an association between ESS and MACE in nc lesions, the possibility of residual confounding cannot be dismissed. Prospective imaging studies with planned 3D reconstruction of the coronary arteries to permit CFD computations are required for definitive confirmation of the present study observations. The classification of lesions into TCFA or ThCFA histopathological phenotypes by RF-IVUS may not be entirely accurate (22). Nonetheless, this categorization has been shown prospectively to have prognostic utility (4,6,7). Whether plaque characterization by alternative imaging modalities, such as OCT or near-infrared spectroscopy, would prove as or more useful than RF-IVUS (and provide greater synergy with ESS profiling) is unknown. Finally, the impact of ESS on non-FA lesions, or in patients without ACS, was not assessed in this study.

We measured flow in the coronary arteries excluding the side branches, as is the usual methodological technique. There are evolving new methodologies that include the side branch blood flow in the CFD calculation that may improve the accuracy of local ESS calculations (21). There are also new computed tomography angiography techniques that may enable noninvasive detection of high-risk coronary lesions (23), as well as advanced engineering approaches to understand the mechanical stresses affecting individual coronary plaques (24).

CONCLUSIONS

Risk stratification of individual untreated, angiographically mild coronary lesions in high-risk patients with ACS may be substantially enhanced by examining each lesion not only for the presence of high-risk anatomic features (large PB, small MLA, TCFA phenotype), but also for the presence of a proinflammatory microenvironment (low local ESS).

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ADDRESS FOR CORRESPONDENCE: Dr. Peter H. Stone, Cardiovascular Division, Brigham & Women's Hospital, 75 Francis Street, Boston, Massachusetts 02115. E-mail: pstone@partners.org.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Baseline anatomic plaque characteristics of large PB, small MLA, and TCFA morphology are predictive of future MACE, but the positive predictive value for future MACE is low because most ostensibly high-risk plaques by anatomic criteria become quiescent. Local low ESS is a proinflammatory and proatherogenic stimulus responsible for the development and progression of coronary plaque. Assessment of the local proinflammatory low ESS along each plaque is synergistic with assessment of the anatomic plaque characteristics to identify those high-risk plaques that will progress to cause new MACE during follow-up.

TRANSLATIONAL OUTLOOK 1: It is possible to use IVUS imaging to characterize plaque anatomic characteristics and also to perform 3D reconstruction of the coronary artery and determine the local ESS profile using CFD. By combining the anatomic substrate and the low ESS pathobiological stimulus one can substantially improve prognostication of high-risk lesions that will progress to cause new MACE and identify those patients who may benefit from pre-emptive intervention.

TRANSLATIONAL OUTLOOK 2: IVUS assessment of CAD is an invasive procedure. The reconstruction process to generate the local ESS profile is now performed off-line and is somewhat time consuming. It will be important to create methodologies to assess plaque anatomy and local ESS while the patient is on the cardiac catheterization laboratory table to enable management decisions concerning pre-emptive PCI at the time of the catheterization procedure.

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