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Synergistic Effect of Cardiovascular Risk Factors on Necrotic Core in Coronary Arteries

A Report From the Global Intravascular Radiofrequency Data Analysis Registry

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OBJECTIVES This study explored whether an individual or a cluster of risk factors affects the extent of necrotic core (NC) assessed by intravascular ultrasound (IVUS) radiofrequency data (RFD) analysis.

BACKGROUND Several systemic diseases contribute to the development of coronary artery disease.

METHODS The Global Intravascular Radiofrequency Data Analysis Registry was a prospective, multicenter, nonrandomized database that enrolled 990 patients with coronary artery disease in whom 1 major coronary artery was imaged by IVUS-RFD. For the multivariable analysis, the population was divided into 4 classes: young women, young men (both ≤62 years), old women, and old men (>62 years). Mean NC area was categorized as 1: top quartile (≥0.62 mm^2) or as 0: lower 3 quartiles.

RESULTS Young patients had less NC compared with older patients (0.40 ± 0.36 mm^2 of NC vs. 0.50 ± 0.46 mm^2 in old patients, p = 0.0007). Nondiabetic patients had less NC than diabetic patients (0.43 ± 0.41 mm^2 of NC vs. 0.51 ± 0.44 mm^2 in diabetic patients, p = 0.02). The NC area was lower in normotensive patients (0.40 ± 0.36 mm^2) than in hypertensive patients (0.48 ± 0.44 mm^2) (p = 0.02). In the bivariate analysis, age, hypertension, diabetes, and prior coronary artery bypass graft were statistically significant, however in logistic regression analysis, only age (odds ratio [OR]: 1.023, 95% confidence interval [CI]: 1.009 to 1.037, p = 0.001) and diabetes (OR: 1.636, 95% CI: 1.174 to 2.279, p = 0.004) remained statistically significant. In a per-class logistic regression analyses including only diabetes as covariate, the OR in young women was 2.1 (95% CI: 0.77 to 6.0, p = 0.14), in young men the OR was 1.6 (95% CI: 0.90 to 2.7, p = 0.11), in old women the OR was 2.3 (95% CI: 1.09 to 4.9, p = 0.03), and in old men the OR was 1.6 (95% CI: 0.96 to 2.7, p = 0.07). Further, when only patients with diabetes and hypertension were included, young men (OR: 2.0, p = 0.041), old women (OR: 3.04, p = 0.046), and old men (OR: 2.2, p = 0.025) were significant.

CONCLUSIONS Individually and collectively, age and diabetes mellitus are associated with an increase in NC by IVUS-RFD analysis. (J Am Coll Cardiol Img 2009;2:629–36) © 2009 by the American College of Cardiology Foundation

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Several systemic diseases contribute to the development of coronary artery disease. For example, in a very large international registry of patients with established coronary artery disease, 38.3% were diabetic patients, 80.3% were hypertensive, 77.0% were hypercholesterolemic, 45.4% were obese, and 13% were current smokers (1). These well-known cardiovascular risk factors not only modify coronary plaque composition (2), but also predispose patients to coronary plaque rupture or acute coronary thrombosis (3). Two of the chief modifiers of plaque morphology are age and sex (4).

A post-mortem study showed that the necrotic core (NC) size and plaque burden are larger in diabetic patients compared with nondiabetic patients (2). Furthermore, the simultaneous presence of both diabetes mellitus and dyslipidemia was associated with an increase in NC size when compared with patients with only diabetes (2). The purpose of the current analysis was to assess whether the extent of NC in coronary arteries, as measured by intravascular ultrasound-radiofrequency data (IVUS-RFD) analysis, is influenced by the presence of one or more cardiovascular risk factors in a worldwide registry of patients.

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome
CI = confidence interval
CSA = cross-sectional area
EEM = external elastic membrane
IVUS = intravascular ultrasound
NC = necrotic core
OR = odds ratio
RFD = radiofrequency data

METHODS

Patient selection. The Global Intravascular Radiofrequency Data Analysis Registry is a prospective, multicenter (42 centers), nonrandomized database of coronary artery disease patients admitted for coronary catheterization and undergoing analysis by IVUS-RFD; it started enrolment in March 2004, and the current analysis includes the first 990 patients enrolled. Patients, irrespective of their clinical presentation, older than 18 years old were eligible if at least 1 of their coronary vessels containing an atherosclerotic lesion by visual assessment was suitable for IVUS interrogation (absence of extensive calcification and/or severe vessel tortuosity). The selection of the investigated artery was left to the operator's decision; in the case report form the investigator reported the target lesion diameter stenosis by visual assessment and/or quantitative coronary angiography. Acute coronary syndromes (ACS) encompassed unstable angina according to the Braunwald classification, non–ST-segment elevation myocardial infarction, and ST-segment elevation myocardial infarction. All of the local ethical committees of the participant centers approved the protocol, and informed written consent was obtained from all patients.

Clinical definitions used in this study. Diabetes mellitus was defined if the patient had a fasting glucose level ≥1.26 g/l, if this risk factor was documented in the medical record, or if the patient was receiving dietary, oral drug, or insulin treatment. Hypercholesterolemia was defined if the patient had a total cholesterol level of more than 200 mg/dl, if this risk factor was documented in the medical record, or if the patient was receiving any lipid-lowering treatment, such as dietary or pharmacological treatment. Arterial hypertension was defined if systolic blood pressure was ≥140 mm Hg or diastolic blood pressure was ≥90 mm Hg, if this risk factor was documented in the medical record, or if the patient was receiving antihypertensive treatment.

IVUS-RFD acquisition and analysis. Image acquisition was performed during diagnostic coronary angiography, pre-intervention, post-balloon dilation, or post-stenting; however, the treated segment and 5 mm of adjacent reference was not included in the analysis.

Details regarding the validation of the technique have been reported (5,6). Briefly, IVUS-RFD analysis uses spectral analysis of IVUS-RFD to build tissue maps that are correlated with a specific spectrum of the radiofrequency signal and assigned color codes (fibrous [labeled green], fibrofatty [labeled greenish-yellow], NC [labeled red] and calcium [labeled white]) (5).

The IVUS-RFD data were acquired using continuous catheter pullback (Eagle-Eye 20-MHz, Volcano Therapeutics, Rancho Cordova, California) and a dedicated IVUS-RFD console (Volcano Therapeutics). The IVUS-RFD data were stored on DVD and sent to the core laboratories (Cardiovascular Research Foundation, New York, New York; Erasmus Medical Center/Cardialysis, Rotterdam, the Netherlands; or Toyohashi Heart Center, Toyohashi, Japan) for off-line analysis. Data acquisition was electrocardiogram-gated and recorded during the automated withdrawal of the catheter using a mechanical pullback device (TrakBack II or R-100, Volcano Therapeutics) at a pullback speed of 0.5 mm/s. The IVUS-RFD sampling during pullback is gated to the peak R-wave and is therefore dependent on heart rate. For instance, during constant heart rate of 60 beats/min, samples will be collected every 0.5 mm.

The IVUS images were reconstructed from the RFD using customized software (pcVH 2.2, Volcano Therapeutics). Longitudinal and cross-sectional views were used to determine the con-

tours. Manual contour detection of both the lumen and the media-adventitia interface was performed, and the radiofrequency data were normalized using a technique known as blind deconvolution (7), an iterative algorithm that deconvolves the catheter transfer function from the backscatter, thus accounting for catheter-to-catheter variability. Geometrical and compositional data were obtained for every slice. Plaque burden was calculated as: external elastic membrane $(EEM)_{area} - Lumen_{area} / EEM_{area} \times 100$. For this study, the mean cross-sectional area (CSA) of NC of the entire vessel pullback per patient was analyzed.

Statistical analysis. The distribution of the amount of NC, expressed as the mean area in mm^2, was right skewed. Accordingly, nonparametric statistics were used to calculate p values for the comparison among groups. Bivariate analysis and multivariable logistic regression analyses were performed to identify predictors of NC. To this aim, the study population was divided into 2 groups: 1) patients (n = 732) with a mean NC area corresponding to the 3 lower quartiles (NC <0.62 mm^2) of the overall NC distribution (coded as 0); and 2) patients (n = 250) with a mean necrotic area corresponding to the upper quartile of the mean NC area (NC ≥ 0.62 mm^2), coded as 1. All variables significantly ($p < 0.10$) associated with mean NC area on bivariate analysis were entered into subsequent models. Next, a logistic regression analysis with the enter method was performed for all pertinent covariates. The only 2 variables that remained statistically significant were age and diabetes. The Hosmer and Lemeshow Goodness-of-Fit test statistic was 0.14. This means that the model explains the variance in the dependent variable to a significant degree.

In a second approach, the population was divided into 4 classes according to the age (the median age was 62 years; age therefore was stratified into 2 classes: ≤62 vs. >62 years of age) and sex: 1) young women (n = 90); 2) young men (n = 406); 3) old women (n = 153); and 4) old men (n = 333). Then, for each class a logistic regression analysis was performed including diabetes as a covariate because diabetes was the only variable that was statistically significant in the previous multivariable analysis. Afterwards, for each class a new logistic regression analysis was performed including a variable that identified the simultaneous presence of diabetes and hypertension (coded as 1) or their absence (coded 0) in a patient.

Results of logistic regression analyses are reported as odds ratios (ORs) with 95% confidence intervals (CIs) and p values. All analyses were performed with SPSS version 12 statistical software (SPSS Inc., Chicago, Illinois).

Table 1. Demographics and Baseline Characteristics (n = 982)

Age (yrs ± SD)	62.1 (11.4)
Male	739 (75.3)
Prior cardiac history	585 (59.8)
Hypertension	625 (63.9)
Diabetes	240 (24.6)
Insulin user	61 (25.3)
Lipid disorder	639 (65.1)
Prior MI	269 (27.9)
Prior CABG	53 (5.4)
Family history of CAD	425 (47.2)
Current smoker	255 (25.8)
Previous smoker	253 (25.7)
Clinical presentation	
Non-ACS	581 (59.1)
ACS	401 (40.9)
Vessel imaged	
LAD	484 (49.3)
LCX	171 (17.4)
RCA	289 (29.4)
Other	38 (3.8)
Medication	
Statin	670 (68.2)
Aspirin	857 (87.6)
Beta-blocker	600 (61.5)
ACE inhibitor	405 (41.2)
Calcium channel blocker	185 (19.0)
Blood test	
Total cholesterol (mg/dl)	179.8 (45.4)
LDL cholesterol (mg/dl)	105.7 (36.7)
HDL cholesterol (mg/dl)	47.4 (14.8)
Triglycerides (mg/dl)	97.8 (98.3)
CK (U/l)	221.8 (402.5)
CK-MB (μg/l)	20.1 (49.3)
CRP (mg/dl)	35.8 (93.8)

Values are n (%).
ACE = angiotensin-converting enzyme; ACS = acute coronary syndrome; CABG = coronary artery bypass graft; CAD = coronary artery disease; CK = creatine kinase; CRP = C-reactive protein; HDL = high-density lipoprotein; LAD = left anterior descending; LCX = left circumflex; LDL = low-density lipoprotein; MI = myocardial infarction; RCA = right coronary artery.

RESULTS

The baseline characteristics are shown in Table 1. The studied vessel was the left anterior descending artery in 484 (49.3%) cases, the left circumflex artery in 171 (17.4%) patients, and the right coronary artery in 289 (29.4%) cases; in 38 (3.8%) patients other vessels were imaged, but 8 patients with imaging of a saphenous vein graft were ex-

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Table 2. Content of Necrotic Core per Cross-Sectional Area According to Clinical Presentation and Cardiovascular Risk Factor Status

	Mean	SD	p Value
Sex			0.20
Female	0.42	0.38	
Male	0.46	0.43	
Age			0.0007
Older than 62 yrs	0.40	0.36	
Younger than 62 yrs	0.50	0.46	
Clinical presentation			0.74
Non-ACS	0.44	0.41	
ACS	0.46	0.42	
Diabetes			0.02
Yes	0.51	0.44	
No	0.43	0.41	
Lipid disorder			0.92
Yes	0.45	0.42	
No	0.45	0.41	
Hypertension			0.002
Yes	0.48	0.44	
No	0.40	0.36	
Prior cardiac history			0.0007
Yes	0.48	0.42	
No	0.41	0.40	
Prior MI			0.04
Yes	0.49	0.44	
No	0.43	0.41	
Prior CABG			0.04
Yes	0.61	0.65	
No	0.44	0.39	
Medication			
ACE inhibitor			0.03
Yes	0.42	0.43	
No	0.47	0.46	
Calcium channel blocker			0.01
Yes	0.50	0.41	
No	0.44	0.42	
Blood test			
Total cholesterol, mg/dl			0.98
>200	0.42	0.33	
≤200	0.45	0.42	
LDL cholesterol, mg/dl			0.83
>100	0.44	0.39	
≤100	0.44	0.40	
HDL cholesterol, mg/dl			0.0001
<50	0.48	0.41	
≤50	0.38	0.35	
Triglycerides, mg/dl			0.30
>150	0.42	0.36	
≤150	0.45	0.38	
CRP, mg/dl			0.07
>3	0.43	0.40	
≤3	0.39	0.40	

Abbreviations as in Table 1.

cluded from the analysis. Image acquisition was performed during 425 diagnostic coronary angiography procedures; the others were acquired pre-intervention (n = 355), after balloon dilation (n = 62), or after stenting (n = 126). The rest were acquired post-thrombectomy. The worst lesion diameter stenosis was 61.4 ± 27.3% (visual assessment) or 63.2 ± 20.3% (quantitative coronary angiography).

Patient age was 62.1 ± 11.4 years, and most patients were male (75.3%). Pullback length was 48.7 ± 21.5 mm. The mean EEM CSA was 15.6 ± 4.8 mm^2, the mean lumen CSA was 8.7 ± 3.0 mm^2, the mean plaque + media CSA (EEM − lumen) was 6.8 ± 2.7 mm^2, and the mean plaque burden was 43.5 ± 9.2%. Overall in this population, the mean CSA of the NC was 0.45 ± 0.41 mm^2 (12.3%), the mean CSA of calcified tissue was 0.31 ± 0.38 mm^2 (8.5%), the mean CSA of fibrotic tissue was 2.2 ± 1.4 mm^2 (60.1%), and the mean CSA of fibrofatty tissue was 0.70 ± 0.58 mm^2 (19.1%). The ACS comprised 40.9% of the total population; these patients had nearly the same amount of NC (0.46 ± 0.42 mm^2) as non-ACS patients (0.44 ± 0.41 mm^2, p = 0.74).

Cardiovascular risk factors and coronary plaque composition. SEX. Male patients had a nonsignificant trend toward more NC (0.46 ± 0.43 mm^2) than female patients (0.42 ± 0.38 mm^2, p = 0.20) (Table 2).

AGE. NC content increased with age; patients ≤62 years had mean NC CSA of 0.40 ± 0.36 mm^2, versus 0.50 ± 0.46 mm^2 in patients >62 years (p = 0.0007).

DIABETES MELLITUS. Nondiabetic patients had on average a mean NC CSA of 0.43 ± 0.41 mm^2 vs. 0.51 ± 0.44 mm^2 in diabetic patients (p = 0.02). Of note, insulin-requiring diabetic patients had an even larger mean NC area (0.57 ± 0.47 mm^2, p = 0.04) than the noninsulin-requiring diabetic population.

HYPERCHOLESTEROLEMIA. There was no difference between patients with hypercholesterolemia and those without hypercholesterolemia.

HYPERTENSION. The mean NC CSA was 0.40 ± 0.36 mm^2 in normotensive patients versus 0.48 ± 0.44 mm^2 in hypertensive patients (p = 0.02).

PRIOR CARDIAC HISTORY OR A MYOCARDIAL INFARCTION OR CORONARY ARTERY BYPASS GRAFT. Patients with a history of cardiovascular disease had a larger mean NC CSA than their counterparts.

SMOKING. Neither previous smokers nor noncurrent smokers had a statistically significant larger mean

Table 3. Logistic Regression Predictors for the Top Quartile Measure of Necrotic Core Area

Parameter	Beta Coefficient	Wald	OR	95% CI	p Value
Age, yrs	0.023	10.4	1.023	1.009 to 1.037	0.001
Hypertension (yes/no)	0.180	1.1	1.197	0.862 to 1.662	0.28
Diabetes mellitus (yes/no)	0.492	8.5	1.636	1.174 to 2.279	0.004
Prior CABG (yes/no)	0.494	2.7	1.638	0.911 to 2.945	0.09
Constant	−2.8			−0.081 to −0.012	0.007

CI = confidence interval; OR = odds ratio; other abbreviations as in Table 1.

NC CSA than nonsmokers (p = 0.23 and p = 0.37, respectively).

Univariable and multivariable analysis of NC area. All significantly associated variables in the bivariate analysis (age, hypertension, diabetes, and prior coronary artery bypass graft) were introduced in the logistic regression model; but only age (OR: 1.023, 95% CI: 1.009 to 1.037, p = 0.001) and diabetes (OR: 1.636, 95% CI: 1.174 to 2.279, p = 0.004) remained statistically significant.

In per-class logistic regression analyses including only diabetes as covariate, in young women the OR was 2.1 (95% CI: 0.77 to 6.0, p = 0.14); in young men the OR was 1.6 (95% CI: 0.90 to 2.7, p = 0.11); in old women the OR was 2.3 (95% CI: 1.09 to 4.9, p = 0.03); and in old men the OR was 1.6 (95% CI: 0.96 to 2.7, p = 0.07). Further, when only a variable that identified patients with diabetes and hypertension was included, in young women the OR was 2.4 (95% CI: 0.69 to 8.6, p = 0.17); in young men the OR was 2.0 (95% CI: 1.03 to 3.8, p = 0.041); in old women the OR was 3.04 (95% CI: 1.02 to 9.1, p = 0.046); and in old men the OR was 2.2 (95% CI: 1.1 to 4.2, p = 0.025) (Tables 3 and 4).

DISCUSSION

The main findings of this study are the following: 1) The relative amount of NC found in this in vivo study resembles that previously reported in pathological studies (8,9). 2) The presence of some individual cardiovascular risk factors is related to an increase in NC. 3) In a per-class logistic regression analysis, it seems that some cardiovascular risk factors assert a synergistic effect on the amount of NC in coronary atherosclerotic plaques.

The relevance of studying NC lies in its role in the instability of atherosclerotic plaque. Rupture of thin-cap fibroatheromas accounts for more than 60% of acute coronary events (4). Ruptured plaques are significantly more obstructive and contain larger NCs, more macrophage infiltration, more calcium, fewer smooth muscles cells, and more positive remodeling than intact thin-cap fibroatheromas (10).

The individual and collective impact of many cardiovascular risk factors in terms of cardiac morbidity and mortality has been described. Individually, these risk factors can either affect the overall plaque composition or specifically the NC (Fig. 1). Similarly, the synergistic effect of 2 or more cardiovascular risk factors can either affect the overall plaque composition or specifically the NC; this more accurately reflects reality because a patient usually is diabetic and hypercholesterolemic, diabetic and hypertensive, and so on. Consider a patient of any age, sex, and diabetes status (Fig. 2). When this patient is analyzed as a part of a given patient population, cardiovascular risk factor "A" could have no effect because the impact of this cardiovascular risk factor depends on the class to which the patient belongs, even if this population is

Table 4. Logistic Regression Analysis for the Top Quartile Measure of Necrotic Core Area

	Young Women (≤62 yrs) n = 90	Young Men (≤62 yrs) n = 406	Old Women (>62 yrs) n = 153	Old Men (>62 yrs) n = 333
Model 1: patients with diabetes	OR: 2.1 95% CI: 0.77–6.0 p = 0.14	OR: 1.6 95% CI: 0.90–2.7 p = 0.11	OR: 2.3 95% CI: 1.09–4.9 p = 0.03	OR: 1.6 95% CI: 0.96–2.7 p = 0.07
Model 2: patients with diabetes and hypertension	OR: 2.4 95% CI: 0.69–8.6 p = 0.17	OR: 2.0 95% CI: 1.03–3.8 p = 0.041	OR: 3.04 95% CI: 1.02–9.1 p = 0.046	OR: 2.2 95% CI: 1.1–4.2 p = 0.025

Abbreviations as in Table 3.

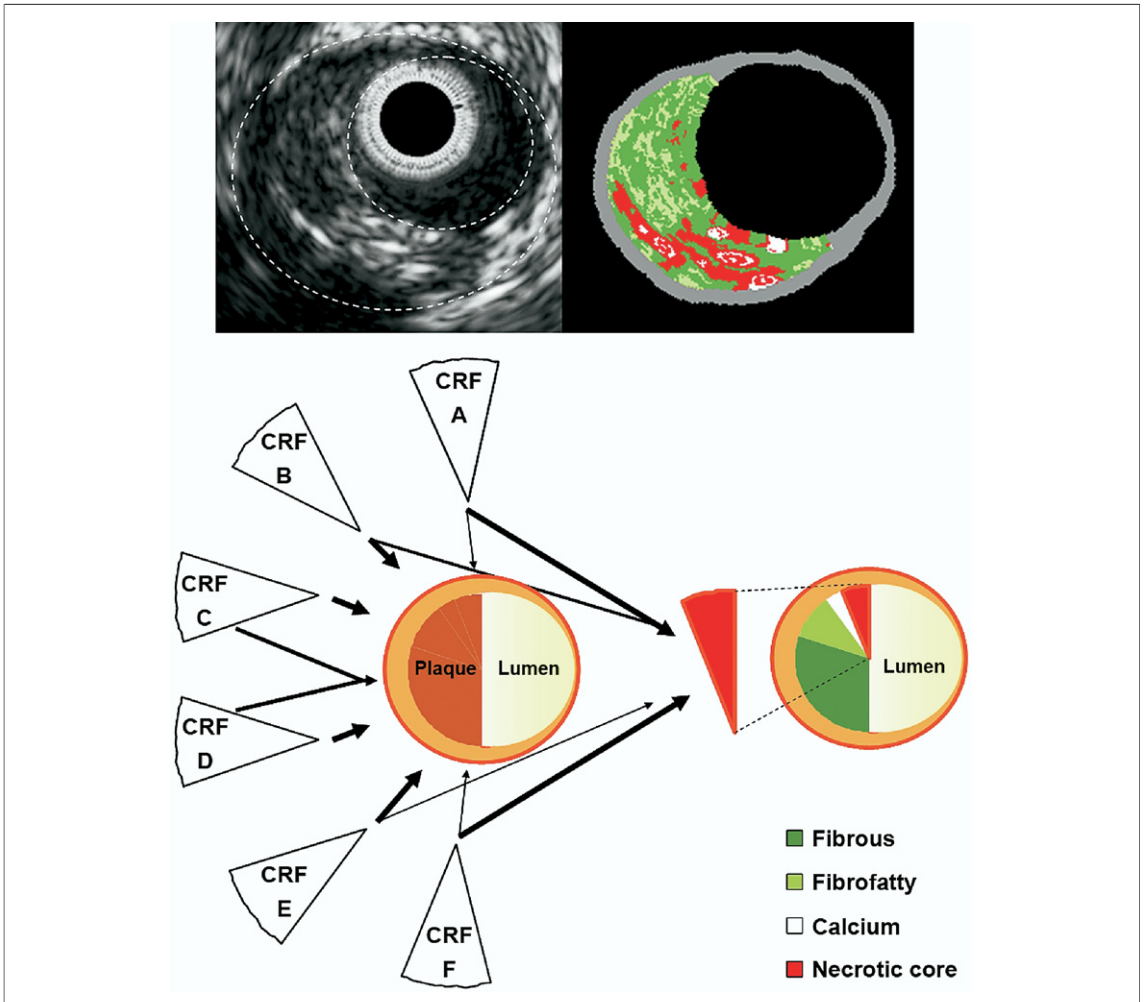

Figure 1. Biological Interaction of CRFs and Coronary Plaque Size and Composition

(Top) Cross-sectional areas of the same coronary atherosclerotic plaque, on the left-hand side a grayscale image and on the right-hand side the corresponding IVUS radiofrequency data image. **(Bottom)** Cardiovascular risk factors (CRF) (A–F indicates any cardiovascular risk factor) act alone or in combination (biological interaction) to assert their effect on overall plaque size and composition. Note that the impact of these CRFs varies **(thickness of the arrow)**. Their effect could exclusively be on overall plaque composition or simultaneously affect necrotic core, once again, individually or collectively. IVUS = intravascular ultrasound.

split by age, sex, or any other cardiovascular risk factor. How can this be tested statistically? One option is to introduce interaction terms in the multivariable analysis to assess the biological interaction among variables that compound the interaction term. However, this requires a complex statistical analysis that is difficult to put into perspective in clinical practice. Instead, we categorized the current population into 4 classes considering 2 variables that are intrinsic and not modifiable: age and sex. Eventually we had 4 groups—young women, young men, old women, and old men—in whom we assessed the effect of diabetes, which was the only independent predictor of NC area in the overall population. Diabetes was associated with an increase in NC area in old women, and a strong trend was observed in old men. When a variable that identified patients with both diabetes and hypertension was entered into the logistic regression analysis per group, being diabetic and hypertensive was associated with an increase in NC not only in old patients, but also in young men. Of note, in this second model all of the ORs were larger than in the first model, in which only diabetes was tested. Thus, the combined presence of diabetes and hypertension exerted a synergistic and differential effect across age/sex groups.

In post-mortem studies, smoking was associated with acute thrombosis (OR: 3.6, $p = 0.004$) and low serum high-density lipoprotein cholesterol was

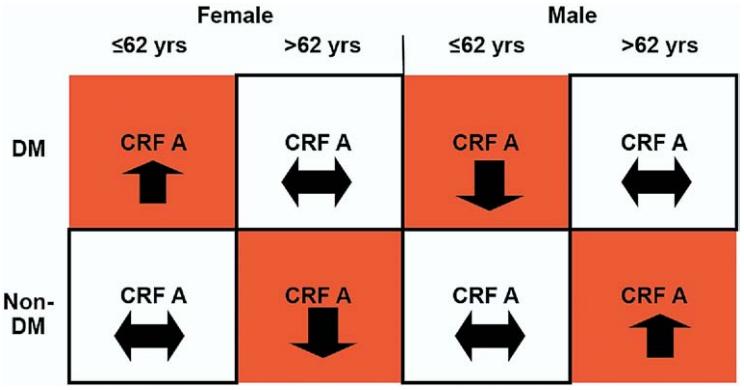

Figure 2. Individual and Collective Impact of CRFs

The population has been divided by age, sex, and diabetes mellitus (DM), resulting in 8 categories. The same cardiovascular risk factor (CRF) "A" is assessed in each of them in terms of change in necrotic core. This CRF "A" can have: 1) no effect **(horizontal arrow)**; 2) increase **(upward arrow)**; or 3) decrease **(downward arrow)** on the amount of necrotic core. When a population-based analysis is conducted, either by age, sex, or clinical presentation, no effect can be found, although there is a significant change in some of the categories.

associated with plaque rupture ($p = 0.008$) (3). In our study the NC was larger among patients with low high-density lipoprotein cholesterol levels, but this variable failed to be an independent predictor in the multivariable analysis. The rest of the cardiovascular risk factors correlated only mildly with the size of the NC. The same group of pathologists later reported the plaque composition among diabetic patients (2). Type II diabetes patients had larger NCs, more calcium, and more inflammation than nondiabetic patients. Patients who were diabetic and hypercholesterolemic had larger NCs compared with patients who were only diabetic patients, whereas patients with diabetes and hypercholesterolemia had a larger macrophage infiltrate compared with patients with normal cholesterol and no diabetes mellitus. Although some of our results were in line with those of this pathological study, we refrained from a direct comparison between pathology and our in vivo study because these pathological studies defined cardiovascular risk factors based on clinical history and post-mortem blood and serum analyses as well as by histology, and IVUS-RFD is not pathology, even though the predictive accuracy of NC detection is reported to be 95.8% (6).

Study limitations. This study has several limitations. The most important is that external validity is limited because the studied population is small and some of the cardiovascular risk factors, such as female sex and diabetes, are not extensively represented. Furthermore, we used analyses that were optimized based on the dataset, that is, we used the top quartile of NC measures and age cut points (i.e., ≤62 years). The use of optimized analyses has the potential to be less generalizable to validated analyses. Other metabolic, chemical, mechanical, and rheologic factors that influence the behavior of a diseased coronary vessel wall were not measured independent from plaque composition and were investigated concurrently in this study.

CONCLUSIONS

Overall plaque composition as analyzed by IVUS-RFD is similar to pathology. Individually and collectively, specific cardiovascular risk factors are associated with an increase in NC.

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Key Words: cardiovascular risk factors ■ clinical presentation ■ intravascular ultrasound ■ plaque composition.

▶APPENDIX

For the sponsor's role, independent statistical analysis, and a list of the Global Intravascular Radiofrequency Data Analysis Registry investigators and participating centers, please see the online version of this article.