Atherosclerosis 320 (2021) 31–37

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Residual inflammatory risk at 12 months after acute coronary syndromes is frequent and associated with combined adverse events*

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ARTICLE INFO

Keywords:
Biomarkers
Inflammation
CRP
Myocardial infarction
Risk factors

ABSTRACT

Background and aims: Residual inflammatory risk (RIR) after acute coronary syndromes (ACS) may identify patients likely to benefit from anti-inflammatory therapies.
Methods: Patients from the Special Program University Medicine ACS cohort were divided into four groups according to level of hsCRP at baseline and after 12 months: persistently high RIR, increased RIR (first low, then high hsCRP), attenuated RIR (first high, then low hsCRP), or persistently low RIR. High RIR was defined as hsCRP $\geq$ 2 mg/L. An independently adjudicated incident of combined adverse events was defined as the composite of myocardial infarction, clinically indicated coronary revascularization or cerebrovascular events.
Results: Among 1209 patients with available hsCRP, clinical and demographic data, 295 (24.4%) patients had persistently high RIR (delta hsCRP median (IQR): 2.3 (−9.9; 0.3) (mg/L) and 72 (5.96%) patients had increased RIR (delta hsCRP median (IQR): +2.45 (1.2; 8.35) (mg/L). A total of 390 (32.26%) patients had attenuated RIR (delta hsCRP median (IQR): 3.55 (−10; −2) (mg/L) and 452 (37.38%) patients had persistently low RIR (delta hsCRP median (IQR): 0.2 (−0.6; 0.1) (mg/L). Of 90 combined adverse events, 31 (10.5%) occurred in the persistently high (multivariable adjusted OR: 1.71, (95% CI 1.08–2.7), $p = 0.022$) compared with the three other groups combined (increased RIR: 3 (4.2%), attenuated RIR 30 (7.7%), persistently low RIR 26 (5.8%).
Conclusions: Persistently elevated hsCRP after ACS is found in a quarter of patients with the highest risk of combined adverse events. This underlines the need to perform anti-inflammatory intervention trials in RIR patients.

* Clinical trial registration: NCT01000701.

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https://doi.org/10.1016/j.atherosclerosis.2021.01.012
Received 14 December 2020; Received in revised form 5 January 2021; Accepted 12 January 2021
Available online 18 January 2021

1. Introduction

Acute coronary syndromes (ACS) constitute life-threatening manifestations of coronary atherosclerosis and remain associated with substantial mortality and morbidity in the subsequent 12 months [1]. Atherosclerosis is a lipid-driven chronic inflammatory disease of the arterial wall [2]. Antibody-based inhibition of interleukin-1β (IL-1β)-mediated inflammation reduces combined adverse events in patients with increased inflammatory biomarkers after myocardial infarction (MI) [3]. Conversely, low-dose methotrexate did neither impact on combined adverse events nor reduce IL-1β, IL-6 or hsCRP levels in patients after MI or with chronic coronary syndromes (CCS) with normal hsCRP levels [4]. Recently, low-dose colchicine was shown to reduce combined adverse events shortly after MI and in patients with CCS [5,6]. Therefore, the use of biomarkers involved in the pathogenesis of inflammation enables the identification of patients with a high inflammatory burden. In this process, C-reactive protein (CRP) integrates several inflammatory pathways following NLRP3 inflammasome assembly and activation of caspase-1 (canonical pathway) or caspase-4 or caspase-5 in humans (noncanonical pathway) to generate active IL-1β and IL-18 which induce IL-6 and CRP [7]. CRP may thus serve as a read-out for applying anti-inflammatory drugs targeting its upstream pathways, including colchicine [8]. CRP is measured by high-sensitivity assays (hsCRP), and a cut-off at 2 mg/L has been widely studied and proposed to identify patients at residual inflammatory risk (RIR) [9].

Within the large multi-center Swiss ACS cohort, we aimed to identify the proportion of patients with RIR based on hsCRP $\geq$ 2 mg/L and determine whether persistently high inflammation at baseline and 12 months after ACS is associated with combined adverse events.

Table 1
Baseline characteristics in cohort population, non-survivors and selected study population.

Parameters	Cohort population	Patients who died at 1 year	Selected study population
	N = 2168	N = 96	N = 1209
Age (years)	n = 2168, 63.74 ± 12.44	n = 96, 74.77 ± 10.05	n = 1209, 62.42 ± 11.49
Sex (female in %)	n = 2168, 463 (21.4%)	n = 96, 21 (21.9%)	n = 1209, 212 (17.5%)
Body weight (kg)	n = 2139, 80.30 ± 15.12	n = 86, 76.09 ± 14.59	n = 1201, 81.00 ± 14.41
Body Mass Index (kg/m^2)	n = 2137, 27.13 ± 4.34	n = 86, 26.11 ± 3.94	n = 1200, 27.21 ± 4.23
Systolic blood pressure	n = 2156, 130.59 ± 23.43	n = 95, 125.41 ± 26.01	n = 1206, 130.78 ± 22.75
Medical history			
Diabetes mellitus	n = 2168, 396 (18.3%)	n = 96, 28 (29.2%)	n = 1209, 187 (15.5%)
Hypertension	n = 2168, 1268 (58.5%)	n = 96, 68 (70.8%)	n = 1209, 690 (57.1%)
Hypercholesterolemia	n = 2166, 1348 (62.2%)	n = 95, 49 (51.6%)	n = 1209, 759 (62.8%)
Current smoker	n = 2133, 861 (40.4%)	n = 91, 29 (31.9%)	n = 1191, 475 (39.9%)
Family history of CAD	n = 2126, 547 (25.7%)	n = 91, 14 (15.4%)	n = 1198, 323 (27.0%)
Chronic kidney disease[a]	n = 2162, 274 (12.7%)	n = 96, 37 (38.5%)	n = 1206, 112 (9.3%)
History of stroke/TIA	n = 2168, 82 (3.8%)	n = 96, 8 (8.3%)	n = 1209, 32 (2.6%)
Previous MI	n = 2166, 326 (15.1%)	n = 96, 21 (21.9%)	n = 1207, 169 (14.0%)
Previous PCl	n = 2167, 381 (17.6%)	n = 96, 25 (26.0%)	n = 1208, 191 (15.8%)
Previous CABG	n = 2168, 122 (5.6%)	n = 96, 10 (10.4%)	n = 1209, 58 (4.8%)
Clinical presentation			
Unstable angina	94 (4.3%)	2 (2.1%)	54 (4.5%)
NSTEMI	930 (42.9%)	40 (41.7%)	507 (41.9%)
STEMI	1144 (52.8%)	54 (56.3%)	648 (53.6%)
Index procedure			
PCI	n = 2168, 1949 (89.9%)	n = 96, 73 (76.0%)	n = 1149, 1051 (91.5%)
Drug-eluting stent	n = 2034, 1868 (91.8%)	n = 83, 67 (80.7%)	n = 1149, 843 (73.4%)
Bare-metal stent	n = 2034, 1522 (74.8%)	n = 83, 47 (56.6%)	n = 1149, 225 (19.6%)
PTCA only	n = 2034, 376 (18.5%)	n = 83, 21 (25.3%)	n = 1149, 134 (11.7%)
CABG	n = 2034, 225 (11.1%)	n = 83, 12 (14.5%)	n = 1149, 41 (3.6%)
Peri-procedural medications			
Unfractionated heparin	n = 2164, 2071 (95.7%)	n = 96, 90 (93.8%)	n = 1207, 1153 (95.5%)
LMWH	n = 2167, 116 (5.4%)	n = 96, 3 (3.1%)	n = 1208, 77 (6.4%)
Bivalirudin	n = 2167, 96 (4.4%)	n = 96, 3 (3.1%)	n = 1208, 64 (5.3%)
Glycoprotein IIb/IIIa antagonists	n = 2167, 585 (27.0%)	n = 96, 18 (18.8%)	n = 1208, 348 (28.8%)
Statin (yes)	n = 2156, 328 (15.2%)	n = 92, 62 (67.4%)	n = 1204, 368 (30.56%)
GRACE risk score			
Long-term	n = 2168, 123.13 ± 26.41	n = 96, 149.83 ± 24.56	n = 1209, 120.16 ± 24.16
hsCRP (median (IQR))	n = 1892, 2.85 (1.1, 8)	n = 80, 7.6 (1.95, 27.85)	n = 1209, 2.5 (1.1, 6.4)
Measurements at 12 months			
LDL-cholesterol (mmol/L)	n = 1000, 2.22 ± 0.87	Not available	n = 765, 2.23 ± 0.86
Total-cholesterol (mmol/L)	n = 1009, 4.13 ± 1.02	Not available	n = 766, 4.13 ± 0.99
Triglyceride (mmol/L)	n = 1001, 1.44 ± 1.06	Not available	n = 766, 1.41 ± 1.09
Statin use at 12 months			
Statin (yes)	n = 1984, 1851 (93.3%)	Not available	n = 1207, 1143 (94.7%)
High-intensity (yes)	n = 1984, 1147 (57.8%)	Not available	n = 1207, 724 (60.0%)

Depicted are counts (%) or means ± SDs.
CABG, coronary artery bypass graft; CAD, coronary artery disease; CKD, chronic kidney disease; LMWH, low-molecular weight heparin; MI, myocardial infarction; PCI, percutaneous coronary interventions; TIA, transient ischemic attack.
[a] Based on creatinine-estimated glomerular filtration rate clearance of <60 mL/min/1.73 m^2, using the Modification of Diet in Renal Disease (MDRD) formula.

2. Materials and methods

2.1. Study design and population

Patients with a primary diagnosis of ACS who were referred for coronary angiography between 2009 and 2012 were enrolled in the Special Program University Medicine Acute Coronary Syndromes and Inflammation cohort with follow-up throughout 12 months [1,10,11]. High RIR was defined as hsCRP $\geq$ 2 mg/L. Patients were divided into four groups based on a cut-off level of hsCRP $\geq$ 2 mg/L at baseline and 12 months, respectively: persistently high RIR, increased RIR (first low, then high hsCRP), attenuated RIR (first high, then low hsCRP), or persistently low RIR as previously described in patients from a percutaneous coronary intervention (PCI) registry [12]. The study was approved by the local ethics committees.

2.2. Clinical endpoints

Independently adjudicated combined adverse events at 12 months were defined as the composite of MI, clinically indicated coronary revascularization, or cerebrovascular events comprising stroke or transient ischemic attacks [1,10,11]. Death was not included in combined adverse events as only 12-month survivors were analyzed with available hsCRP data at baseline and 12 months follow-up. High-intensity statin use comprised atorvastin 40–80 mg once daily or rosuvastatin 20–40 mg once daily and was ascertained at 12-month follow-up.

2.3. Biomarker analyses

Serum aliquots were collected at baseline from blood draws at the time of coronary angiography and after 12 months and stored at −80 °C until measurement in the Zurich Core Laboratory. CRP was measured in serum aliquots using a high-sensitivity latex enhanced immunoturbidimetric assay on a Cobas c 501® autoanalyser (Roche Diagnostics, Mannheim, Germany) [13].

2.4. Global registry of acute coronary events

The Global Registry of Acute Coronary Events (GRACE 1.0) score [14] was used to calculate long-term prediction of mortality and to assess the degree of disease severity in patients included in the current study.

2.5. Statistical analysis

Baseline characteristics are presented as means with standard deviations and medians for continuous variables, and categorical variables were shown as counts with percentages for each category of RIR. We used logistic regression models to evaluate possible associations between combined adverse events at 12 months follow-up for RIR groups, adjusted to the long-term GRACE risk score, including comprehensive prognostic information [14]. We used the logistic regression model as we have a complete follow-up of the included patients. Due to the low event rate for each category of RIR, we adjusted for GRACE risk score because the most important risk factors for ACS patients are integrated into this score. Two-sided *p*-values were reported throughout, and *p*-values smaller than 0.05 were considered statistically significant. Statistical analyses were performed using Stata statistical software® (Version 16.1, Stata Corp, and College Station, Tex).

3. Results

3.1. Persistently high RIR at 12 months in a quarter of ACS patients

Among 2168 patients included in the SPUM-ACS Biomarker cohort 1, 1209 patients had available hsCRP measurements both at baseline and 12-month follow-up (Supplementary Fig. S1). Table 1 shows that baseline characteristics were similar between the entire cohort and the current study group. In particular, the GRACE risk scores and hsCRP levels were similar at baseline, with no difference between groups for LDL-cholesterol levels and statin use at 12 months. Nearly a quarter of these patients after the index ACS event were in the category persistently high RIR, approximately 6% in the category increased RIR, whereas approximately a third fell in the categories attenuated RIR and persistently low RIR, respectively. Table 2 shows hsCRP levels for each category at baseline and 12 months complemented by the delta change in hsCRP levels during 12 months after the index ACS event. A separate analysis of patients who died within the 12-month follow-up (n = 96) showed that compared with the study population, those patients were at substantially higher risk for adverse events as calculated by the GRACE risk score and had higher hsCRP levels at baseline (Table 1).

3.2. Persistently high RIR associated with smoking, chronic kidney disease, and extensive coronary artery disease and lower high-intensity statin use

Baseline characteristics show that patients with persistently high RIR were more likely to be smokers, have chronic kidney disease, and to be referred to revascularization by CABG (Table 3). Conversely, patients with persistently low RIR were more likely to present with STEMI at the time of index ACS and to be treated with bivalirudin and/or glycoprotein IIb/IIIa antagonists. Of note, overall statin use was similar in the four categories at baseline. However, at 12 months, overall use of statins and especially the use of high-intensity statins was lower in the

Table 2
Prevalence of categories of persistently high, increased, attenuated or persistently low residual inflammatory risk.

	Persistently high RIR	Increased RIR	Attenuated RIR	Persistently low RIR	Overall population
	n = 295	n = 72	n = 390	n = 452	n = 1209
BL hsCRP (mg/L)					
Mean ± SD	19.07 ± 32.01	1.32 ± 0.55	13.80 ± 27.23	0.93 ± 0.54	9.53 ± 23.41
Median (IQR)	7.0 (4.2, 15.3)	1.4 (0.9, 1.8)	4.5 (3.0, 11.1)	0.9 (0.5, 1.4)	2.5 (1.1, 6.4)
Min-Max	2.1–180.5	0.03–2.0	2.1–205.2	0.03–2.0	0.03–205.2
12 months hsCRP (mg/L)					
Mean ± SD	6.88 ± 9.53	7.1 ± 7.3	1.03 ± 0.51	0.7 ± 0.45	2.7 ± 5.76
Median (IQR)	3.9 (2.7, 7.0)	4.15 (2.5, 9.7)	1.0 (0.6, 1.4)	0.6 (0.4, 1.0)	1.1 (0.6, 2.4)
Min-Max	2.1–99.0	2.0–44.6	0.1–2.0	0.1–1.9	0.1–99.0
Delta[a] hsCRP (mg/L)					
Mean ± SD	−12.19 ± 32.19	5.79 ± 7.35	−12.77 ± 27.28	−0.23 ± 0.57	−6.84 ± 23.22
Median (IQR)	−2.3 (−9.9, 0.3)	2.45 (1.2, 8.35)	−3.55 (−10, −2)	−0.2 (−0.6, 0.1)	−0.9 (−3.9, 0.07)
Min-Max	−176 to 76.9	42.9 to 5.79	−0.1 to −12.77	−1.7 to 1.4	−204.9 to 76.9

[a] Delta hsCRP is defined as ($hsCRP_{12\ months} - hsCRP_{baseline}$).

Table 3
Baseline characteristics according to residual inflammatory risk (n = 1209).

Parameters	Persistently high RIR	Increased RIR	Attenuated RIR	Persistently low RIR	*p*-value
	n = 295	n = 72	n = 390	n = 452	
Age (years)	n = 295, 62.21 ± 11.43	n = 72, 65.27 ± 11.41	n = 390, 63.14 ± 11.59	n = 452, 61.48 ± 11.38	0.028
Sex (female in %)	n = 295, 65 (22.0%)	n = 72, 6 (8.3%)	n = 390, 74 (19.0%)	n = 452, 67 (14.8%)	0.011
Body weight (kg)	n = 293, 83.10 ± 16.63	n = 71, 80.33 ± 13.16	n = 389, 81.02 ± 13.74	n = 448, 79.71 ± 13.47	0.019
Body Mass Index (kg/m^2)	n = 293, 28.35 ± 5.19	n = 71, 26.81 ± 3.81	n = 389, 27.18 ± 3.87	n = 447, 26.54 ± 3.73	<0.001
Medical history					
Diabetes mellitus	n = 295, 53 (18.0%)	n = 72, 10 (13.9%)	n = 390, 67 (17.2%)	n = 452, 57 (12.6%)	0.155
Hypertension	n = 295, 197 (66.8%)	n = 72, 46 (63.9%)	n = 390, 220 (56.4%)	n = 452, 227 (50.2%)	<0.001
Hypercholesterolemia	n = 295, 187 (63.4%)	n = 72, 43 (59.7%)	n = 390, 242 (62.1%)	n = 452, 287 (63.5%)	0.914
Current smoker	n = 287, 147 (51.2%)	n = 71, 25 (35.2%)	n = 385, 150 (39.0%)	n = 448, 153 (34.2%)	<0.001
Family history of CAD	n = 293, 80 (27.3%)	n = 71, 14 (19.7%)	n = 388, 106 (27.3%)	n = 446, 123 (27.6%)	0.568
Chronic kidney disease[a]	n = 295, 44 (14.9%)	n = 72, 11 (15.3%)	n = 389, 34 (8.7%)	n = 450, 23 (5.1%)	<0.001
History of stroke/TIA	n = 295, 4 (1.4%)	n = 72, 2 (2.8%)	n = 390, 13 (3.3%)	n = 452, 13 (2.9%)	0.437
Previous MI	n = 295, 49 (16.6%)	n = 72, 9 (12.5%)	n = 389, 46 (11.8%)	n = 451, 65 (14.4%)	0.335
Previous PCl	n = 295, 55 (18.6%)	n = 72, 12 (16.7%)	n = 389, 47 (12.1%)	n = 452, 77 (17.0%)	0.094
Previous CABG	n = 295, 17 (5.8%)	n = 72, 4 (5.6%)	n = 390, 16 (4.1%)	n = 452, 21 (4.6%)	0.770
Killip class	n = 294	n = 72	n = 389	n = 450	
Killip I	255 (86.7%)	63 (87.5%)	357 (91.8%)	408 (90.7%)	0.140
Killip II	30 (10.2%)	5 (6.9%)	24 (6.2%)	35 (7.8%)	0.275
Killip III	6 (2.0%)	2 (2.8%)	5 (1.3%)	3 (0.7%)	0.284
Killip IV	3 (1.0%)	2 (2.8%)	3 (0.8%)	4 (0.9%)	0.462
Clinical presentation					
Unstable angina	10 (3.4%)	6 (8.3%)	13 (3.3%)	25 (5.5%)	0.127
NSTEMI	140 (47.5%)	34 (47.2%)	183 (46.9%)	150 (33.2%)	<0.001
STEMI	145 (49.2%)	32 (44.4%)	194 (49.7%)	277 (61.3%)	<0.001
Index procedure					
PCI	n = 277, 246 (88.8%)	n = 69, 64 (92.8%)	n = 367, 339 (92.4%)	n = 436, 402 (92.2%)	0.342
Drug-eluting stent	n = 277, 203 (73.3%)	n = 69, 54 (78.3%)	n = 367, 258 (70.3%)	n = 436, 328 (75.2%)	0.336
Bare-metal stent	n = 277, 49 (17.7%)	n = 69, 11 (15.9%)	n = 367, 83 (22.6%)	n = 436, 82 (18.8%)	0.318
PTCA only	n = 277, 25 (9.0%)	n = 69, 6 (8.7%)	n = 367, 42 (11.4%)	n = 436, 61 (14.0%)	0.189
CABG	n = 277, 20 (7.2%)	n = 69, 4 (5.8%)	n = 367, 9 (2.5%)	n = 436, 8 (1.8%)	0.001
Peri-procedural medications					
Unfractionated heparin	n = 293, 281 (95.9%)	n = 72, 68 (94.4%)	n = 390, 376 (96.4%)	n = 452, 428 (94.7%)	0.626
LMWH	n = 294, 25 (8.5%)	n = 72, 3 (4.2%)	n = 390, 25 (6.4%)	n = 452, 24 (5.3%)	0.298
Bivalirudin	n = 294, 11 (3.7%)	n = 72, 1 (1.4%)	n = 390, 19 (4.9%)	n = 452, 33 (7.3%)	0.061
Glycoprotein IIb/IIIa antagonists	n = 294, 71 (24.1%)	n = 72, 18 (25.0%)	n = 390, 115 (29.5%)	n = 452, 144 (31.9%)	0.124
Statin (yes)	n = 293, 87 (29.7%)	n = 72, 21 (29.2%)	n = 388, 115 (29.6%)	n = 451, 145 (32.2%)	0.834
Statin use at 12 months					
Statin (yes)	n = 294, 270 (91.8%)	n = 72, 66 (91.7%)	n = 390, 368 (94.4%)	n = 451, 439 (97.3%)	0.006
High-intensity (yes)	n = 294, 142 (48.3%)	n = 72, 38 (52.8%)	n = 390, 238 (61.0%)	n = 451, 306 (67.8%)	<0.001
GRACE risk score					
Long-term	n = 295, 119.86 ± 24.83	n = 72, 124.63 ± 24.23	n = 390, 122.16 ± 23.84	n = 452, 117.91 ± 23.82	0.028

Depicted are counts (%) or means ± SDs.
CABG, coronary artery bypass graft; CAD, coronary artery disease; CKD, chronic kidney disease; LMWH, low-molecular weight heparin; MI, myocardial infarction; PCI, percutaneous coronary interventions; TIA, transient ischemic attack.
Killip I: No clinical signs or symptoms of congestive heart failure; Killip II: Third heart sound, rales or radiographic evidence of CHF.
Killip III: Pulmonary edema; Killip IV: Cardiogenic shock.
[a] Based on creatinine-estimated glomerular filtration rate clearance of <60 mL/min/1.73 m^2, using the Modification of Diet in Renal Disease (MDRD) formula.

persistently high RIR and increased RIR groups (Table 3).

As the different clinical and hemodynamic context of STEMI and NSTEMI may affect hsCRP levels, we performed independent analyses of STEMI and NSTEMI patients.

The persistently high RIR group remains associated with the highest risk for combined adverse events in both STEMI (Supplementary Table S1) and NSTEMI (Supplementary Table S3) compared with the three remaining groups. There was no major difference in median (IQR) hsCRP levels between patients with STEMI 2.2 (1.0, 5.75) mg/L (Supplementary Table S2) and NSTEMI 3.2 (1.4, 8.5) mg/L (Supplementary Table S4). However, the number of events in the RIR groups is very low, and a separate statistical analysis will not provide reliable model coefficients. Thus, we refrained from modeling separately for STEMI and NSTEMI patients. A continuous model for hsCRP and outcome is shown in the Supplement (Supplementary Table S5) emphasizing the need for a cut-off.

3.3. Increased combined adverse events in patients with persistently high RIR

Table 4 shows the prevalence of individual components of the composite combined adverse events endpoint. As only survivors were analyzed by definition, no deaths were detected in either group. The highest combined adverse events rate was found in the persistently high RIR category. Fig. 1 shows the logistic regression analysis for associations between combined adverse events at 12 month follow-up and RIR groups. Patients in the persistently high RIR category had a higher event rate compared with the three other groups combined. Furthermore, direct comparison of patients in the persistently high RIR group with the persistently low RIR group as a reference showed a higher risk for combined adverse events in patients with a high inflammatory burden at 12 months. The GRACE risk score was significantly associated with combined adverse events per 10 score unit increase.

Table 4
Clinical outcomes and drug use at 12-month follow-up according to residual inflammatory risk (n = 1209).

Parameters	Persistently high RIR	Increased RIR	Attenuated RIR	Persistently low RIR
	n = 295	n = 72	n = 390	n = 452
12 months				
Myocardial infarction	13 (4.4%)	1 (1.4%)	18 (4.6%)	6 (1.3%)
Revascularization	23 (7.8%)	2 (2.8%)	24 (6.2%)	27 (6.0%)
Revascularization (clinically indicated)	22 (7.5%)	2 (2.8%)	24 (6.2%)	24 (5.3%)
Cerebrovascular events (CVE:stroke or TIA)	8 (2.7%)	1 (1.4%)	4 (1.0%)	2 (0.4%)
Stroke (any)	6 (2.0%)	0 (0.0%)	3 (0.8%)	1 (0.2%)
CVE (ischemic stroke)	5 (1.7%)	0 (0.0%)	2 (0.5%)	1 (0.2%)
CVE (intracerebral hemorrhage)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
CVE (unclear etiology)	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)
TIA	2 (0.7%)	1 (1.4%)	1 (0.3%)	1 (0.2%)
Stent thrombosis (definite)	3 (1.0%)	0 (0.0%)	4 (1.0%)	3 (0.7%)
Combined adverse events[a]	31 (10.5%)	3 (4.2%)	30 (7.7%)	26 (5.8%)

[a] Combined adverse events defined as MI, clinically indicated revascularization or cerebrovascular event.

4. Discussion

In this prospective cohort study of ACS patients who were all managed according to guideline recommended interventions and optimal medical therapy (OMT) at 12 months after ACS [1] a quarter of patients had persistently increased hsCRP and [2] were more likely to experience combined adverse events, justifying the term residual inflammatory risk (RIR).

This study represents the first analysis on the prevalence and association of RIR with combined adverse events at 12 months in a contemporary prospectively recruited all-comer ACS (NSTEMI, STEMI) population. Similar findings were reported from a retrospective registry of patients undergoing PCI for mostly CCS or unstable angina [12]. The course of hsCRP determined RIR, adding incremental information to the GRACE risk score which indeed was similar in the four risk categories. Prior studies in ACS patients demonstrated high proportions of patients with a high inflammatory burden identified by a hsCRP level ≥2 mg/L [15–17]. In our study, 30% of patients (persistently high RIR and increased RIR groups combined) had hsCRP levels ≥2 mg/L at 12 months. The lower incidence (43% in PROVE-IT, 47% in IMPROVE-IT) [17] is likely attributable to a longer follow-up in the SPUM-ACS cohort and the wide-spread use of OMT, including high-intensity statins [18]. In the current study, the mean LDL-cholesterol level was 2.23 mmol/L at 12 months in the entire cohort. The rate of overall and especially high-intensity statin use was lower in the persistently high and increased RIR groups in line with a combined residual cholesterol and inflammatory risk in these patients.

Our study which followed patients for 12 months after ACS differs markedly from previous studies. First, the current study extends data from our recent publication which showed that elevated hsCRP levels by a single measurement at the index ACS event predict combined adverse events [13]. This finding is further supported by our separate analysis of patients in the current study who died in the first 12 months with very high hsCRP levels at baseline (median 7.6 mg/dL) compared with the current study population (2.5 mg/dL) who survived the first 12 months. These data are in line with the notion of ACS as a major inflammatory event with hsCRP levels at baseline that are commonly greater than 10 mg/L unlike in patients with chronic coronary syndromes.

Furthermore, it is an intriguing finding that baseline hsCRP levels could be low at the time of ACS but then increase to higher levels at 12 months. Several explanations are possible [1]: Time between onset of acute chest pain and blood draw at baseline was variable, as was the type of presentation (STEMI vs. NSTEMI). However, neither the type of ACS nor the time interval had an impact on hsCRP level in the SPUM-ACS cohort [13]. [2] Progression of atherosclerotic burden in the coronary vasculature [3], Comorbidities developing after ACS. In support of the latter, patient characteristics associated with residual inflammation independent from the acute ACS event were more frequent in the persistently high RIR group. Indeed, our data emphasize the need for *serial* hsCRP measurements to identify patients at increased risk for adverse events as early as possible given that nearly half of all patients had low hsCRP levels (<2 mg/L) at baseline. We have previously shown that measuring hsCRP only at baseline in the SPUM-ACS cohort is a poor marker of future risk compared with the GRACE risk score, hsTnT and NT-proBNP [11].

Translation into the clinics of recently published anti-inflammatory trials using low-dose colchicine in patients shortly after MI or with CCS [5,6] is hampered by the lack of identified subgroups that will benefit the most while experiencing least side-effects. Serial hsCRP levels may serve as a valuable stratifying tool and it is noteworthy that both trials were not designed to target patients at high inflammatory risk. Nonetheless, as low-dose colchicine is an inexpensive and rather safe drug, a restrictive biomarker-guided approach is likely to exempt patients that may benefit from colchicine despite low-grade inflammation. The proposed biomarker-guided approach may hold the greatest promise for anti-inflammatory drugs with a less favorable safety profile.

4.1. Limitations

The study is limited to survivors with serial laboratory data available. Thus, it is unclear if hsCRP impacted on mortality. However, we report patient characteristics for non-survivors which show that those with higher hsCRP levels at baseline were at higher risk of death. Due to random availability of hsCRP there is no systemic bias as shown when comparing the entire cohort with the current study group. The lack of a time-dependent analysis – assessment of hsCRP at time of adverse event - does not allow to assess whether the events were related to a change in the inflammatory status over time. Serial measurements of hsCRP earlier than 12 months after the index ACS may enable a more rapid identification of patients at RIR. Finally, due to the small group size (40% of the patients included in the analysis are missing the values for LDL-cholesterol), meaningful statistical analysis with respect to LDL-cholesterol, total cholesterol, and triglycerides, and the four RIR categories is not possible.

4.2. Conclusions

Residual risk for combined adverse events in ACS patients with persistently elevated hsCRP levels is frequent and clinical trials targeting inflammatory pathways involved upstream of CRP should be conducted in this category of high-risk patients.

Financial support

This work was supported by the Swiss National Science Foundation (SPUM 33CM30-124112 and 32473B_163271); the Swiss Heart

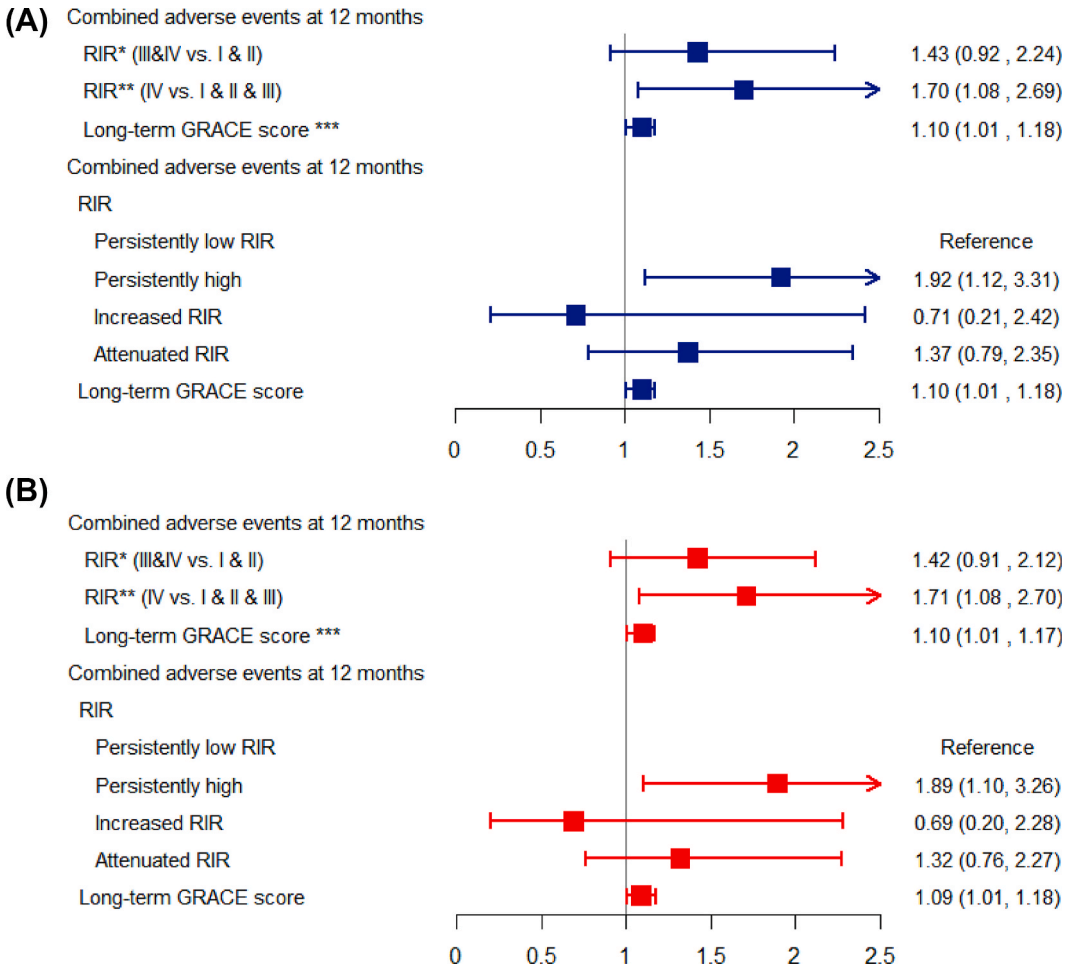

Fig. 1. Results of the univariable (A) and multivariable (B) logistic models for RIR categories adjusted to long-term GRACE risk score for combined adverse events (n = 1209).
The variables included in the long-term GRACE risk score for long-term mortality comprise age, heart rate, systolic blood pressure, serum creatinine, history of congestive heart failure, history of MI, elevated cardiac markers (conventional troponins as per local laboratories), ST-segment depression and no in-hospital PCI). GRACE: global registry of acute coronary events; combined adverse events defined as MI, clinically indicated revascularization or cerebrovascular event; RIR: residual inflammatory risk.

Foundation; the Foundation Leducq and the Foundation for Cardiovascular Research – Zurich Heart House, Zurich. The SPUM consortium was also supported by Roche Diagnostics, Rotkreuz, Switzerland (providing the kits for high-sensitivity C-reactive protein), Eli Lilly, Indianapolis (USA), AstraZeneca, Zug; Medtronic, Münchenbuchsee; Merck Sharpe and Dome (MSD), Lucerne; Sanofi-Aventis, Vernier; St. Jude Medical, Zurich (all Switzerland).

CRediT authorship contribution statement

Roland Klingenberg: Conceptualization, Methodology, Investigation, Resources, Writing - original draft, Visualization, Funding acquisition. **Soheila Aghlmandi:** Methodology, Investigation, Writing - original draft, Visualization, Formal analysis, Investigation, Writing - review & editing. **Baris Gencer:** Investigation, Resources, Writing - review & editing. **David Nanchen:** Investigation, Resources, Writing - review & editing. **Lorenz Räber:** Investigation, Resources, Writing - review & editing. **David Carballo:** Investigation, Resources, Writing - review & editing. **Sebastian Carballo:** Investigation, Resources, Writing - review & editing. **Barbara E. Stähli:** Investigation, Resources, Writing - review & editing. **Ulf Landmesser:** Writing - review & editing, Supervision, Project administration. **Nicolas Rodondi:** Writing - review & editing, Supervision, Project administration. **François Mach:** Writing - review & editing, Supervision, Project administration. **Stephan Windecker:** Writing - review & editing, Supervision, Project administration. **Heiner C. Bucher:** Writing - review & editing, Formal analysis, Supervision. **Arnold von Eckardstein:** Investigation, Writing - review & editing, Supervision. **Thomas F. Lüscher:** Writing - review & editing, Supervision, Project administration. **Christian M. Matter:** Writing - review & editing, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We appreciate the work of the clinical event committee, study nurses, core lab technicians, central data monitors, electronic data capturing system (2 mt GmbH Ulm, Germany), and members of the local catheter laboratory teams.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.

org/10.1016/j.atherosclerosis.2021.01.012.

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