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Nonobstructive High Risk Plaques Increase the Risk of Future Culprit Lesions Comparable to Obstructive Plaques Without High Risk Features: the ICONIC Study

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Abstract

Background

High-risk plaque (HRP) and nonobstructive coronary artery disease (CAD) independently predict adverse events, but their importance to future culprit lesions has not been resolved. Our objective was to determine in patients prior to confirmed acute coronary syndrome (ACS) the association between the degree of obstructive CAD as evaluated by coronary computed tomographic angiography (coronary CT), and the absolute number and prevalence of HRP. The secondary objective was to examine the relative importance of nonobstructive HRP on becoming a culprit lesion.

Methods and Results

Within the ICONIC study, a nested case-control study of patients undergoing coronary CT, we included ACS cases with culprit lesions confirmed by invasive coronary angiography and coregistered to baseline coronary CT. Quantitative CT was used to evaluate obstructive (≥50%) and nonobstructive (<50%) diameter stenosis, with HRP defined as ≥2 features of spotty

calcification, positive remodeling, or low-attenuation plaque. 234 patients with downstream ACS over 3.86 ±2.66 years exhibited 198/898 plaques with HRP on coronary CT. Nonobstructive lesions comprised 81.4% of HRP, while HRP was less prevalent in nonobstructive (19.8%) than obstructive lesions (46.8%, $P<0.001$). Among the 124 patients with identifiable culprit lesion precursors, the adjusted hazard ratio (HR) was 1.85 (95% CI: 1.26-2.72) for HRP, with no interaction between %DS and HRP ($P=0.82$). Compared to nonobstructive HRP+ lesions, obstructive HRP- lesions exhibited a nonsignificant HR of 1.41 (95% CI: 0.61-3.25; $P=0.42$).

Conclusions

Nonobstructive HRP+ lesions outnumber those that are obstructive, and confer risk that is clinically comparable to obstructive HRP- lesions. HRP should be reported even in the presence of nonobstructive CAD.

Although obstructive coronary artery disease (CAD) evaluation forms the basis of risk stratification in cardiac disease, the majority of myocardial infarction (MI) precursors are derived from nonobstructive plaque (1-6). High-risk plaque (HRP) evaluation via atherosclerotic plaque characteristics (APCs) by coronary computed tomographic angiography (coronary CT) has been demonstrated to predict patients at high-risk for coronary events (7-9). Recent sub-studies of the PROMISE trial have highlighted the prognostic value of nonobstructive CAD and HRP in the coronary CT arm (5,10). However, the association of HRP and APCs in patients specifically with downstream acute coronary syndrome (ACS), and for culprit lesions responsible for ACS, remains unclear (10-13).

The aim of this study was to determine in patients prior to confirmed ACS the association between the degree of obstructive CAD as evaluated by baseline coronary CT, and the absolute number and prevalence of HRP. We also examined the relative importance of HRP for the outcome of becoming a culprit lesion in obstructive versus nonobstructive CAD.

Methods

Patient Population and Study Design

The ICONIC study, a nested case-control study within the CONFIRM registry of 25,251 consecutive patients undergoing baseline coronary CT, was comprised of 234 adjudicated patients with subsequent ACS events and propensity matched non-event controls (2). As previously described, patients were excluded for prior CAD, death without antecedent ACS, insufficient data for adjudication, and interval elective revascularization of a culprit segment (2). Only ACS cases (40 ST-elevation myocardial infarction, 114 non-ST elevation myocardial infarction, 6 MI that could not be distinguished, and 74 unstable angina) were included in the current study.

For culprit lesion subanalysis, masked adjudication of culprits by invasive coronary angiography (ICA) was performed using the ROMICAT convention of one culprit per patient, and subsequently aligned to lesions on baseline coronary CT (2). 162 culprit lesions were identified via ICA, of which 129 could be co-registered to baseline coronary CT (5 had no baseline CAD visible by coronary CT, 12 had baseline lesions unmeasurable due to artifact

or spatial resolution, and 16 had lesions by coronary CT elsewhere but none that could be aligned to the ICA-identified lesion). An additional 5 lesions were total occlusions that were not analyzed for plaque volume or plaque characteristics. In total, 124 patients were included for culprit lesion subanalysis.

Imaging Procedure and Lesion Analysis

All coronary CT evaluations were conducted using single-source and dual source ≥64-detector rows scanners (Vendors varying by institution), and imaging data obtained via prospective axial triggering or retrospective helical ECG-gating (2). Coronary CT measurements were evaluated by a blinded core lab using semi-automated plaque analysis software (MEDIS QAngio CT Research Edition v2.1.9.1, Medis Medical Imaging Systems, Leiden, Netherlands) (2,14).

A lesion with atherosclerosis was defined as any tissue >1mm^2 within or adjacent to the lumen that can be discriminated from surrounding pericardial tissue, epicardial fat, or lumen, and identified in >2 planes. Quantitative computed tomography (QCT) was performed for percent diameter stenosis (%DS), calculated by comparison to the most proximal normal cross-section ≤ 5mm from the lesion in question. Obstructive lesions were defined as ≥50%DS, and nonobstructive lesions <50%DS (15,16). Other QCT measurements included plaque volume, length, cross-sectional plaque burden, minimal lumen diameter, minimal lumen area, and plaque volume

by composition: calcified (Hounsfield Unit (HU)>350), noncalcified (HU≤350), and fibrofatty and necrotic core (HU≤130). Remodeling index was calculated using comparisons of mean vessel area within 5mm proximal and distal to the lesion.

Lesions were additionally evaluated for qualitative APCs: positive remodeling (PR) defined as a remodeling index ≥1.1, spotty calcification (SC) defined by visualized observed calcification ≤3.3mm in any direction within a plaque, and low-attenuating plaque (LAP) defined as <30 HU detected. Using these characteristics, HRP lesions were defined as the presence of two or more of the above APCs within any one plaque (2). Napkin ring sign (NRS), defined as a circumferential area of a non-calcified plaque that displays greater attenuation than the central portion, was also assessed as an APC, though not included in the definition of HRP due to low prevalence (2,17). Vessel location and distance to the ostium were also recorded.

Per-patient level maximal %DS was summarized as the maximum QCT %DS among all lesions, with total occlusions assigned as 100%, and classified into 6 subgroups (0%, 1-24%, 25-49%, 50-69%, 70-99%, and 100%). For culprit lesion subanalysis, patients were classified into four subgroups: Nonobstructive HRP-, nonobstructive HRP+, obstructive HRP-, and obstructive HRP+.

Primary and Secondary Outcomes

The primary outcome was HRP number and prevalence. The secondary outcome was the odds of becoming a culprit lesion.

Statistical Analysis

Continuous variables were reported as mean ± standard deviation (SD) and categorical variables as counts with percentage. Trends for continuous variables between %DS subgroups were assessed using Pearson's correlation coefficient and trends for categorical variables were assessed using Cochran Armitage test or Chi-squared test if Cochran Armitage test was not applicable. For the secondary outcome of becoming a culprit lesion, marginal Cox proportional hazard model adjusted for patient effects was performed to assess the predictive value of HRP, %DS and its interaction. Multivariable models were constructed using backward stepwise regression. Two-sided P-values of <0.05 were considered statistically significant. All statistical analyses were conducted using R (Version 3.3.0, R Development Core Team, 2016) and SAS (Version 9.4, SAS Institute Inc., Cary, NC, USA) software packages.

Results

Patient Characteristics

234 patients (age 62.2 ±11 years, 63% male) with ACS were included in this study. Mean time to ACS was 3.86 ±2.66 years. The most common baseline %DS subgroup in patients prior to ACS was 25-49% (43% of patients). There

was no significant association among cases between maximal %DS and underlying risk factors, chest pain typicality, or type of ACS (Table 1).

Association of HRP and APCs with %DS on Baseline Coronary CT

A total of 898 baseline lesions were observed in 234 patients. The number of lesions was highest for lower %DS, and the majority (819, 91.2%) were non-obstructive (Figure 2A, Table 2). HRP was observed in 198 (22%) of baseline lesions in patients. PR was the most common APC overall (77.8% of lesions), with a lower prevalence of SC (13.3%), and LAP (17.2%). The absolute number of APCs was significantly greater in nonobstructive lesions, comprising 91.4% of all lesions with PR, 80.6% with LAP, and 81.5% of all lesions with SC. All APCs (PR, SC, LAP) were significantly more prevalent with increasing %DS ($p<0.0001$).

The absolute number of HRP+ lesions was higher with lower %DS, with nonobstructive lesions comprising 81.4% of all lesions with HRP (Figure 2B). Similar to the trend for APCs, the prevalence of HRP was significantly lower in non-obstructive (19.8%) than in obstructive lesions (46.8%, test for trend $P<0.001$, Figure 2C).

Culprit Lesion Subset

124 patients with confirmed culprit lesion precursors exhibited 595 baseline lesions. 78.23% of culprit lesions were nonobstructive, and 32.26%

exhibited HRP. Compared to the lowest %DS of 1-24%, the risk of becoming a culprit lesion increased with greater %DS: 25-49%DS lesions (Hazard Ratio (HR) 2.49, 95% Confidence Interval (CI) 1.66-3.74), 50-99%DS lesions (HR 3.96, 95% CI 2.16-7.26) (Table 4). HRP also increased the risk of becoming a culprit lesion (HR 1.85, 95% CI 1.26-2.72). Both %DS and HRP remained significant predictors after multivariate adjustment. There was no significant interaction between ≥50%DS and HRP (p = 0.82).

As compared to nonobstructive HRP- lesions, nonobstructive HRP+ lesions exhibited significantly elevated risk of becoming a culprit lesion (adjusted HR 1.62, 95% CI: 1.06-2.5). Obstructive HRP- lesions also exhibited significantly elevated risk as compared to nonobstructive HRP- lesions (adjusted HR 2.55, 95% CI: 1.25-5.18) (Figure 3). There was no statistically significant difference in the risk of becoming a culprit lesion between nonobstructive HRP+ lesions and obstructive HRP- lesions (adjusted HR 1.41, 95% CI: 0.61-3.25, P=0.42).

Discussion

In this large multicenter cohort of patients with baseline coronary CT and subsequent ACS, we observed that nonobstructive HRP+ lesions far outnumber obstructive HRP+ lesions, and increase the risk of becoming a culprit to a level similar to that of obstructive HRP- lesions (P=0.42). 81.4% of all HRP lesions are nonobstructive, despite the prevalence of HRP increasing with %DS. Furthermore, HRP independently increases the risk of

becoming a culprit in both obstructive and nonobstructive CAD (HR 1.85, 95% CI: 1.26-2.72), without significant interaction with %DS (P=0.82). Our results are consistent with an underappreciated aspect of HRP analyses in coronary CT trials. In PROMISE and SCOT-HEART trials, both which define obstructive CAD at the higher threshold of $\geq$70%DS, the presence of nonobstructive HRP+ lesions increased the per-patient hazard ratio within the clinical range of obstructive HRP- lesions (HR 4.31, 95% CI: 2.25-8.26 and HR 9.31, 95% CI: 4.21-20.61 respectively in PROMISE and HR 5.81, 95% CI: 1.50-22.46 and HR, 7.73 5% CI: 1.73-34.54 in SCOT-HEART) (10,18). Our study highlights the importance of nonobstructive HRP on a per-lesion as well as a per-patient basis. Furthermore, we find no difference in the per-lesion risk of HRP by strata of %DS. This differs from the PROMISE trial, which observed that HRP significantly elevated risk in patients with nonobstructive, but not obstructive, lesions (10). Their study in a relatively low-risk population, however, may have had less statistical power for patients with obstructive lesions, and they did not perform interaction testing to formally evaluate effect modification. Invasive imaging trials, such as PROSPECT, also did not evaluate interactions between HRP and %DS (19). Our data thus lends support to reporting HRP even among nonobstructive lesions, as recommended by the CADRADS guideline.

The abundance of nonobstructive HRP- lesions in patients with future ACS, despite the higher likelihood of HRP in obstructive lesions, has been

observed by invasive imaging and coronary CT (10,11). Tian et. al. utilizing invasive imaging in patients undergoing ICA – including ACS patients – found the absolute number of thin cap fibroatheromas was three times greater in non-severe (<70%) stenosis as compared to severe stenosis (11). Using coronary CT, which permits the evaluation of mild (<30%) stenosis not well evaluated by invasive imaging, we observe more than four times the absolute number of HRP in nonobstructive as compared to obstructive lesions prior to ACS, and more than 60 times the number of HRP in non-severe as compared to severe stenosis. We calculate that within the PROMISE trial, the abundance of nonobstructive HRP+ patients resulted in a large attributable fraction of MACE (18.3%), higher than the attributable fraction of obstructive HRP+ (14.5%) and obstructive HRP- (8.4%) CAD (20). We also observed that the prevalence of HRP increased with increasing %DS, similar to prior invasive and coronary CT studies(10,11). Thus, in clinical practice, while obstructive HRP+ lesions are infrequent, salient, and thus attractive candidates for invasive intervention, nonobstructive HRP+ lesions represent a greater denominator of underappreciated risk for treatment on a per-patient level. Improved medical management in both obstructive and nonobstructive CAD partially accounts for the long-term benefit of the coronary CT arm in the SCOT-HEART trial (13). Our study lends support for shared decision-making for nonobstructive CAD, particularly if HRP+. Future analyses should evaluate the role of HRP+ and HRP- nonobstructive lesions

in optimal medical management, and the generalizability of our results to nonobstructive HRP diagnosed by invasive coronary imaging.

Study Limitations

HRP is well validated for elevated risk, but its utility in risk assessment and therapy has not been defined (10-12,19,21). The ICONIC study is unique in specifically examining the impact of baseline HRP on later culprit lesions identified by ICA at the time of first ACS, but cannot estimate diagnostic performance or generate risk scores given its case-control design. There may be information and referral bias inherent to the design of ICONIC as a retrospective nested case-control study. Total occlusions were not evaluated for HRP, which may have further biased results. With a larger sample size, the HR of nonobstructive HRP+ lesions and obstructive HRP- lesions may have reached statistical significance; nevertheless, the magnitude of risk is still clinically comparable, as is consistent with the PROMISE and SCOT-HEART substudies(10,18). We could not evaluate dynamic changes in HRP that may have occurred between baseline coronary CT and ACS, which may be better addressed by serial coronary CT studies (22). Finally, due to the case-control design of ICONIC, our substudy results cannot be generalized to primary prevention, and the risk of nonobstructive HRP in primary prevention may differ from what we observe. Furthermore, lesions with only one APC below the threshold of classification into HRP may also represent a large

denominator of risk. Future studies should derive and validate risk scores to integrate HRP evaluation into clinical decision-making.

Conclusions

In ACS cases with baseline coronary CT, HRP+ plaques that are nonobstructive far outnumber those that are obstructive, and confer risk of a magnitude that is clinically comparable to an obstructive HRP- lesion. HRP should be clinically reported even in the presence of nonobstructive CAD. Future studies should assess methods to integrate HRP and nonobstructive CAD into risk assessment for clinical decision-making.

Clinical Perspectives

In patients with no prior CAD and incident ACS after coronary CT, nonobstructive HRP+ lesions are much more common than obstructive HRP+ lesions, and exhibit comparable risk of becoming a culprit lesion to obstructive HRP- lesions. HRP should be reported even in the presence of nonobstructive CAD. Nonobstructive HRP represents a large denominator of underappreciated risk for medical therapy. We extend observations on the adverse effect of HRP from outcomes to predictions of specific culprit lesions among patients with later ACS with baseline coronary CT and no prior CAD. HRP and nonobstructive CAD should be integrated into risk assessment for clinical decision-making and medical management.

Relationship to Industry:
Dr. James K. Min receives funding from the Dalio Foundation, National Institutes of Health, and GE Healthcare. Dr. Min serves on the scientific advisory board of Arineta and GE Healthcare, and has an equity interest in Cleerly. All other authors have no relevant disclosures.

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FIGURES

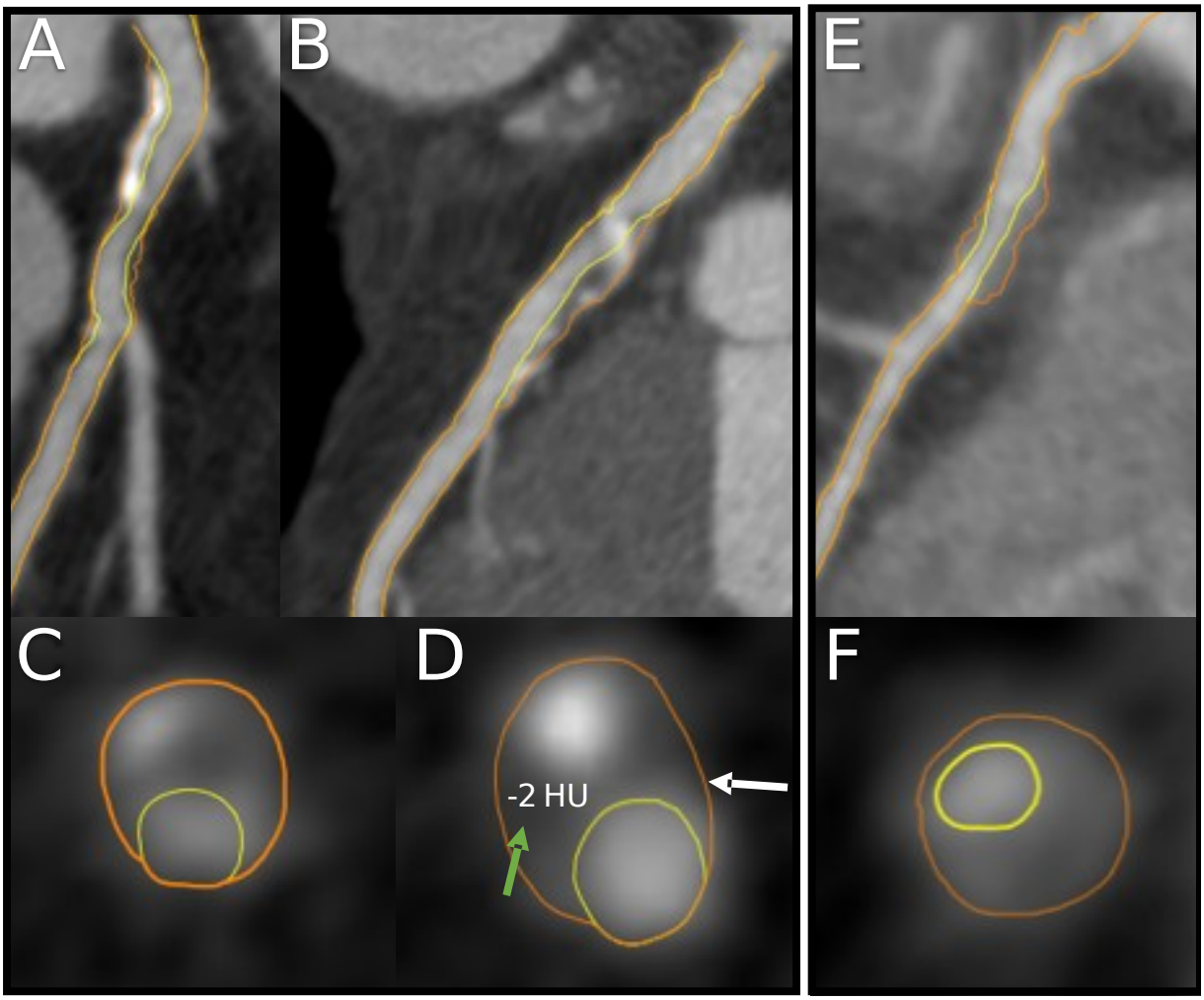
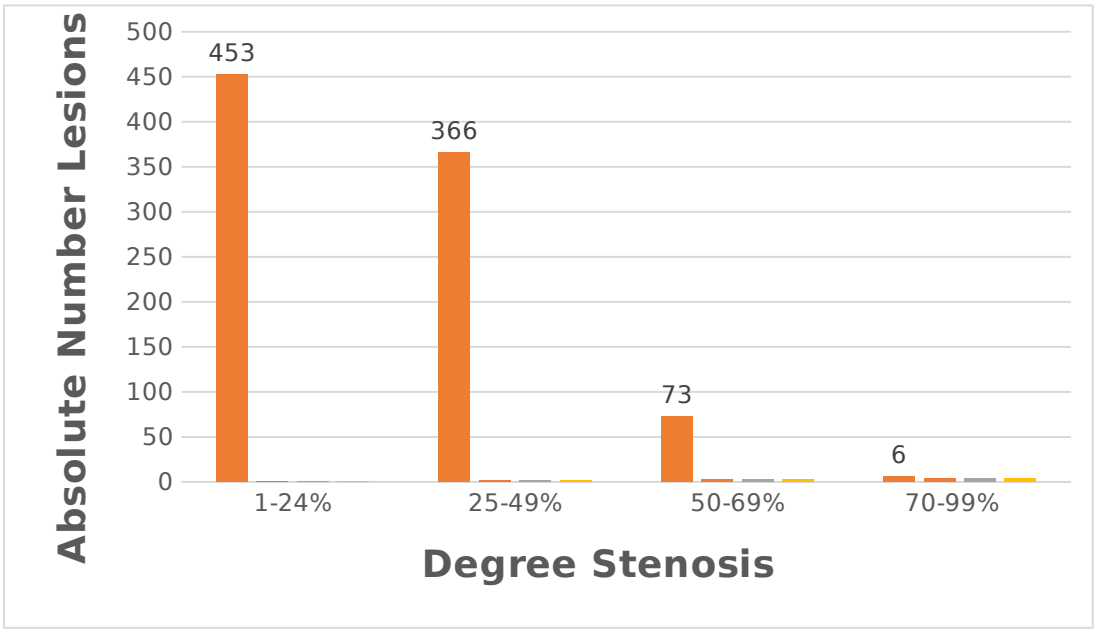


Figure 1. Coronary CT angiograms demonstrating HRP in culprit lesion precursors

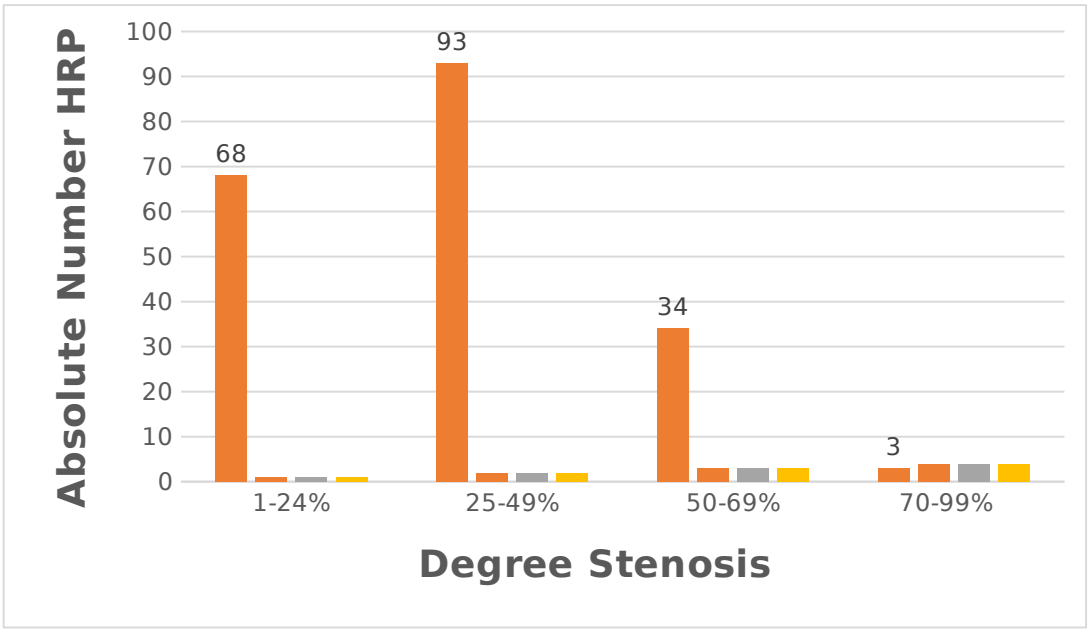
A 61-year-old male ex-smoker exhibited a high-risk plaque extending from the A) left main to the B) proximal left anterior descending artery with C) 41% diameter stenosis severity and D) positive remodeling (white arrow) and low attenuation plaque (green arrow). There is also diffuse calcification. One month later, the patient presented with a non-ST elevation myocardial infarction.

A 55-year old male with hypertension and hyperlipidemia exhibited a high-risk plaque with E) only 35% diameter stenosis severity, but F) positive remodeling, low attenuation plaque, and napkin ring sign. The patient presented with a non-ST elevation myocardial infarction 2 months later.

A


Absolute Number Lesions
500
450
400
350
300
250
200
150
100
50
0
453
366
73
6
1-24%
25-49%
50-69%
70-99%
Degree Stenosis

B


Absolute Number HRP
100
90
80
70
60
50
40
30
20
10
0
68
93
34
3
1-24%
25-49%
50-69%
70-99%
Degree Stenosis

C

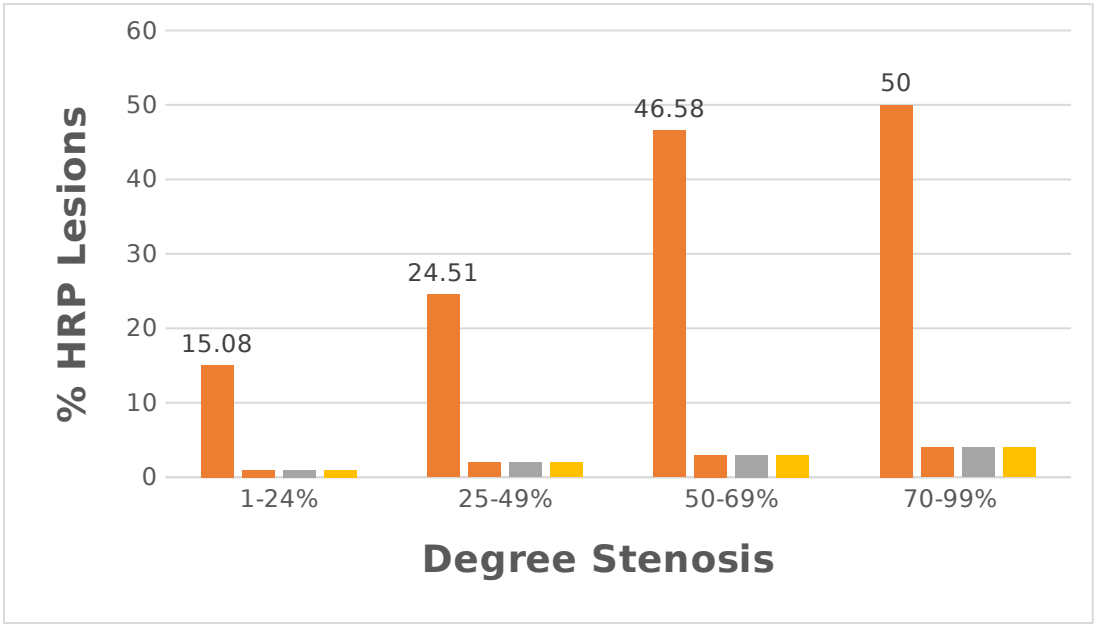
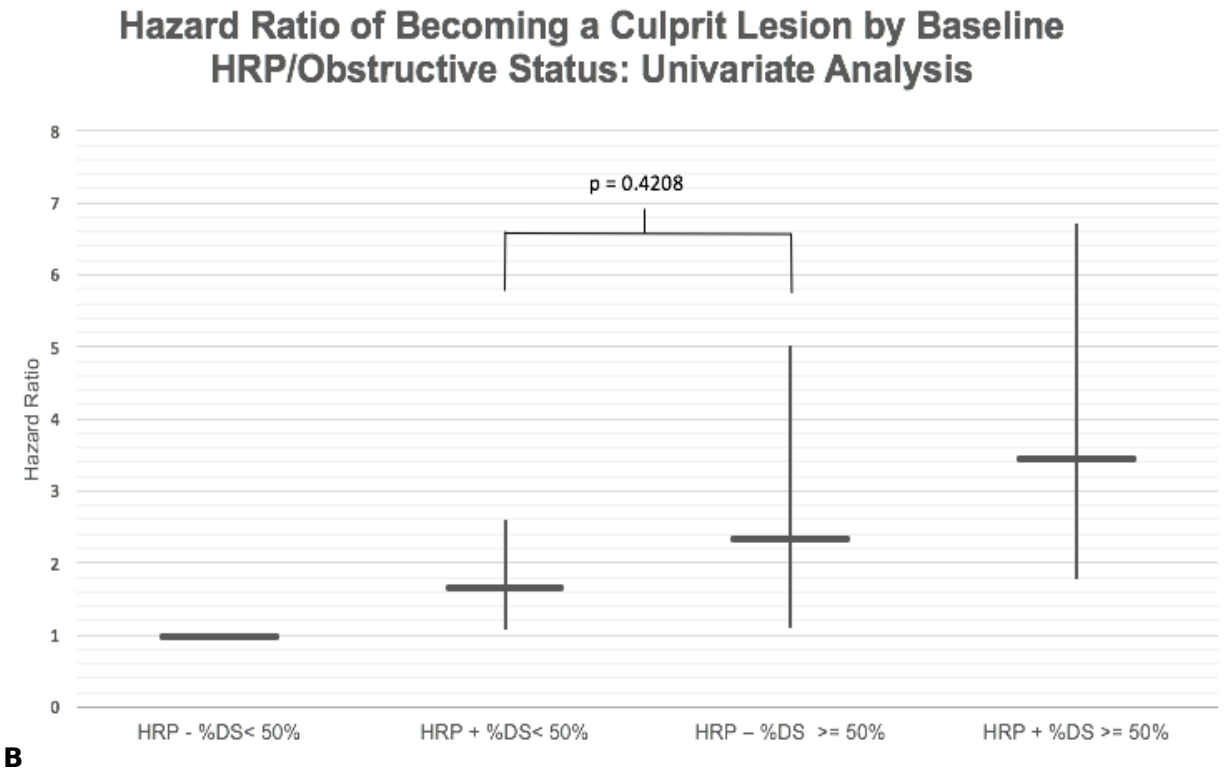

% HRP Lesions
60
50
40
30
20
10
0
15.08
24.51
46.58
50
1-24%
25-49%
50-69%
70-99%
Degree Stenosis

Fig. 2

Absolute Number and Prevalence of Plaque and HRP by %Diameter Stenosis

(A) Absolute number of total lesions by % diameter stenosis. Lesser %DS lesions are more numerous, with 91% of lesions nonobstructive. (B) Absolute number of HRP lesions by %DS. The greatest number of HRP lesions is also seen in nonobstructive (%DS<50) lesions, with the most overall from 25-49% stenosis. (C) Prevalence of HRP by %DS. While the absolute number of HRP is higher in nonobstructive lesions, obstructive lesions are more likely to exhibit HRP, with the greatest prevalence at 70-99% stenosis.

A



B

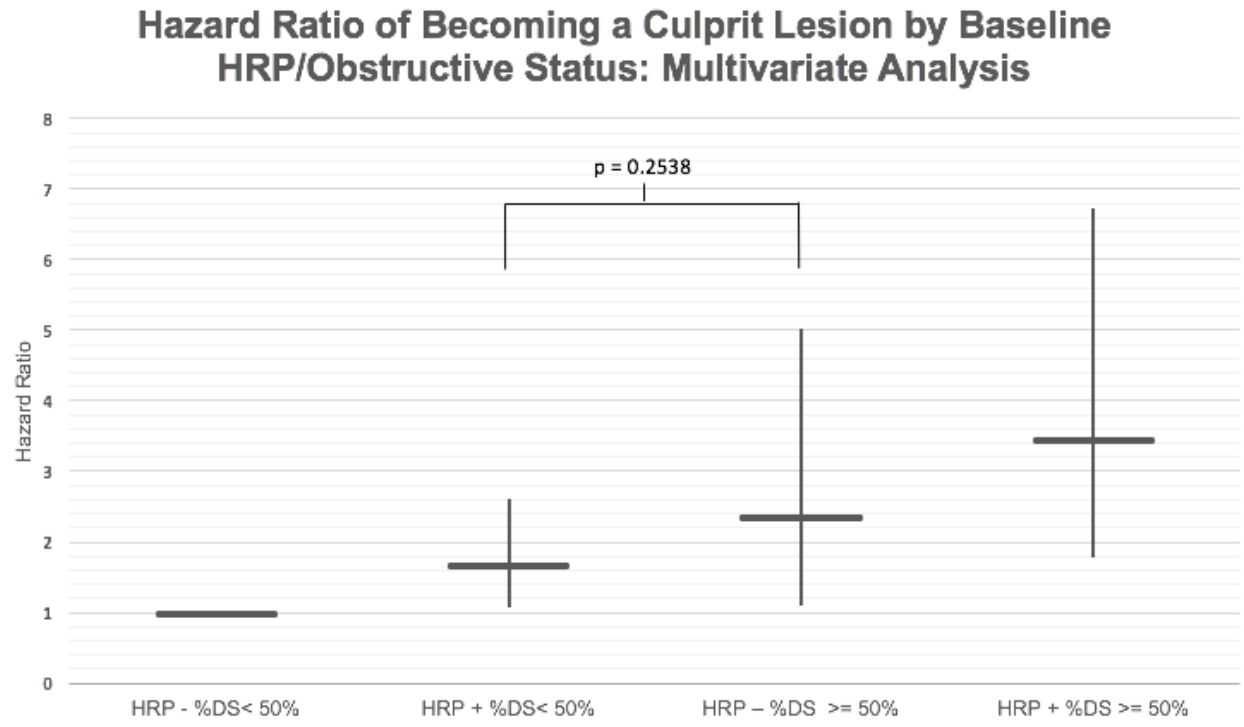


Figure 3
Hazard Ratio of Becoming a Culprit Lesion: Univariate and Multivariate Analysis

Adjusted and unadjusted hazard ratio of becoming a culprit lesion by combinations of the presence of HRP and obstructive CAD. The presence of HRP elevates the risk of nonobstructive lesions to a level that nears that of an HRP- obstructive lesion (P=0.25). There is no significant interaction between HRP and obstructive %DS (P=0.64).

TABLES

TABLE 1 Patient Characteristics of ACS patients by Baseline Maximally Stenotic Segment

Maximum % Diameter Stenosis	0% (n=15)	1-24% (n=37)	25-49% (n=101)	50-69% (n=51)	70-99% (n=6)	100% (n=24)	P-test for trend
Age, N (%)	63 (49, 69)	60 (52, 68)	64 (54, 69)	68 (58, 74)	59.5 (47, 61)	63 (55, 71)	0.1021
Sex (Male), N (%)	6 (40)	29 (78)	63 (62)	31 (61)	5 (83)	15 (63)	0.8538
BMI, Median (IQR)	26.4 (23.4, 31.6)	27.6 (24.9, 30.7)	26 (24.0, 29.5)	26.8 (23.8, 30)	29 (27.7, 30.5)	26.1 (24.1, 29.2)	0.2694
Risk factors							
Hypertension, N (%)	9 (60)	21 (57)	63 (62)	34 (67)	4 (67)	17 (71)	0.1697
Hyperlipidemia, N (%)	8 (53)	19 (51)	56 (55)	28 (55)	5 (83)	13 (54)	0.6184
Diabetes, N (%)	3 (20)	1 (3)	26 (26)	11(22)	1(17)	4 (17)	0.5436
Smoking current, N (%)	5 (33)	12 (32)	27 (27)	16 (31)	3 (50)	9 (38)	0.4995
Smoking past, N (%)	2 (13)	14 (38)	32 (32)	19 (37)	4 (67)	8 (33)	0.2648
Family History, N (%)	8 (53)	14 (38)	45 (45)	13 (25)	5 (83)	9 (38)	0.493
Race/ethnicity							
White, N (%)	7 (47)	19 (51)	48 (48)	26 (51)	3 (50)	9 (38)	0.3823
East Asian, N (%)	3 (20)	3 (8)	25 (25)	13 (25)	1 (17)	8 (33)	0.0546
Others, N (%)	2 (13)	3 (8)	4 (4)	3 (6)	0 (0)	0 (0)	0.0678

Angina Severity							
None, N (%)	1 (7)	14 (38)	12 (12)	6 (12)	1 (17)	3 (13)	0.1811
Noncardiac, N (%)	4 (27)	5 (14)	11 (11)	7 (14)	0 (0)	1 (4)	0.0799
Atypical CP, N (%)	6 (40)	9 (24)	46 (46)	19 (37)	2 (33)	12 (50)	0.1804
Typical CP, N (%)	3 (20)	8 (22)	26 (26)	18 (35)	3 (50)	5 (21)	0.3537
Dyspnea Y/N, N (%)	1 (7)	8 (22)	16 (16)	9 (18)	1 (17)	5 (21)	0.718
ACS Type							
STEMI, N (%)	2 (13)	10 (27)	15 (15)	6 (12)	2 (33)	5 (21)	0.9312
NSTEMI/MI NOS, N (%)	10 (67)	19 (51)	50 (50)	23 (45)	3 (50)	15 (63)	0.9893
UA, N (%)	3 (20)	8 (22)	36 (36)	22 (43)	1 (17)	4 (17)	0.9557

BMI = body mass index; CP = chest pain; ACS = acute coronary syndrome; STEMI = ST elevation myocardial

infarction; MI NOS = myocardial infarction not otherwise specified; UA = unstable angina

TABLE 2 Individual Lesion CT characteristics by Baseline Diameter Stenosis

% Diameter Stenosis	1-24% (n=453)	25-49% (n=366)	50-69% (n=73)	70-99% (n=6)	p Test for Trend
Stenosis measures					
Minimal lumen diameter, mm^2 mean (SD)	2.08 (1.71, 2.59)	1.61 (1.31, 1.93)	1.24 (1.06, 1.46)	0.65 (0.34, 1.05)	<0.0001
%DS, mean (SD)	14.67 (8.09, 19.4)	34.50 (29.14, 41.62)	56.31 (52.38, 63.16)	75.20 (71.88, 84.79)	<0.0001
Lesion Location					
LAD, N (%)	158 (35)	170 (46)	35 (48)	2 (33)	0.0018
RCA, N (%)	165 (36)	109 (30)	25 (34)	2 (33)	0.1798
LM, N (%)	16 (4)	12 (3)	1 (1)	0 (0)	0.3777
LCx, N (%)	114 (25)	75 (20)	12 (16)	2 (33)	0.0764
Distance to ostium, mm (SD)	38.50 (23.00, 62.33)	37.72 (23.92, 55.30)	37.83 (27.45, 54.52)	30.13 (23.74, 55.52)	0.407
QCT measurements					
Plaque volume, mm^3 (SD)	18.05 (8.00, 38.91)	50.31 (17.92, 128.43)	150.63 (86.34, 303.3)	166.94 (96.94, 568.18)	<0.0001
Calcified plaque, % (SD)	3.63 (0.81, 10.47)	11.19 (2.44, 35.31)	45.28 (10.81, 94.34)	95.08 (22.69, 238.22)	<0.0001
Non-calcified plaque, % (SD)	12.55 (4.53, 28.92)	32.81 (8.39, 80.79)	97.7 (40.06, 197.87)	90.07 (37.84, 177.96)	<0.0001
Fibrofatty + necrotic core, % (SD)	1.16 (0.09, 6.06)	4.78 (0.38, 23.97)	20.15 (6.53, 64.31)	9.05 (7.69, 21.5)	<0.0001
Remodeling index, N (SD)	1.33 (1.16, 1.55)	1.30 (1.09, 1.57)	1.28 (1.11, 1.55)	1.38 (1.11, 1.81)	0.6891
Lesion length, (mm) mean (SD)	16.12 (12.75, 22.28)	24.00 (16.03, 38.78)	43.91 (28.91, 61.18)	49.36 (33.46, 85.67)	<0.0001
Atherosclerotic Plaque Characteristics					
PR, N (%)	376 (83)	263 (72)	55 (75)	5 (83)	0.0031
SC, N (%)	44 (10)	53 (14)	20 (27)	2 (33)	<0.0001

TABLE 3 Hazard Ratio of Becoming a Culprit Lesion by Stenosis Severity and HRP

%Diameter Stenosis	Unadjusted HR	P-value	Adjusted HR*	P value
1-24%	1		1	
25-49%	2.49 (1.66, 3.74)	<0.0001	2.24 (1.47, 3.42)	0.0002
50-99%	3.96 (2.16, 7.26)	<0.0001	4.19 (2.33, 7.54)	<0.0001
High-risk plaque	1.85 (1.26, 2.72)	0.002	1.77 (1.21, 2.60)	0.003
Interaction HRP and DS (≥50%)	0.89 (0.31, 2.5)	0.8187	1.26 (0.48, 3.34)	0.6393

***Backward stepwise adjustment for clinical characteristics**

HR = hazard ratio; HRP = high risk plaque; DS = degree stenosis;