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Residual Inflammatory Risk in Patients With Low LDL Cholesterol Levels Undergoing Percutaneous Coronary Intervention

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ABSTRACT

BACKGROUND Data on the impact of residual inflammatory risk (RIR) in patients undergoing percutaneous coronary intervention (PCI) with baseline low-density lipoprotein cholesterol (LDL-C) ≤70 mg/dl are scarce.

OBJECTIVES The purpose of this study was to characterize the prevalence and impact of persistent high RIR after PCI in patients with baseline LDL-C ≤70 mg/dl.

METHODS All patients undergoing PCI between January 2009 and December 2016 in a single tertiary center, with baseline LDL-C ≤70 mg/dl and serial high-sensitivity C-reactive protein (hsCRP) assessments (at least 2 measurements ≥4 weeks apart) were retrospectively analyzed. High RIR was defined as hsCRP >2 mg/l. Patients were categorized as persistent low RIR (first low then low hsCRP), attenuated RIR (first high then low hsCRP), increased RIR (first low then high hsCRP), or persistent high RIR (first high then high hsCRP). Primary endpoint of interest was major adverse cardiac and cerebrovascular accident (MACCE) (death, myocardial infarction, or stroke), within 1 year of the second hsCRP measurement.

RESULTS A total of 3,013 patients were included, with persistent low, attenuated, increased, and persistent high RIR in 1,225 (41.7%), 414 (13.7%), 346 (11.5%), and 1,028 (34.1%) patients, respectively. Overall, there was a stepwise increase in the incidence rates of MACCE, transitioning from the persistent low to the attenuated, increased, and persistent high RIR (respectively, 64.4 vs. 96.6 vs. 138.0 vs. 152.4 per 1,000 patient-years; $p < 0.001$). After adjustment, the presence of persistent high RIR remained strongly associated with MACCE (adjusted hazard ratio: 2.10; 95% confidence interval: 1.45 to 3.02; $p < 0.001$).

CONCLUSIONS Among patients undergoing PCI with baseline LDL-C ≤70 mg/dl, persistent high RIR is frequent and is associated with increased risk of MACCE. Targeting residual inflammation in patients with optimal LDL-C control may further improve outcomes after PCI. (J Am Coll Cardiol 2019;73:2401–9) © 2019 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

CI = confidence interval

HR = hazard ratio

hsCRP = high-sensitivity C-reactive protein

LDL-C = low-density lipoprotein cholesterol

MACCE = major adverse cardiac and cerebrovascular events

MI = myocardial infarction

PCI = percutaneous coronary intervention

RIR = residual inflammatory risk

Patients with coronary artery disease undergoing percutaneous coronary intervention (PCI) are at high risk of future adverse ischemic events. In the last 3 decades, several strategies have been developed to further reduce the risk of adverse events in this population, with improved stent technologies, development of more potent antiplatelet therapy and control of residual risk factors of atherosclerosis (1–5). In this regard, widespread use of statins targeted to decrease levels of low-density lipoprotein cholesterol (LDL-C) below 70 mg/dl is recommended by guidelines, based on the results of numerous randomized trials (6–8). However, residual cholesterol risk may only be 1 part of the residual risk equation (9,10). Indeed, increased inflammatory status pre- and post-PCI has also been associated with poor prognosis (11,12), and control of the residual inflammatory risk (RIR) in the CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcomes Study) trial has recently opened new perspectives in the field of secondary prevention (13,14). As such, RIR may be defined as C-reactive protein (CRP) >2 mg/l, while residual cholesterol risk is commonly described as LDL-C ≥70 mg/dl (6,7,9). However, the prevalence and clinical impact of RIR among patients with controlled cholesterol risk undergoing PCI is unclear.

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We aimed to characterize the prevalence of persistent high RIR in patients undergoing PCI in a high-volume tertiary care facility with controlled cholesterol risk and evaluate its association with clinical outcomes.

METHODS

STUDY DESIGN AND POPULATION. Data from the prospective PCI registry of a large-volume center (The Mount Sinai Hospital, New York, New York) was used for this retrospective analysis. Baseline and procedural characteristics as well as discharge medication were collected through a review of medical records, and 1-year outcomes were obtained by trained research coordinators. The registry was approved by the local institutional review board. All patients undergoing PCI between January 1, 2009, and December 31, 2016, with a baseline LDL-C ≤70 mg/dl and ≥2 serial hsCRP measurements available were included. At least 4 weeks between hsCRP measurements was required to account for temporary high hsCRP in patients with index acute coronary syndrome or other potential transient causes of inflammation such as current infection. If >1 follow-up hsCRP measurement was available, the first was included in the analysis. High inflammatory status was defined as hsCRP >2 mg/l (13). Abbott Laboratories commercial kit and analyzer (Architect C16000, Abbott Laboratories, Abbott Park, Illinois) was used to measure hsCRP, with a level of detection of 0.1 mg/l and low intra-assay coefficient of variability (≤6%). Patients were then further stratified into 4 groups according to the RIR as previously described (15). Persistent high RIR was defined as the presence of high inflammatory status at baseline and at follow-up. Patients with first high then low hsCRP were considered as attenuated RIR, while patients with first low then high hsCRP were considered as increased RIR. Patients with hsCRP ≤2 mg/dl at both baseline and follow-up were categorized as persistent low RIR.

CLINICAL ENDPOINTS. The primary endpoint of interest was the composite of major adverse cardiac and cerebrovascular event (MACCE), defined as the composite of all-cause death, myocardial infraction (MI), or stroke within 1 year following the second hsCRP measurement. Secondary endpoints of interest were the individual component of MACCE, as well as

Scientific. Dr. Sharma has performed industry-sponsored lectures for Abbott Laboratories, AngioScore, Inc., Boston Scientific Corporation, Cardiovascular Systems, Inc., Daiichi-Sankyo Co., Ltd./Eli Lilly and Company Partnership, Medtronic, Inc., and The Medicines Company; has served on the Scientific Advisory Board for Cardiovascular Systems, Inc.; and has served on the Speakers Bureau for Abbott Vascular, Boston Scientific, and Cardiovascular Systems, Inc. Dr. Mehran has received institutional research grant support from Eli Lilly/Daiichi-Sankyo, Bristol-Myers Squibb, AstraZeneca, The Medicines Company, OrbusNeich, Bayer, CSL Behring, Abbott Laboratories, Watermark Research Partners, Novartis Pharmaceuticals, Medtronic, AUM Cardiovascular, and Beth Israel Deaconess Medical Center; is a member of the executive committees for Janssen Pharmaceuticals, Bristol-Myers Squibb, and Osprey Medical; is a member of the data safety monitoring board of Watermark Research Partners; has received institutional (payment to institution) advisory board funding from Bristol-Myers Squibb and Novartis; has served as a consultant for Medscape, The Medicines Company, Boston Scientific, Merck & Company Cardiovascular Systems, Sanofi USA, Shanghai BraccoSine Pharmaceutical, and AstraZeneca; and holds equity in Claret Medical and Elixir Medical Corporation. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Brendan Everett, MD, MPH, served as Guest Associate Editor for this paper.

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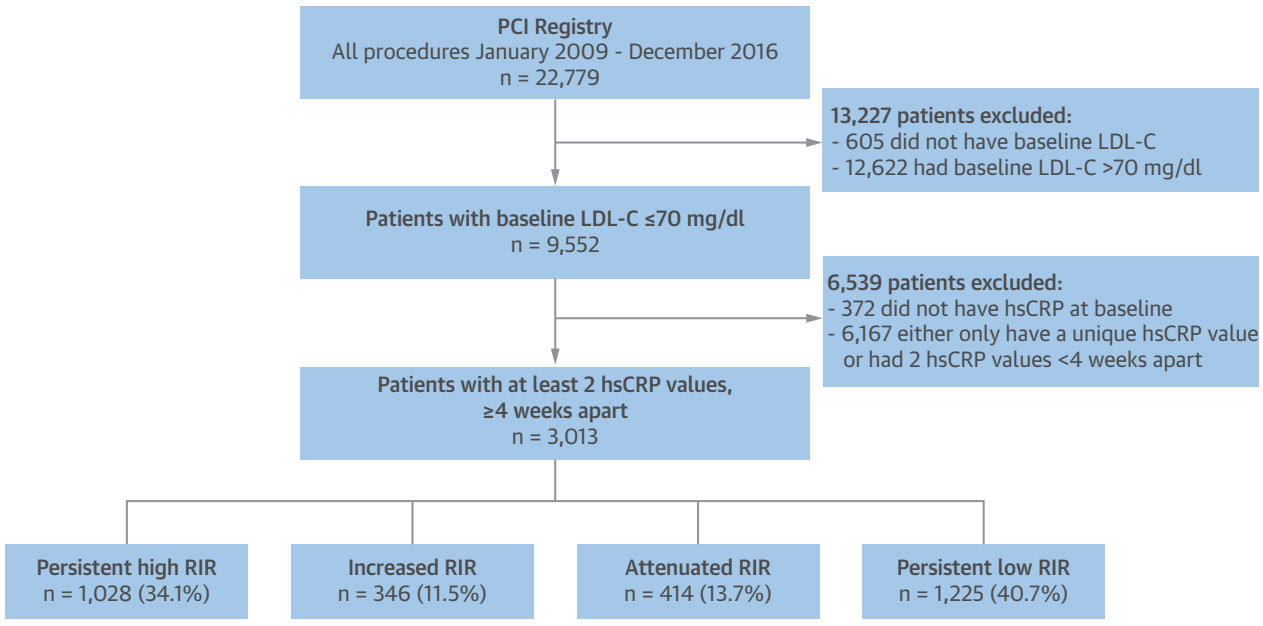
FIGURE 1 Flow Chart of the Study



hsCRP = high-sensitivity C-reactive protein; LDL-C = low density lipoprotein cholesterol; PCI = percutaneous coronary intervention; RIR = residual inflammatory risk.

the risk of probable or definite stent thrombosis according to the academic research consortium definition (16); any target lesion revascularization; any target vessel revascularization; and the composite of all-cause death, MI, stroke, or any target vessel revascularization.

STATISTICAL ANALYSIS. Descriptive statistics are reported as mean ± SD, median (interquartile range [IQR]), or number and percentage when appropriate. The chi-square test was used to compare differences between categorical variables. The independent-samples Student's *t*-test was used to compare continuous variables with normal distribution, and the Mann-Whitney *U* test was used to compare continuous variables without a normal distribution. Outcomes were assessed using the Kaplan-Meier method and compared using the log-rank test. The independent associations between the RIR status and outcomes were assessed with a Cox regression model and expressed as adjusted hazard ratio (HR) with 95% confidence interval (CI). Covariates included in the model were: age, sex, body mass index, hyperlipidemia, systemic hypertension, diabetes mellitus, chronic kidney disease, prior peripheral artery disease, cerebrovascular disease, coronary artery bypass graft surgery, acute coronary syndromes as index presentation, statin prescription at discharge, oral anticoagulant prescription at discharge, dual antiplatelet therapy at discharge, and LDL-C level at follow-up. Patients with persistent low RIR were used as the reference group in the multivariable model. Statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, North Carolina). A 2-tailed probability value <0.05 were considered statistically significant.

RESULTS

BASELINE CHARACTERISTICS. Figure 1 shows the patients' flow chart for the current study. Of the 9,552 patients who underwent PCI between January 2009 and December 2016 with baseline LDL-C ≤70 mg/dl, a total of 3,013 (31.5%) patients presented with serial hsCRP measurements ≥4 weeks apart and were therefore included in the analysis. Baseline demographics and procedural characteristics of patients with and without serial hsCRP are presented in Online Table 1. A total of 1,225 (40.7%) patients were categorized with consistent low RIR, 1,028 (34.1%) patients with persistent high RIR, and 346 (11.5%) and 414 (13.7%) patients with increased and attenuated RIR, respectively. Median time between measurements was 16 weeks (IQR: 6 to 66 weeks) for patients with persistent high RIR, 19 weeks (IQR: 6 to 79 weeks) for patients with consistent low RIR, and 16.5 weeks (IQR: 6 to 68 weeks) and 35 weeks

TABLE 1 Baseline and Procedural Characteristics According to Residual Inflammatory Status

	Overall (N = 3,013)	Persistent Low RIR (n = 1,225, 41.7%)	Attenuated RIR (n = 414, 13.7%)	Increased RIR (n = 346, 11.5%)	Persistent High RIR (n = 1,028, 34.1%)	p Value
Age, yrs	65.73 ± 10.97	65.54 ± 10.63	66.63 ± 11.35	66.34 ± 10.81	65.38 ± 11.26	0.15
Caucasian	1,198 (39.8)	494 (40.3)	167 (40.3)	150 (43.4)	387 (37.6)	0.26
Female	730 (24.2)	223 (18.2)	88 (21.3)	83 (24.0)	336 (32.7)	**<0.001**
BMI, kg/m^2	28.25 ± 4.64	27.43 ± 3.94	27.96 ± 4.62	27.90 ± 4.53	29.53 ± 5.20	**<0.001**
Hyperlipidemia	2,938 (97.5)	1,205 (98.4)	395 (95.4)	336 (97.1)	1,002 (97.5)	**0.01**
Hypertension	2,916 (96.8)	1,190 (97.1)	394 (95.2)	339 (98.0)	993 (96.6)	0.13
Current smoker	376 (12.5)	133 (10.9)	49 (11.8)	46 (13.3)	148 (14.4)	0.079
Diabetes mellitus	1,745 (57.9)	658 (53.7)	227 (54.8)	201 (58.1)	659 (64.1)	**<0.001**
Atrial fibrillation	211 (7.0)	46 (3.8)	31 (7.5)	32 (9.2)	102 (9.9)	**<0.001**
Chronic kidney disease	992 (32.9)	299 (24.4)	133 (32.1)	113 (32.7)	447 (43.5)	**<0.001**
Dialysis	167 (5.5)	13 (1.1)	17 (4.1)	18 (5.2)	119 (11.6)	**<0.001**
Anemia	1,346 (44.7)	434 (35.4)	189 (45.7)	157 (45.4)	566 (55.1)	**<0.001**
Statin at admission	2,600 (86.3)	1,094 (89.3)	346 (83.6)	301 (87.0)	859 (83.6)	**<0.001**
Previous MI	957 (31.8)	358 (29.2)	137 (33.1)	117 (33.8)	345 (33.6)	0.10
Previous CABG	653 (21.7)	266 (21.7)	79 (19.1)	84 (24.3)	224 (21.8)	0.39
Peripheral artery disease	303 (10.1)	92 (7.5)	32 (7.7)	35 (10.1)	144 (14.0)	**<0.001**
Cerebrovascular disease	319 (10.6)	104 (8.5)	40 (9.7)	41 (11.8)	134 (13.0)	**0.004**
LVEF, %	52.89 ± 12.66	54.12 ± 12.16	51.52 ± 12.41	53.66 ± 12.62	51.73 ± 13.21	**<0.001**
Clinical presentation						
Asymptomatic	114 (3.8)	54 (4.4)	13 (3.1)	16 (4.6)	31 (3.0)	0.25
Stable angina	1,678 (55.7)	758 (61.9)	204 (49.3)	199 (57.5)	517 (50.3)	**<0.001**
USA	959 (31.8)	375 (30.6)	116 (28.0)	109 (31.5)	359 (34.9)	**0.043**
NSTEMI	226 (7.5)	26 (2.1)	71 (17.1)	21 (6.1)	108 (10.5)	**<0.001**
STEMI	29 (1.0)	8 (0.7)	9 (2.2)	1 (0.3)	11 (1.1)	**0.025**
Discharge prescription						
Aspirin	2,951 (97.9)	1,203 (98.2)	402 (97.1)	342 (98.8)	1,004 (97.7)	0.30
Statin	2,795 (92.8)	1,156 (94.4)	376 (90.8)	323 (93.4)	940 (91.4)	**0.02**
Beta-blockers	2,523 (83.7)	1,023 (83.5)	346 (83.6)	300 (86.7)	854 (83.1)	0.45
Clopidogrel	2,491 (82.7)	998 (81.5)	324 (78.3)	288 (83.2)	881 (85.7)	**0.004**
DAPT	2,920 (96.9)	1,190 (97.1)	397 (95.9)	336 (97.1)	997 (97.0)	0.63
Oral anticoagulant agent	165 (5.5)	32 (2.6)	26 (6.3)	23 (6.6)	84 (8.2)	**<0.001**
Baseline laboratory						
Hemoglobin, g/dl	12.77 ± 1.68	13.17 ± 1.51	12.73 ± 1.72	12.83 ± 1.54	12.28 ± 1.77	**<0.001**
Serum creatinine, mg/dl	1.40 ± 1.51	1.11 ± 0.73	1.36 ± 1.49	1.38 ± 1.47	1.78 ± 2.05	**<0.001**
CK-MB, U/l	1.50 (1.00 to 2.40)	1.50 (1.00 to 2.30)	1.50 (1.00 to 2.80)	1.70 (1.05 to 2.30)	1.60 (1.00 to 2.80)	**0.013**
Total cholesterol, mg/dl	116.30 ± 34.62	113.93 ± 22.03	115.67 ± 25.56	112.99 ± 21.88	120.50 ± 49.90	**<0.001**
LDL-C, mg/dl	52.99 ± 12.00	52.80 ± 12.03	54.02 ± 11.73	52.23 ± 12.46	53.08 ± 11.89	0.20
HDL, mg/dl	39.76 ± 12.57	40.89 ± 12.49	38.84 ± 12.96	40.72 ± 13.31	38.42 ± 12.10	**<0.001**
Triglycerides, mg/dl	90.00 (63.00 to 130.00)	82.00 (57.00 to 122.00)	90.00 (63.00 to 127.00)	89.00 (62.00 to 134.00)	99.00 (70.00 to 145.00)	**<0.001**
Platelets, /mm^3	200.09 ± 62.50	189.47 ± 53.78	202.64 ± 56.00	194.75 ± 58.63	213.44 ± 72.55	**<0.001**
hsCRP, mg/l	9.34 ± 56.87	0.83 ± 0.46	20.19 ± 88.29	1.09 ± 0.51	17.88 ± 78.22	**<0.001**
Follow-up laboratory						
LDL, mg/dl	59.27 ± 22.97	57.60 ± 20.51	57.44 ± 23.16	60.45 ± 24.59	61.62 ± 24.87	**<0.001**
hsCRP, mg/l	16.07 ± 104.45	0.79 ± 0.47	1.08 ± 0.49	63.07 ± 226.73	24.48 ± 116.38	**<0.001**
ΔCRP	−0.06 (−1.20 to 0.80)	0 (−0.30 to 0.21)	−3.01 (−7.80 to −1.60)	2.84 (1.37 to 8.30)	−0.10 (−3.60 to 2.40)	**<0.001**

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(IQR: 7 to 118 weeks) for patients with attenuated and increased RIR, respectively ($p < 0.001$ for overall comparison). Baseline and procedural characteristics are detailed in Table 1. Mean age in the overall population was 65.7 ± 11.0 years, without significant differences among the groups. Women represented approximately a quarter of the overall population, with the highest proportion in patients with persistent high RIR. Comorbidities such as diabetes mellitus or chronic kidney disease were more frequent in patients with increased RIR or persistent high RIR. Overall, statins were used at baseline in 2,600 (86.3%) patients and were prescribed at discharge in 2,795 (92.8%) patients.

TABLE 1 Continued

	Overall (N = 3,013)	Persistent Low RIR (n = 1,225, 41.7%)	Attenuated RIR (n = 414, 13.7%)	Increased RIR (n = 346, 11.5%)	Persistent High RIR (n = 1,028, 34.1%)	p Value
Procedural characteristics						
ACC/AHA type B2/C lesion	2,515 (83.5)	1,039 (84.8)	342 (82.6)	293 (84.7)	841 (81.8)	0.24
Severe calcification	385 (12.8)	157 (12.8)	53 (12.8)	44 (12.7)	131 (12.7)	0.99
Pre-TIMI flow grade 0 or 1	288 (9.6)	114 (9.3)	46 (11.1)	34 (9.8)	94 (9.1)	0.69
Multivessel disease	2,513 (83.4)	1,020 (83.3)	355 (85.7)	274 (79.2)	864 (84.0)	0.09
SYNTAX score	12.94 ± 11.28	13.17 ± 11.12	13.64 ± 12.06	12.54 ± 11.81	12.53 ± 10.95	0.44
Bare-metal stent	148 (4.9)	39 (3.2)	29 (7.0)	22 (6.4)	58 (5.6)	**0.002**
Drug-eluting stent	2,678 (88.9)	902 (87.7)	1,096 (89.5)	374 (90.3)	306 (88.4)	0.43
Number of treated lesions	1.58 ± 0.78	1.61 ± 0.81	1.57 ± 0.74	1.57 ± 0.74	1.55 ± 0.76	0.36
Number of implanted stents	1.43 ± 0.84	1.43 ± 0.86	1.45 ± 0.81	1.47 ± 0.82	1.41 ± 0.85	0.62
Stent length	34.57 ± 21.03	35.09 ± 21.28	34.07 ± 20.16	33.61 ± 19.09	34.50 ± 21.74	0.66

Values are mean ± SD, n (%), or median (interquartile range). **Bold** indicates statistical significance.

ΔCRP = difference between CRP level at follow-up and CRP level at baseline; ACC = American College of Cardiology; AHA = American Heart Association; BMI = body mass index; CABG = coronary artery bypass grafting surgery; CK-MB = creatinine kinase-muscle/brain; DAPT = dual antiplatelet therapy; CRP = C-reactive protein; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; LVEF = left ventricle ejection fraction; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; RIR = residual inflammatory risk; STEMI = ST-segment elevation myocardial infarction; USA = unstable angina; TIMI = Thrombolysis In Myocardial Infarction.

1-YEAR OUTCOMES ACCORDING TO THE RESIDUAL INFLAMMATORY RISK. In the overall cohort, the incidence rate of MACCE was 106.6 per 1,000 person-years, while the incidence rates of all-cause death and the composite of death, MI, stroke or target vessel revascularization were 35.9 per 1,000 person-years and 207.7 per 1,000 person-years, respectively. As detailed in **Table 2**, Online Figure 1, and Online Table 2, the incidence rates of MACCE were the highest in patients with increased or persistent high RIR. There was a stepwise increase in the incidence rates of MACCE; all-cause death; MI; and the composite of death, MI, stroke, or target vessel revascularization transitioning from the persistent low to the attenuated, increased, and persistent high RIR. Overall incidence rates of stroke and stent thrombosis were 2.7 per 1,000 patient-years and 3.3 per 1,000 patient-years, respectively, without significant differences among the groups.

After multivariable adjustment, results remained qualitatively similar; a stepwise increase of the risk of MACCE, as well as all-cause death; MI; and the composite of death, MI, stroke, or target vessel revascularization was observed (**Table 3**). Compared to patients with persistent low RIR, the risk increase was significant with patients presenting an increased RIR and a persistent high RIR.

DISCUSSION

The main findings of the current analysis are as follows: 1) despite controlled LDL-C levels at baseline and optimized medical treatment, the risk of adverse events following PCI remained high; 2) a significant proportion (34.1%) of patients with LDL-C ≤70 mg/dl

TABLE 2 Incidence Rates of Adverse Outcomes According to the Residual Inflammatory Status

	Overall (N = 3,013)	Persistent Low RIR (n = 1,225, 41.7%)	Attenuated RIR (n = 414, 13.7%)	Increased RIR (n = 346, 11.5%)	Persistent High RIR (n = 1,028, 34.1%)	p Value
MACCE	106.6 (93.4-121.7)	64.4 (49.5-83.9)	96.6 (66.7-139.9)	138.0 (97.1-196.2)	152.4 (126.0-184.4)	**<0.001**
All-cause death, myocardial infarction, stroke, or target vessel revascularization	207.7 (184.8-224.6)	139.1 (115.9-166.8)	216.4 (168.0-334.4)	256.8 (197.2-334.4)	262.6 (226.4-304.7)	**<0.001**
All-cause death or myocardial infarction	105.6 (92.4-120.6)	64.4 (49.5-83.9)	93.1 (63.8-135.7)	138.0 (97.1-196.2)	150.8 (124.5-182.6)	**<0.001**
All-cause death	35.9 (28.7-44.8)	13.6 (7.7-24.0)	19.9 (8.9-44.3)	42.1 (22.6-78.2)	67.3 (50.8-89.0)	**<0.001**
Myocardial infarction	75.5 (64.6-88.4)	52.7 (39.4-70.6)	72.4 (47.2-111.0)	96.2 (75.7-122.2)	102.4 (68.0-154.1)	**0.009**
Stent thrombosis	3.3 (1.6-6.8)	2.3 (0.6-9.1)	3.3 (0.5-23.6)	4.2 (0.6-30.0)	4.1 (1.3-12.8)	**<0.001**
Stroke	2.7 (0.6-9.1)	2.3 (0.5-9.1)	3.3 (0.5-23.6)	4.2 (0.6-30.0)	2.7 (0.7-11.0)	0.96
Target vessel revascularization	112.3 (98.8-127.8)	85.2 (67.7-107.1)	124.9 (90.1-173.1)	138.3 (97.3-196.6)	132.5 (107.9-162.7)	**0.014**
Target lesion revascularization	90.6 (78.5-104.5)	70.8 (55.1-91.0)	88.4 (60.2-129.9)	119.1 (81.7-173.6)	106.7 (84.9-134.0)	**0.046**

Results are provided as incidence rates per 1,000 person-years of observation (95% confidence interval) following the second hsCRP measurement (95% confidence interval). **Bold** indicates statistical significance.

MACCE = major adverse cardiac and cerebrovascular event (composite of death, myocardial infarction or any stroke); RIR = residual inflammatory risk.

TABLE 3 Unadjusted and Adjusted Models for Outcomes According to Residual Inflammatory Risk

Event	Residual Inflammatory Status	Unadjusted Model		Adjusted Model*	
		HR (95% CI)	p Value	HR (95% CI)	p Value
MACCE	Persistent high RIR	2.35 (1.70–3.25)	**<0.001**	2.10 (1.45–3.02)	**<0.001**
	Increased RIR	2.09 (1.35–3.25)	**0.001**	1.91 (1.21–3.03)	**0.006**
	Attenuated RIR	1.49 (0.95–2.36)	0.083	1.52 (0.95–2.44)	0.08
All-cause death, myocardial infarction, stroke, or target vessel revascularization	Persistent high RIR	1.90 (1.50–2.41)	**<0.001**	1.71 (1.32–2.22)	**<0.001**
	Increased RIR	1.83 (1.33–2.53)	**<0.001**	1.67 (1.20–2.34)	**0.003**
	Attenuated RIR	1.56 (1.14–2.13)	**0.005**	1.50 (1.08–2.08)	**0.015**
All-cause death or myocardial infarction	Persistent high RIR	2.32 (1.68–3.22)	**<0.001**	2.09 (1.45–3.02)	**<0.001**
	Increased RIR	2.09 (1.35–3.25)	**0.001**	1.93 (1.22–3.05)	**0.005**
	Attenuated RIR	1.44 (0.91–2.28)	0.12	1.53 (0.95–2.45)	0.078
All-cause death	Persistent high RIR	4.94 (2.63–9.28)	**<0.001**	3.24 (1.62–6.50)	**<0.001**
	Increased RIR	3.07 (1.33–7.11)	**0.009**	2.70 (1.14–6.41)	**0.025**
	Attenuated RIR	1.46 (0.55–3.88)	0.45	1.20 (0.44–3.29)	0.72
Myocardial infarction	Persistent high RIR	1.81 (1.24–2.64)	**0.0021**	1.89 (1.23–2.89)	**0.0034**
	Increased RIR	1.88 (1.14–3.11)	**0.014**	1.79 (1.06–3.04)	**0.031**
	Attenuated RIR	1.37 (0.82–2.30)	0.23	1.61 (0.95–2.73)	0.079
Stent thrombosis	Persistent high RIR	1.81 (0.30–10.85)	0.51	1.79 (0.27–11.79)	0.55
	Increased RIR	1.83 (0.17–20.20)	0.62	2.29 (0.19–27.75)	0.51
	Attenuated RIR	1.46 (0.13–16.13)	0.76	1.52 (0.13–17.36)	0.74
Stroke†	Persistent high RIR	1.21 (0.17–8.61)	0.85	2.88 (0.24–34.56)	0.40
	Increased RIR	1.84 (0.17–20.35)	0.62	3.30 (0.19–57.46)	0.41
	Attenuated RIR	1.46 (0.13–16.14)	0.76	3.25 (0.20–53.73)	0.41
Target vessel revascularization	Persistent high RIR	1.59 (1.17–2.16)	**0.0034**	1.37 (0.97–1.93)	0.071
	Increased RIR	1.66 (1.09–2.52)	**0.019**	1.50 (0.96–2.35)	0.074
	Attenuated RIR	1.49 (1.00–2.22)	0.052	1.34 (0.88–2.05)	0.17
Target lesion revascularization	Persistent high RIR	1.52 (1.08–2.13)	**0.016**	1.29 (0.88–1.88)	0.19
	Increased RIR	1.69 (1.08–2.66)	**0.023**	1.51 (0.93–2.44)	0.097
	Attenuated RIR	1.25 (0.79–1.97)	0.35	1.20 (0.74–1.94)	0.46

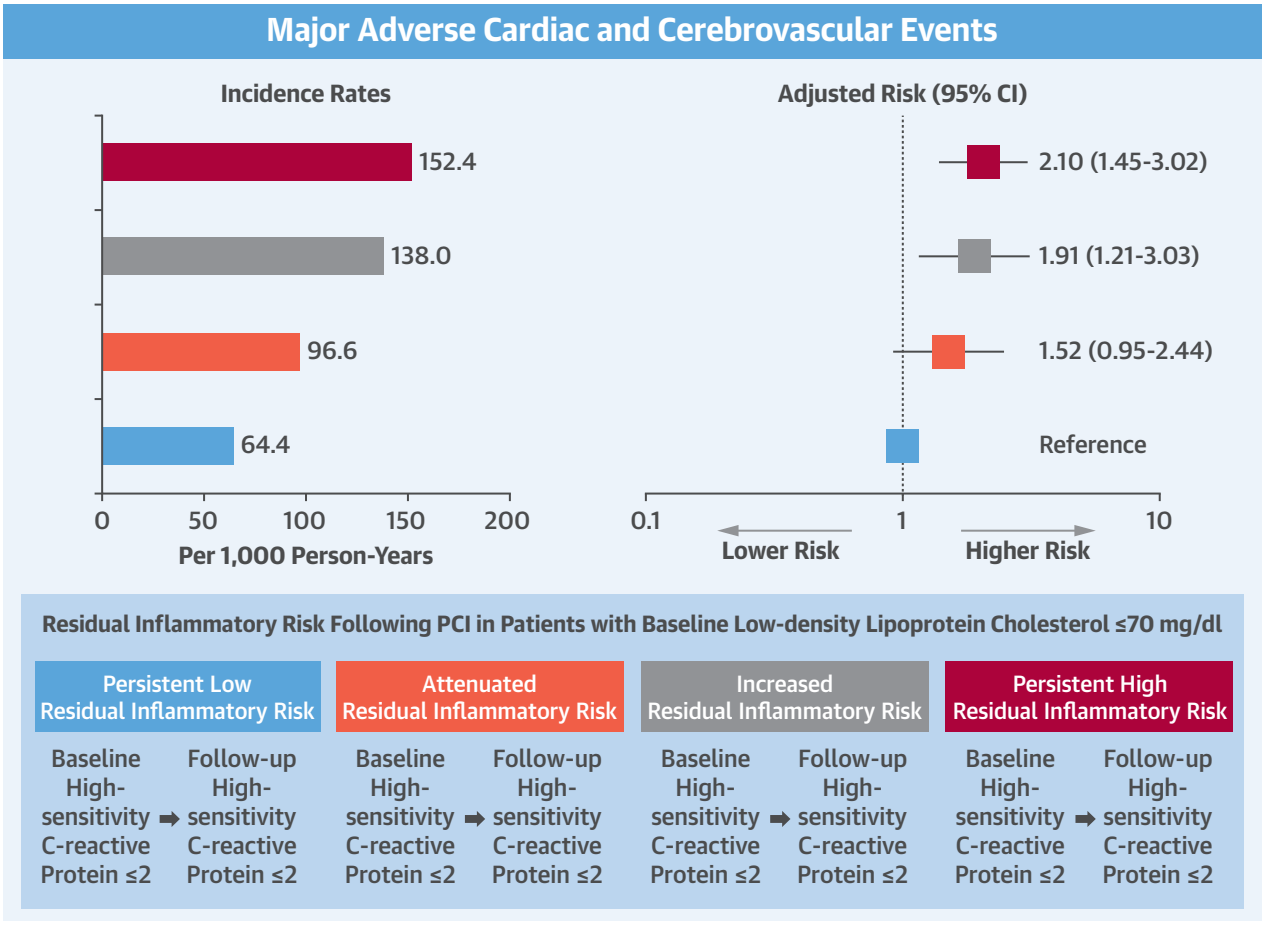
Patients with persistent low RIR were used as reference. *Covariates of the fully adjusted model: age, sex, body mass index, hyperlipidemia, systemic hypertension, diabetes mellitus, chronic kidney disease, prior peripheral artery disease, cerebrovascular disease, coronary artery bypass graft surgery, acute coronary syndromes as index event and statin prescription at discharge, oral anticoagulant prescription at discharge, dual antiplatelet therapy at discharge, and LDL-C level at follow-up. †Covariates of the adjusted model for stroke are age, sex, body mass index, acute coronary syndrome as index event, diabetes mellitus, systemic hypertension, chronic kidney disease, prior coronary artery bypass graft surgery and statin prescription at discharge. **Bold** indicates statistical significance.

CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 2.

at admission presented with persistent RIR; 3) a stepwise increase of the risk of adverse events was observed according to RIR status at follow-up (**Central Illustration**); 4) the association between persistent high RIR and increased rates of MACCE; all-cause death; MI; and the composite of death, MI, stroke, or target vessel revascularization remained present after multivariable adjustment on baseline characteristics, discharged medication, and LDL-C level at follow-up.

Secondary prevention after PCI is mostly based on antithrombotic treatment and strict control of cardiovascular risk factors. Guidelines recommend lowering LDL-C levels below 70 mg/dl using high-intensity statins (6,7). However, the impact of statins on cholesterol levels may be limited by a high interindividual variability and statin intolerance. Therefore, a significant proportion of patients may not achieve the LDL-C goal of ≤70 mg/dl, despite the prescription of statins (8,17,18). This residual cholesterol risk may be addressed by the use of proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors which were shown to result in a further reduction in LDL-C levels on top of statin treatment and reduced the risk of recurrent ischemic events in large randomized trials including such high-risk patients (19,20). However, available data on patients undergoing PCI without persistent cholesterol residual risk (i.e., patients with LDL-C levels ≤70 mg/dl) are scarce. The present study brings real-world evidence that even this population remains at high risk of adverse events, despite optimized medical therapy, including statins prescription at discharge in >90% of the patients. Our study further demonstrates that residual inflammatory risk remains prevalent in such a population, with nearly one-half of the patients presenting with hsCRP >2 mg/l at follow-up. As previously reported, patients with persistent RIR were more frequently women, were active smokers, or had diabetes mellitus (21,22). The predictive value

CENTRAL ILLUSTRATION **1-Year Impact of Residual Inflammatory Risk in Patients Undergoing PCI With Baseline LDL-C ≤70 mg/dl**



Guedeney, P. et al. J Am Coll Cardiol. 2019;73(19):2401-9.

Ci = confidence interval; LDL-C = low-density lipoprotein cholesterol; PCI = percutaneous coronary intervention.

of elevated hsCRP for long-term clinical ischemic events in patients undergoing PCI has been previously described and is explained by the role of chronic inflammation in the progression of atherothrombosis (21,23). In this regard, the beneficial impact of statins is not limited to the control of the residual cholesterol risk by reducing LDL-C levels. In fact, statins are also associated with anti-inflammatory effects (24). Indeed, in the JUPITER (Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) trial, the strongest reduction of vascular events was obtained in patients in whom rosuvastatin treatment resulted in both LDL-C and CRP reduction (25). Similar results were observed in IMPROVE-IT (Improved Reduction of Outcomes Vytorin Efficacy International Trial) with ezetimibe/simvastatin and in the FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Patients with Elevated Risk) trial with evolocumab on top of optimized lipid-lowering therapy (26,27). As a consequence, residual cholesterol and inflammation risks have been described as 2 sides of the same atherosclerotic prevention coin (9). The CANTOS trial demonstrated that reducing inflammation, via the interleukin-1β monoclonal antibody canakinumab, is associated with lower risk of recurrent cardiovascular events in patients with prior MI and increased baseline hsCRP ≥2 mg/l, without interfering with lipid levels (13). Of note, the magnitude of clinical benefit was directly correlated to the magnitude of CRP reduction (28). Thus, patients with LDL-C ≤70 mg/dl at baseline and persistent

high RIR following PCI could represent an ideal population for targeting inflammation, warranting prospective validation trials. Moreover, the use of canakinumab was demonstrated to be safe and efficient in patient with chronic kidney disease, which was a prevalent comorbidity among patients with persistent high RIR in the present study (29). Other inflammation modulating agents are being evaluated to reduce the risk of ischemic events in high-risk patients. Recently, the CIRT (Cardiovascular Inflammation Reduction Trial) did not demonstrate any significant impact of low-dose methotrexate on the composite of cardiovascular death, nonfatal myocardial infarction, or stroke (30). Of note, low-dose methotrexate did not reduce levels of interleukin-1β, conversely to canakinumab. The COLCOT (Colchicine Cardiovascular Outcomes Trial) (NCT02551094) is evaluating the impact of colchicine following an MI. Finally, although the patients included in the present analysis did not have residual cholesterol risk, as commonly defined (i.e., LDL-C >70 mg/dl), further reduction of LDL-C with or without the use of PCSK9 inhibitors below the current guideline-recommended LDL-C levels for secondary prevention was associated with further reduction of cardiovascular risk, without clear off-setting adverse effects (31,32).

STUDY LIMITATIONS. This is a single-center prospective registry, and our results may not be generalized to all patients undergoing PCI in other centers. Because of the retrospective nature of the study, serial hsCRP measurements were not performed in all patients in a standardized fashion, but were left to the physicians' discretion, with difference in the delay between measurements; this further limits the generalization of our results. Despite the numerous covariates included in the adjusted models, other potentially relevant variables, such as change in the statins' intensity during follow-up, were not included. Furthermore, inherent to the observational nature of this study, there is likely significant residual unmeasured confounding, and our results should therefore be considered hypothesis-generating.

CONCLUSIONS

In this large PCI registry, a persistent high RIR was observed in one-third of patients undergoing PCI with low LDL-C at baseline and was independently associated with adverse clinical outcomes. Prospective trials evaluating inflammation modulating intervention in these patients are warranted.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Among patients undergoing PCI with baseline LDL-C levels ≤70 mg/dl, residual inflammation as assessed by persistent elevations of high-sensitivity C-reactive protein is associated with an increased risk of ischemic events.

TRANSLATIONAL OUTLOOK: Further studies are needed to determine whether treatment aimed at ameliorating residual inflammation in patients with optimal LDL-C control improve clinical outcomes after PCI.

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APPENDIX For supplemental tables and a figure, please see the online version of this paper.