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CLINICAL RESEARCH
Interventional cardiology

Residual cholesterol and inflammatory risk in statin-treated patients undergoing percutaneous coronary intervention†

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Abstract

Background and Aims Elevated LDL-cholesterol levels and inflammation, as assessed by high-sensitivity C-reactive protein, correlate with cardiovascular risk. However, data on the relative impact of residual LDL-cholesterol and inflammatory risk among statin-treated patients undergoing percutaneous coronary intervention (PCI) is lacking. Hence, this study aimed to investigate the impact of residual cholesterol/inflammatory risk in patients on statin therapy undergoing PCI.

Methods From 2012 to 2022, patients at a tertiary centre undergoing PCI were analysed. Patients were stratified according to LDL-cholesterol (≥70 vs <70 mg/dL) and high-sensitivity C-reactive protein (≥2 vs <2 mg/L) levels: no residual cholesterol or inflammatory risk, residual cholesterol risk, residual inflammatory risk, and combined residual cholesterol and inflammatory risk. Patients presenting with acute myocardial infarction, cancer, no statin treatment at admission, or high-sensitivity C-reactive protein levels >10 mg/L were excluded. The primary endpoint was major adverse cardiovascular events (MACEs), defined as the composite of all-cause mortality, spontaneous myocardial infarction, and stroke 1 year after the index PCI.

Results A total of 15 494 patients were included. After 1-year follow-up, individuals with isolated residual inflammatory risk had the highest MACE rate (5.1%), followed by patients with combined cholesterol and inflammatory risk, no residual risk, and isolated residual cholesterol risk. After multivariable Cox regression analysis, patients with residual inflammatory risk had a 1.8-fold higher risk for MACE (adjusted hazard ratio: 1.78, 95% confidence interval 1.36–2.33, $P < .001$) compared with those with no residual cholesterol or inflammatory risk. This was similar in patients with combined residual cholesterol and inflammatory risk (adjusted hazard ratio: 1.56, 95% confidence interval 1.19–2.04, $P = 0.001$). Of note, no independent association of isolated residual cholesterol risk (adjusted hazard ratio: 1.01, 95% confidence interval .76–1.35, P-value = .920) with MACE was noted (P-trend across all groups <.001).

Conclusions Among statin-treated patients undergoing PCI, residual inflammation but not cholesterol risk was associated with an increased risk of MACE during follow-up.

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‡ The first two authors contributed equally to the study.

Structured Graphical Abstract

Key Question

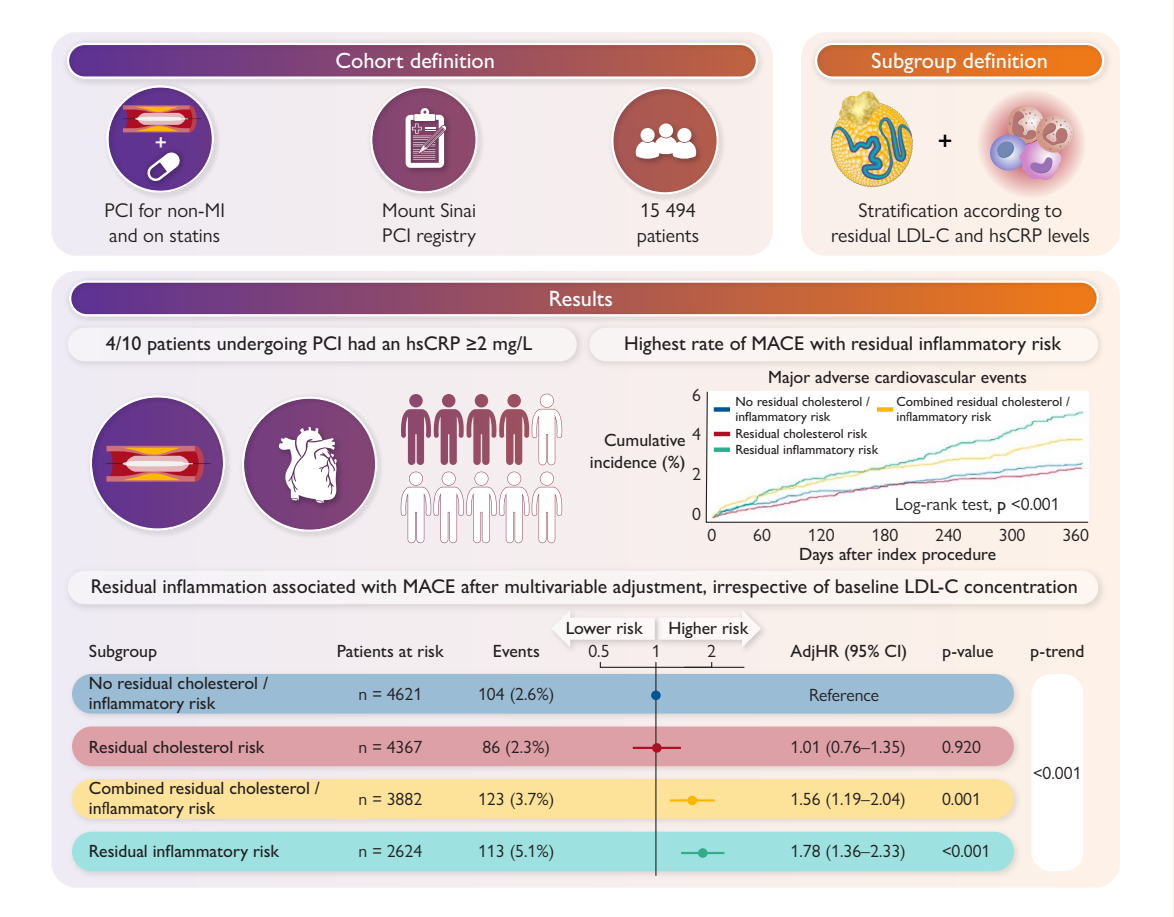
What is the relative impact of residual cholesterol and inflammatory risk in patients on statins undergoing percutaneous coronary intervention (PCI)?

Key Finding

In a large cohort of patients on statins undergoing PCI, residual risk for adverse cardiovascular events was driven by inflammatory rather than residual cholesterol risk.

Take Home Message

A strategy solely addressing residual cholesterol risk is unlikely to significantly reduce major adverse cardiovascular events in PCI patients. Addressing inflammatory risk in addition to lipid-lowering treatments may be a more appropriate strategy for reducing recurrent adverse events after PCI.



Keywords PCI • Statins • Residual risk • Inflammation • Cholesterol • HsCRP • LDL-C

Introduction

Over the last decades, unequivocal evidence has been generated regarding the essential role of ApoB-containing lipoproteins in the development and progression of atherosclerotic cardiovascular disease (ASCVD).[1] This has led to the development of a multitude of pharmacological secondary preventive strategies with the aim of lowering circulating lipoprotein levels, most focusing on LDL-cholesterol (LDL-C), which has become one of the cornerstones in the treatment of ASCVD.[2–4]

Next to lipid concentrations, the pivotal role of inflammation for incident cardiovascular events in patients with established ASCVD despite adherence to guideline-directed medical therapy has been demonstrated.[5] In addition, trials targeting essential steps within the inflammatory cascade were able to showcase the efficacy of anti-inflammatory agents, which led to a reduction in adverse cardiovascular events in patients with coronary artery disease (CAD).[6–8] This benefit was also observed even among patients already undergoing treatment with lipid-lowering medications, primarily statins, which also exert anti-inflammatory effects.[9]

Notably, a recent pooled analysis from the Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes (PROMINENT), Reduction of Cardiovascular Events with Icosapent Ethyl—Intervention Trial (REDUCE-IT), and Long-term Outcomes Study to Assess Statin Residual Risk with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia (STRENGTH) investigators revealed that biomarkers indicating low-grade vascular inflammation, i.e. high-sensitivity C-reactive protein (hsCRP), exhibited a stronger correlation with adverse outcomes compared with LDL-C levels in statin-treated patients who were either at high risk for or displayed ASCVD.[10] However, data are scarce with regard to the relative effects of cholesterol and inflammation on clinical outcomes in real-world patients undergoing percutaneous coronary intervention (PCI) for stenotic CAD.

Hence, this study investigated and compared the relative impact of residual cholesterol and inflammatory risk on subsequent adverse clinical outcomes in statin-treated patients undergoing PCI in a large single-centre registry.

Methods

Study design and patient population

All patients, who underwent PCI between 2012 and 2022 at the Mount Sinai Hospital (New York, NY, USA) enrolled in the institutional PCI registry, were considered for inclusion in this prospective cohort study. Baseline and procedural characteristics and medications were collected from electronic health records after providing written and informed consent. The presence of comorbidities was ascertained via patient self-report, hospital medical records, and referral documentation, as well as laboratory measures [such as an estimated glomerular filtration rate <60 mL/min/1.73 m^2 for the diagnosis of chronic kidney disease (CKD)]. The PCI approach and techniques used during the procedure were at the operator's discretion. Similarly, pharmacotherapy was directed by the treating interventional cardiologist.

Laboratory specimens were ascertained at admission ahead of PCI. Lipid concentrations, including total cholesterol, triglycerides, HDL-cholesterol (HDL-C), and deductive measurements, such as LDL-C (calculated via the Friedewald formula), were obtained. The Abbott Laboratories commercial kit and analyser (Abbott Alinity Instrumentation, Abbott Laboratories, Abbott Park, IL, USA) was used for hsCRP measurement, with a previously reported detection limit of .1 mg/L and intra-assay coefficient of variability ≤6%. All laboratory measurements were implemented within the clinical routine.

Patients not on statin therapy at the time of index PCI; patients without either baseline LDL-C or hsCRP levels; patients who presented with either non-ST-elevation myocardial infarction (NSTEMI) or ST-elevation myocardial infarction (STEMI); patients who had hsCRP levels over 10 mg/L; patients who had a history of neoplastic disease at initial presentation; and patients lost to follow-up within 30 days of baseline PCI were excluded. Baseline characteristics of the overall included population as well as the excluded patients can be found in Supplementary data online, *Table S1*.

Eligible patients were separated into four groups according to their baseline LDL-C and hsCRP levels as follows: no residual cholesterol or inflammatory risk (LDL-C <70 mg/dL + hsCRP <2 mg/L), residual cholesterol risk (LDL-C ≥70 mg/dL + hsCRP <2 mg/L), residual inflammatory risk (LDL-C <70 mg/dL + hsCRP ≥2 mg/L), and combined residual cholesterol and inflammatory risk (LDL-C ≥70 mg/dL + hsCRP ≥2 mg/L).

The study was conducted in compliance with the Declaration of Helsinki. Furthermore, the Mount Sinai institutional PCI registry is registered with the local institutional review board, and approval was given for this study.

Outcomes

The primary outcome was the incidence of major adverse cardiovascular events (MACEs), a composite of all-cause mortality, spontaneous myocardial infarction (MI), and stroke. Moreover, as a secondary outcome, an expanded MACE endpoint (MACE$^+$), which also included target lesion revascularization (TLR) within 1 year following PCI, was investigated. Further secondary outcomes included all individual components of the primary endpoint, TLR, and target vessel revascularization (TVR), all within 1 year following PCI.

The standard operating procedure for our institutional database is minimum follow-up at 30 days and 1 year after PCI, which is carried out by trained research personnel and performed during a clinic visit or through a phone call. Information from additional unplanned clinic visits or unplanned hospital admissions was entered as appropriate. A dedicated clinical event committee consisting of three cardiologists adjudicated all registered adverse events that resulted in readmission to Mount Sinai Hospital using hospital healthcare records.[11] Myocardial infarction was defined according to the third universal definition of MI; stroke was defined as loss of neurological function caused by an ischaemic or haemorrhagic event with residual symptoms lasting ≥24 h or leading to death; TLR was defined as any unplanned revascularization of the lesion treated at the index PCI; and lastly, TVR was defined as any unplanned revascularization of the vessel treated at the index PCI.[12]

Incident events outside of Mount Sinai Hospital were gathered through telephone interviews and verified with medical records from external providers. No event adjudication was performed for external events outside of Mount Sinai Hospital.

Statistical analysis

For the overall cohort and all above-named subgroups, baseline and procedural characteristics were reported as mean and standard deviation (SD) or median and the interquartile range (IQR) for continuous variables, and counts with percentages for categorical variables. Comparisons between the groups were performed using χ^2 test, independent-samples *t*-test, and Mann–Whitney *U* test as appropriate.

The cumulative 1-year incidence of the primary outcome and its individual components was calculated using the Kaplan–Meier method. Risks for all outcomes at 1 year were assessed with a Cox regression model and expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). The subgroup of patients with no residual cholesterol or inflammatory risk (i.e. LDL-C <70 mg/dL + hsCRP <2 mg/L) served as a reference. Adjusted HRs (adjHRs) were calculated using a multivariable Cox regression model accounting for the following variables between subgroups: age, sex, body mass index (BMI), race/ethnicity, current smoking, arterial hypertension, diabetes mellitus, CKD, and prior MI.

Sensitivity analyses excluding the following patient populations were implemented: (i) patients aged ≥65 years; (ii) male patients; (iii) patients with a history of diabetes; (iv) patients with a history of insulin-dependent diabetes; (v) patients with a history of CKD; (vi) patients with a history of dialysis; (vii) patients with triglycerides ≥150 mg/dL at baseline; (viii) patients with non-HDL-C ≥100 mg/dL at baseline; and (ix) patients with reduced HDL-C at baseline (<40 mg/dL in males and <50 mg/dL in females).

All probability testing was two-sided, and *P*-values <.05 were considered statistically significant. All statistical analysis was performed with Stata version 16, licensed from StataCorp.

Results

Baseline characteristics

After implementing inclusion and exclusion criteria, 15 494 patients were available for the current analysis (*Figure 1*). In brief, mean patient age was 66.0 ± 10.9 years and 27.0% were female. At baseline, median LDL-C and hsCRP levels were 72.0 (IQR: 56.0–93.0) mg/dL and 1.6 (IQR: .7–3.3) mg/L, respectively (the distribution of LDL-C blood concentrations is included in Supplementary data online, *Figure S1*). The

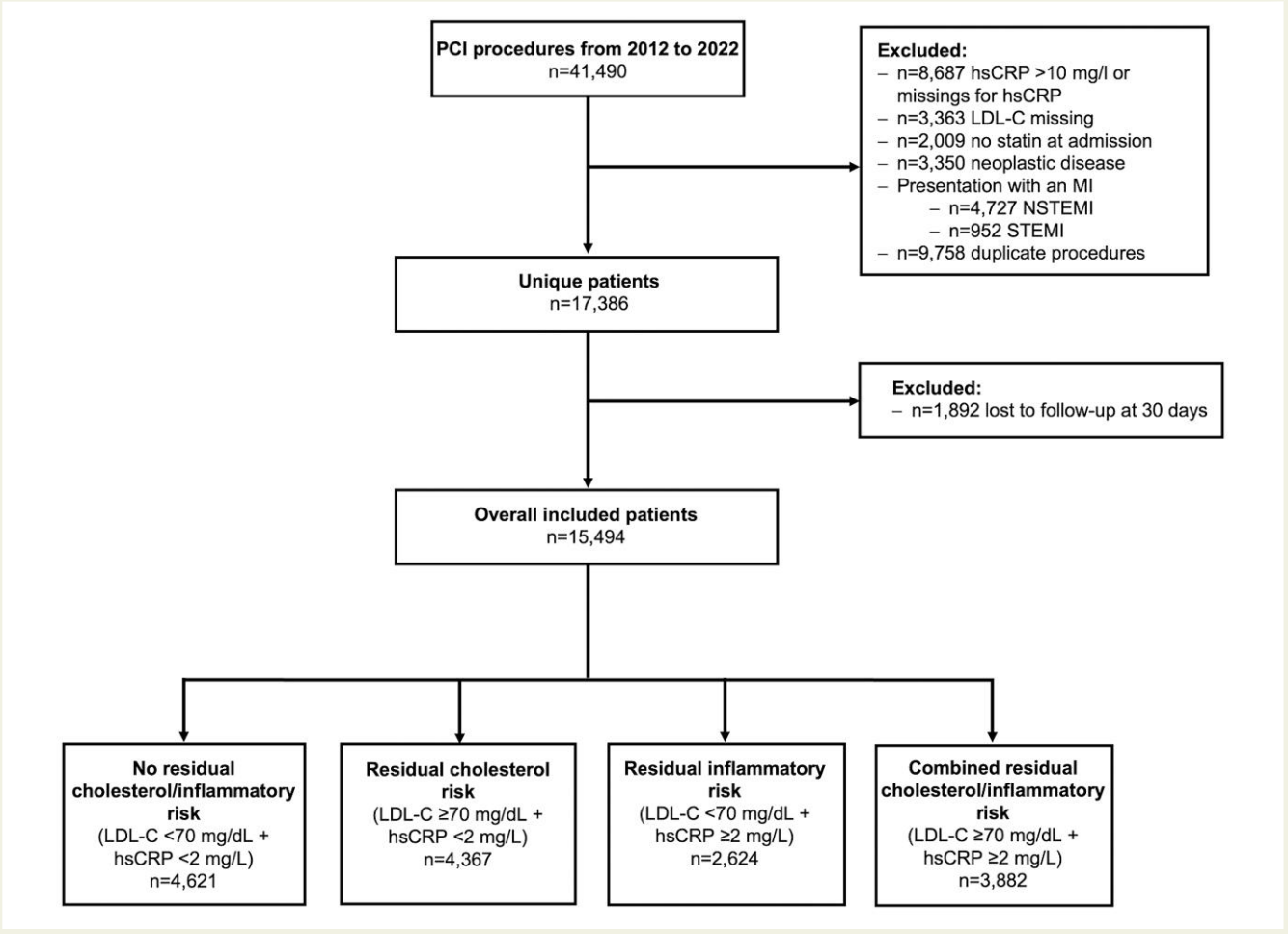


Figure 1 Study flow chart of the included and excluded individuals for the overall cohort and stratified according to LDL-cholesterol and high-sensitivity C-reactive protein concentrations. HsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction

included and excluded patient populations exhibited comparable characteristics (also see Supplementary data online, *Table S1*).

From the overall cohort, 4621 (29.8%) patients had no residual cholesterol or inflammatory risk, 4367 (28.2%) had residual cholesterol risk alone, 2624 (16.9%) had residual inflammatory risk alone, and 3882 (25.1%) had both residual cholesterol and inflammatory risk. *Table 1* displays baseline demographic, clinical, and laboratory measurements, according to the residual cholesterol and inflammatory risk groupings. Patients with residual inflammatory risk were the oldest, with a mean age of 67.1 ± 10.9 years and the combined high residual cholesterol and inflammation group had the highest proportion of females (35.7%).

Comorbidities, such as diabetes mellitus or CKD, were more prevalent in individuals with an increased inflammatory burden.

Details concerning clinical presentation and procedural characteristics stratified according to the investigated subgroups are reported in Supplementary data online, *Table S2*. In the majority of patients, lesions of the left anterior descending coronary artery were treated. Of note, no differences across the groups were documented in relation to bifurcation interventions, lesion length, and number of intervened complex lesions. Finally, the rates of periprocedural complications were similar between groups.

Clinical outcomes

During a median follow-up of 366 days (IQR: 352–366 days), a total of 426 events of the primary three-component MACE endpoint occurred in the total study population. Kaplan–Meier curves with incident MACE rates are displayed in *Figure 2*, while the Kaplan–Meier curves for the individual components of the primary MACE endpoint are showcased in Supplementary data online, *Figure S2*. Patients with residual inflammatory risk had the highest rate of the composite endpoint with 113 (5.1%) events, followed by patients with combined inflammatory and cholesterol residual risk ($n = 123$, 3.7%), persons with neither cholesterol nor inflammatory risk ($n = 104$, 2.6%), and individuals with residual cholesterol risk ($n = 86$, 2.3%; $P < .0001$ for log-rank test).

In unadjusted Cox regression analysis, the HR for 1-year risk of MACE was highest among individuals with residual inflammatory risk and in those with both residual cholesterol and inflammatory risk. No increased risk for adverse events was noted among those with isolated residual cholesterol risk. After multivariable adjustment, isolated residual inflammatory risk (adjHR: 1.78, 95% CI 1.36–2.33, $P < .001$) and combined residual inflammatory and cholesterol risk (adjHR: 1.56, 95% CI 1.19–2.04, $P = .001$) were independently associated with 1-year risk of MACE after PCI. Isolated residual cholesterol risk was not associated

Table 1 Baseline characteristics of the study population stratified according to LDL-cholesterol and high-sensitivity C-reative protein concentrations

	LDL-C <70 mg/dL + hsCRP <2 mg/L *n* = 4621 (29.8%)	LDL-C ≥ 70 mg/dL + hsCRP <2 mg/L N = 4367 (28.2%)	LDL-C < 70 mg/dL + hsCRP ≥2 mg/L N = 2624 (16.9%)	LDL-C ≥ 70 mg/dL + hsCRP ≥2 mg/L N = 3882 (25.1%)
Patient characteristics				
Age, years	66.9 ± 10.6	65.6 ± 11.0	67.1 ± 10.9	64.8 ± 11.2
BMI, kg/m^2	27.5 ± 4.5	27.8 ± 4.9	30.0 ± 6.0	30.3 ± 5.9
Female sex	905 (19.6%)	1168 (26.7%)	725 (27.6%)	1384 (35.7%)
Race/ethnicity				
Caucasian	1976 (51.4%)	1844 (50.3%)	1134 (51.2%)	1491 (45.5%)
African American	262 (6.8%)	395 (10.8%)	242 (10.9%)	479 (14.6%)
Asian	941 (24.5%)	757 (20.6%)	384 (17.3%)	519 (15.8%)
Hispanic	663 (17.3%)	671 (18.3%)	455 (20.5%)	786 (24.0%)
Medical history				
Current smoker	399 (8.6%)	466 (10.7%)	308 (11.7%)	619 (15.9%)
Diabetes mellitus	2319 (50.2%)	1750 (40.1%)	1503 (57.3%)	1902 (49.0%)
Insulin dependent	657 (28.3%)	457 (26.1%)	590 (39.3%)	688 (36.2%)
Hypertension	4392 (95.1%)	3993 (91.4%)	2528 (96.3%)	3631 (93.6%)
Peripheral artery disease	333 (7.2%)	291 (6.7%)	298 (11.4%)	421 (10.8%)
Cerebrovascular disease	421 (9.1%)	364 (8.3%)	321 (12.2%)	437 (11.3%)
Atrial fibrillation	342 (7.4%)	235 (5.4%)	294 (11.2%)	285 (7.3%)
Chronic kidney disease	1099 (23.8%)	926 (21.2%)	913 (34.8%)	992 (25.6%)
Dialysis	65 (1.4%)	47 (1.1%)	182 (6.9%)	111 (2.9%)
Prior PCI	2547 (55.1%)	1707 (39.1%)	1435 (54.7%)	1527 (39.3%)
Prior MI	1255 (27.2%)	849 (19.4%)	765 (29.2%)	824 (21.2%)
Family history of CAD	959 (20.8%)	977 (22.4%)	508 (19.4%)	841 (21.7%)
Medications				
Statins	4621 (100%)	4367 (100%)	2624 (100%)	3882 (100%)
PCSK9 inhibitors	14 (.3%)	7 (.2%)	6 (.2%)	3 (.1%)
DAPT	4379 (94.8%)	4155 (95.3%)	2425 (92.5%)	3654 (94.3%)
Oral anticoagulants	308 (6.7%)	226 (5.2%)	275 (10.5%)	291 (7.5%)
Beta-blocker	3759 (81.4%)	3425 (78.6%)	2157 (82.3%)	3069 (79.2%)
RAAS inhibitors	3081 (66.7%)	2608 (59.7%)	1758 (70.0%)	2433 (62.7%)
Laboratory values				
hsCRP, mg/L	.8 (.4–1.2)	.9 (.5–1.3)	3.8 (2.7–5.7)	3.7 (2.7–5.6)
LDL-C, mg/dL	54.2 (46.0–62.2)	89.0 (78.4–107.4)	55.6 (46.6–62.8)	94.0 (80.2–114.0)
Total cholesterol, mg/dL	110.0 (99.0–121.0)	151.0 (136.0–172.0)	112.0 (100.0–123.0)	157.0 (140.0–180.0)
Triglycerides, mg/dL	73.0 (51.0–106.0)	84.0 (59.0–121.0)	85.0 (60.0–122.0)	99.0 (68.0–143.0)

Continued

Table 1 *Continued*

	LDL-C <70 mg/dL + hsCRP <2 mg/L *n* = 4621 (29.8%)	LDL-C ≥ 70 mg/dL + hsCRP <2 mg/L N = 4367 (28.2%)	LDL-C < 70 mg/dL + hsCRP ≥2 mg/L N = 2624 (16.9%)	LDL-C ≥ 70 mg/dL + hsCRP ≥2 mg/L N = 3882 (25.1%)
HDL-C, mg/dL	38.0 (31.0–46.0)	40.0 (34.0–48.0)	36.0 (30.0–44.0)	38.0 (32.0–45.0)
HbA1c, %	6.8 (6.1–7.8)	6.7 (6.0–7.9)	7.0 (6.2–8.2)	7.1 (6.1–8.6)
eGFR, mL/min	76.8 (61.6–92.1)	78.7 (63.3–92.8)	70.7 (51.7–88.4)	77.0 (59.5–93.8)

Values are mean ± standard deviation, median (interquartile range), or *n* (%).
BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; DAPT, dual antiplatelet therapy; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; MI, myocardial infarction; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PCI, percutaneous coronary intervention; PCSK9, proprotein convertase subtilisin/kexin type 9; RAAS, renin-angiotensin-aldosterone system.

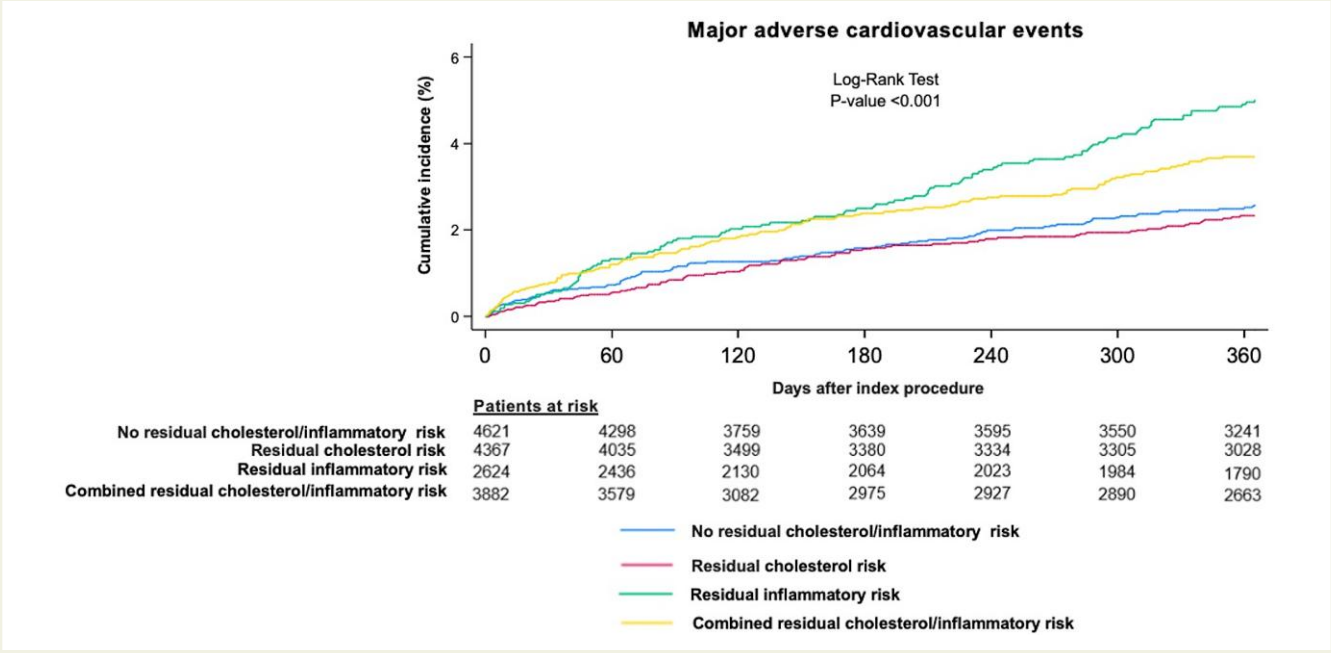


Figure 2 Cumulative incidence of major adverse cardiovascular events as a composite of all-cause mortality, spontaneous myocardial infarction, and stroke stratified according to LDL-cholesterol and high-sensitivity C-reactive protein concentrations 1 year after the index procedure. No residual cholesterol or inflammatory risk (LDL-cholesterol <70 mg/dL + high-sensitivity C-reative protein <2 mg/L), residual cholesterol risk (LDL-cholesterol ≥70 mg/dL + high-sensitivity C-reative protein <2 mg/L), residual inflammatory risk (LDL-cholesterol <70 mg/dL + high-sensitivity C-reative protein ≥2 mg/L), and combined residual cholesterol and inflammatory risk (LDL-cholesterol ≥70 mg/dL + high-sensitivity C-reative protein ≥2 mg/L). HsCRP, high-sensitivity C-reative protein; LDL-C, low-density lipoprotein cholesterol

with an increased risk of MACE (adjHR: 1.01, 95% CI .76–1.35, $P = .920$) compared with patients with neither residual cholesterol nor inflammation risk, with a *P*-trend of <.001 across all groups (*Table 2*).

Concerning secondary endpoints, an independent association of inflammatory risk (adjHR: 1.36 95% CI 1.15–1.62, $P < .001$) with the expanded MACE^{+} endpoint was seen. One-year mortality risk was significantly elevated in the isolated residual inflammatory risk group (adjHR: 2.59, 95% CI 1.75–3.84, $P < .001$) and the combined residual cholesterol and inflammatory risk group (adjHR: 1.70, 95% CI 1.12–2.59, $P = .013$), but not the residual cholesterol risk group (adjHR: .98, 95% CI .61–1.55, $P = .923$; *P*-trend <.001). For spontaneous MI, an independent association was noticed only in patients with combined residual cholesterol and inflammatory risk (adjHR: 1.47, 95% CI 1.02–2.11, $P = .038$). No association of residual risk with incident stroke, TVR, or TLR was documented. Further details, including unadjusted as well as adjusted results with regard to the individual components of the composite primary endpoint, are displayed in *Table 2*.

The results of the sensitivity analysis are reported in Supplementary data online, *Tables S3–11*. Notably, the observed effect of residual inflammatory risk on the composite MACE outcome was largely consistent across the different implemented sensitivity subgroups.

Discussion

This study examined the relative impact of residual cholesterol (LDL-C ≥70 mg/dL vs <70 mg/dL) and inflammatory risk (hsCRP ≥2 mg/L vs

Table 2 Crude event rates, unadjusted and adjusted hazard ratios for the primary and secondary endpoints stratified according to LDL-cholesterol and high-sensitivity C-reactive protein concentrations 1 year after the index procedure

	Event (%)	HR (95% CI)	*P*-value	adjHR (95% CI)	*P*-value	Trend *P*-value
Primary endpoint						
MACE						
LDL-C <70 mg/dL + hsCRP <2 mg/L	69 (2.4%)	Ref.		Ref.		<.001
LDL-C ≥70 mg/dL + hsCRP <2 mg/L	60 (2.3%)	.92 (.65–1.30)	.637	1.01 (.76–1.35)	.920	
LDL-C <70 mg/dL + hsCRP ≥2 mg/L	82 (5.2%)	2.09 (1.52–2.88)	<.001	1.78 (1.36–2.33)	<.001	
LDL-C ≥70 mg/dL + hsCRP ≥2 mg/L	82 (3.5%)	1.41 (1.03–1.95)	.034	1.56 (1.19–2.04)	.001	
Secondary endpoints						
MACE[+]						
LDL-C <70 mg/dL + hsCRP <2 mg/L	305 (7.7%)	Ref.		Ref.		.021
LDL-C ≥70 mg/dL + hsCRP <2 mg/L	224 (6.1%)	.78 (.66–.93)	.005	.84 (.71–1.00)	.057	
LDL-C <70 mg/dL + hsCRP ≥2 mg/L	244 (10.9%)	1.42 (1.20–1.68)	<.001	1.36 (1.15–1.62)	<.001	
LDL-C ≥70 mg/dL + hsCRP ≥2 mg/L	265 (8.0%)	1.05 (.89–1.24)	.571	1.09 (.91–1.29)	.345	
All-cause mortality						
LDL-C <70 mg/dL + hsCRP <2 mg/L	42 (1.1%)	Ref.		Ref.		<.001
LDL-C ≥70 mg/dL + hsCRP <2 mg/L	32 (.9%)	.82 (.52–1.29)	.387	.98 (.61–1.55)	.923	
LDL-C <70 mg/dL + hsCRP ≥2 mg/L	67 (3.0%)	2.83 (1.92–4.15)	<.001	2.59 (1.75–3.84)	<.001	
LDL-C ≥70 mg/dL + hsCRP ≥2 mg/L	50 (1.5%)	1.44 (.96–2.17)	.080	1.70 (1.12–2.59)	.013	
Spontaneous myocardial infarction						
LDL-C <70 mg/dL + hsCRP <2 mg/L	58 (1.5%)	Ref.		Ref.		.023
LDL-C ≥70 mg/dL + hsCRP <2 mg/L	52 (1.4%)	.96 (.66–1.39)	.826	1.08 (.74–1.58)	.691	
LDL-C <70 mg/dL + hsCRP ≥2 mg/L	48 (2.2%)	1.47 (1.00–2.15)	.050	1.33 (.90–1.96)	.153	
LDL-C ≥70 mg/dL + hsCRP ≥2 mg/L	69 (2.1%)	1.44 (1.02–2.04)	.040	1.47 (1.02–2.11)	.038	
Stroke						
LDL-C <70 mg/dL + hsCRP <2 mg/L	13 (.3%)	Ref.		Ref.		.623
LDL-C ≥70 mg/dL + hsCRP <2 mg/L	9 (.3%)	.74 (.32–1.73)	.487	.72 (.31–1.70)	.457	
LDL-C <70 mg/dL + hsCRP ≥2 mg/L	9 (.4%)	1.23 (.52–2.87)	.636	1.18 (.50–2.80)	.703	

Continued

Table 2 *Continued*

	Event (%)	HR (95% CI)	*P*-value	adjHR (95% CI)	*P*-value	Trend *P*-value
LDL-C ≥70 mg/dL + hsCRP ≥2 mg/L	12 (.4%)	1.12 (.51–2.45)	.783	1.10 (.49–2.46)	.824	
Target lesion revascularization						
LDL-C <70 mg/dL + hsCRP <2 mg/L	221 (5.7%)	Ref.		Ref.		.623
LDL-C ≥70 mg/dL + hsCRP <2 mg/L	166 (4.6%)	.80 (.65–.98)	.031	.84 (.68–1.03)	.092	
LDL-C <70 mg/dL + hsCRP ≥2 mg/L	148 (6.8%)	1.19 (.96–1.46)	.105	1.15 (.93–1.42)	.207	
LDL-C ≥70 mg/dL + hsCRP ≥2 mg/L	162 (5.0%)	.89 (.72–1.08)	.239	.87 (.70–1.08)	.201	
Target vessel revascularization						
LDL-C <70 mg/dL + hsCRP <2 mg/L	311 (8.0%)	Ref.		Ref.		.829
LDL-C ≥70 mg/dL + hsCRP <2 mg/L	269 (7.4%)	.92 (.79–1.09)	.348	.97 (.82–1.15)	.747	
LDL-C ≥70 mg/dL + hsCRP ≥2 mg/L	195 (8.9%)	1.11 (.93–1.33)	.246	1.08 (.90–1.30)	.395	
LDL-C <70 mg/dL + hsCRP ≥2 mg/L	253 (7.8%)	.99 (.84–1.16)	.866	.99 (.83–1.18)	.925	

Model adjusted for age, gender, BMI, race/ethnicity (Caucasian as reference group), current smoking, hypertension, diabetes, CKD, and prior MI.
AdjHR, adjusted hazard ratio; CI, confidence interval; CKD, chronic kidney disease; hsCRP, high-sensitivity C-reative protein; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events; MI, myocardial infarction.

<2 mg/L) on MACE at 1 year among a contemporary cohort of CAD patients treated with PCI for a non-MI. Our key findings are as follows: (i) over 40% of patients undergoing PCI had elevated hsCRP concentrations; (ii) specific differences in baseline characteristics, including a higher BMI and higher burden of comorbidities including CKD, were found in patients with elevated hsCRP; (iii) patients with elevated hsCRP (≥2 mg/L) concentrations showed the highest rates of the composite MACE endpoint; and (iv) an independent association of residual inflammatory risk with MACE was noted, and this finding was irrespective of LDL-C concentrations (see *Structured Graphical Abstract*). This effect was largely consistent across various sensitivity analyses.

These current data emphasize the importance of inflammation as a main driver for adverse clinical outcomes even after adherence to guideline-directed secondary preventive measures, and have direct implications for clinicians treating patients undergoing PCI. Importantly, the observed impact of residual inflammatory risk was consistent even when removing individuals with commonly elevated hsCRP (e.g. patients with diabetes or CKD), as well as patients with elevated triglyceride or non-HDL-C concentrations. However, a modifying effect was observed for patients aged 65 years or older and for female patients, with an attenuation of the observed effect in the subgroup with combined residual cholesterol and inflammatory risk. However, given the relatively smaller sample size of the sensitivity analyses, these results are likely underpowered, and thus susceptible to potential bias.

Whilst the dose-dependent association of LDL-C lowering with incident cardiovascular events has been described in a multitude of studies, even when very low levels of LDL-C are achieved, a substantial residual risk for adverse events persists.[13] This was highlighted by the results from the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial, where even after lowering LDL-C levels to a median of 30 mg/dL, an event rate of 5.9% of the composite of cardiovascular death, MI, or stroke occurred during follow-up of 2.2 years in the evolocumab subgroup.[14] This substantial residual risk for adverse events could at least be partly attributable to inflammation.[15] The intricate interplay between LDL-C and inflammation quantified via hsCRP is still incompletely understood, as LDL-C lowering through evolocumab showed the greatest absolute risk reductions in patients with elevated hsCRP.[16] Notably, in our investigation for patients with residual inflammatory risk, the population with the highest risk for adverse events, a median LDL-C of 55.6 mg/dL was noted, underscoring the importance of inflammation even when guideline-recommended levels of LDL-C are achieved.

The results of this study corroborate a recent meta-analysis from Ridker and colleagues, where a similar finding was noted in a pooled analysis of patients from the PROMINENT, REDUCE-IT, and STRENGTH clinical trials.[10,17–19] Here, in 31 245 patients taking statins, hsCRP proved to be a more powerful indicator of adverse events than LDL-C levels. An increase in mortality mainly drove this finding. Moreover, comparable findings were recently documented for high-risk patients with statin intolerance.[20] However, the current analysis differs from the named studies in several aspects. First, in all of the previously named trials, the presence of elevated triglyceride concentrations between 200 and 500 mg/dL was a prerequisite for inclusion. In contrast, our patients were recruited within the clinical routine, and

broad inclusion and limited exclusion criteria were implemented for the current study. Second, the mentioned trials recruited both patients with established atherosclerotic disease (in 56–71%), as well as patients without ASCVD (in 29–44%). For our study, solely individuals who were hospitalized for PCI in the setting of non-MI were included, thus representing a fundamentally different patient population. Hence, the current finding that an elevated inflammatory burden, rather than LDL-C levels, drives residual risk in PCI patients is novel and has direct clinical implications for clinicians caring for patients treated with coronary interventions, where so far, a scarcity of data with regard to the relative impact of cholesterol and inflammation on residual risk has been present.

Despite the main finding of this study being that inflammation is a major driver of residual risk after PCI, the fundamental role of lipid-lowering agents in secondary prevention should not be diminished. Of note, all patients included in the current analysis received statin treatment. Moreover, statins and other lipid-lowering medication, such as ezetimibe and bempedoic acid, have demonstrated their ability to lower the inflammatory burden.[9,21–23] Therefore, initiation of lipid lowering in patients with CAD should remain one of the cornerstones in the treatment of PCI patients.[2–4,24]

To date, three randomized controlled trials (RCTs) have demonstrated that administering of pharmacological anti-inflammatory agents can significantly decrease adverse cardiovascular events among patients with established atherosclerotic disease.[6–8] The Colchicine Cardiovascular Outcomes Trial (COLCOT) trial ($n = 4745$) examined the impact of colchicine .5 mg once daily in patients who had an MI in the preceding 30 days. The composite endpoint of death from cardiovascular causes, resuscitated cardiac arrest, MI, stroke, or urgent hospitalization for angina leading to coronary revascularization occurred less frequently in those treated with colchicine (5.5% vs 7.1%, HR .77; 95% CI .61–.96; $P = .02$). The difference in the primary outcome was driven by fewer MIs and angina requiring revascularization. The rate of cardiovascular death and all-cause death did not differ significantly between groups. Notably, the frequency of the latter outcome after a median of 22.6 months was low (1.1% colchicine group and 2.1% placebo group) compared with the rate of TLR recorded in this study. Importantly, the difference in the primary outcome was more marked beyond the 12 month follow-up time point, and information on hsCRP was only available for 207 (4.4%) patients in this trial.[7] In contrast, the Low-Dose Colchicine 2 (LoDoCo2) trial ($n = 5522$) studied patients with chronic coronary syndrome. The composite endpoint of cardiovascular death, MI, ischaemic stroke, or ischaemia-driven coronary revascularization occurred less frequently in those treated with colchicine at a median follow-up of 28.6 months (6.8% vs 9.6%, HR .69; 95% CI .57–.83; $P < .001$). Spontaneous MI (1.1% vs 1.5%) and ischaemia-driven revascularization (.6% vs .9%) occurred significantly less frequently in those treated with colchicine. All-cause death was higher, although not reaching statistical significance, in those treated with colchicine.[8] Importantly, neither of the above studies systematically collected blood for hsCRP levels; thus, treatment was not targeted and establishing a biological basis for using an anti-inflammatory drug, such as colchicine, was limited.[7,8] In 2017, the Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS) randomized patients with a previous MI and biological evidence of inflammation (hsCRP ≥2 mg/L) to the interleukin-1β inhibitor canakinumab at various doses or placebo. A dose of canakinumab 150 mg reduced the primary endpoint of MI, stroke, or cardiovascular death compared with a placebo at a median follow-up of 3.7 years (4.5 vs 3.8 per 100 person-years, HR .85; 95% CI .74–.98; $P = .021$). The absolute risk reduction between groups for the primary endpoint was relatively small (.6%) and driven by fewer non-fatal MIs. CANTOS did demonstrate a reduction in hsCRP with canakinumab (54% with 150 mg) and, in doing so, identified a biomarker to potentially select appropriate patients for anti-inflammatory therapy that may modify their residual risk of adverse outcomes.[6] Nonetheless, a direct comparison of clinical outcomes between these RCTs and our registry must be carried out with caution. Patients were only stratified by hsCRP in one trial; and anti-inflammatory therapies were tested in each trial. In addition, the comparison of revascularization outcomes is challenging given the various definitions used and the duration of follow-up differed.

Of note, whereas the above-mentioned studies showed a reduction of select cardiovascular endpoints in the respective anti-inflammatory treatment arm, no decrease in the rates of all-cause or cardiovascular death, respectively, was noted.[6–8] This is an intriguing finding, as both the pooled analysis from the PROMINENT, REDUCE-IT, and STRENGTH trials and the results of our study were primarily driven by increased rates of mortality rather than other cardiovascular outcomes.[10] Notably, our study observed no association with any residual risk constellation for the expanded MACE$^+$ endpoint—which includes TLR in addition to all-cause mortality, MI, and stroke. This underscores the fact that the inflammatory pathways and their impact on hard clinical outcomes and the progression and destabilization of atherosclerotic disease are incompletely understood. This is corroborated by the findings from the recent Colchicine and Spironolactone in Patients with MI/SYNERGY Stent Registry (CLEAR SYNERGY) trial. Here, among patients with an MI, administration of colchicine, did not lead to a reduction of the primary endpoint (cardiovascular death, MI, stroke, or unplanned coronary revascularization). However, no screening for the inflammatory burden, i.e. hsCRP concentrations at baseline was implemented in this trial.[25] Ongoing trials with newer anti-inflammatory agents might shed more light on the intricate interplay between inflammation, LDL-C, and clinical outcomes.[26] Nonetheless, the findings of our study support the use of hsCRP for identifying a subset of patients at an increased risk of adverse events. Furthermore, while the findings of this study support the theory that inflammation is associated with increased adverse events during follow-up after PCI, hsCRP is a systemic biomarker and is imperfect at identifying individuals who may benefit from anti-inflammatory therapy. This is reflected in the inconsistent outcomes of the studies mentioned above. Ongoing trials with newer anti-inflammatory agents aim to shed more light on the intricate interplay between inflammation, LDL-C, and clinical outcomes.[26] This may facilitate a more targeted approach and delivery of anti-inflammatory therapy to those most likely to gain clinical benefit.

Colchicine represents a potential treatment option which has recently been approved by the US Food and Drug Administration for use in adult patients with established ASCVD or with multiple risk factors for cardiovascular disease.[7,8,27] Moreover, newer targeted anti-inflammatory therapies, such as interleukin-6 inhibitors, are currently under investigation in large outcome trials.[26] However, the appropriate target population in whom treatment with established or newer anti-inflammatory agents should be implemented has yet to be defined. In the future, instead of solely prioritizing additive lipid-lowering therapies in PCI patients, clinicians might consider a more tailored approach with the integration of anti-inflammatory treatments alongside pharmacological agents that target cholesterol. This approach could offer a comprehensive strategy to mitigate residual risk.[28] The current analysis could help in identifying individuals with CAD treated by PCI as a suitable target group for these agents and further associated clinical studies.

Study limitations

Whilst we describe a large-scale single-centre analysis of PCI patients, several limitations have to be considered. Whereas baseline medication, including statins, was documented for all individuals, data on the intensity and adherence to lipid-lowering therapy were unavailable. For the current analysis, we excluded individuals with hsCRP concentrations >10 mg/L at baseline, as is recommended by the Centres for Disease Control and Prevention and the American Heart Association.[29] Nevertheless, in certain instances, the presence of an active infection or other conditions linked to heightened inflammatory activity may have influenced the findings presented. Also, unmeasured confounding of this cohort study is possible, although we aimed to account for this by adjusting for likely confounders. Notably, patients lost to follow-up during the initial 30 days were excluded. Hence, the population studied is conditional on surviving 30 days after PCI. Follow-up for the study population was limited to the first 12 months post-PCI, which, however, represents the period associated with the highest risk of MACE after PCI.[30] Whilst all events that led to a readmission to the Mount Sinai Hospital were adjudicated as described in the Methods section, incident events outside of Mount Sinai were not assessed by the adjudication committee. In addition, specific causes of mortality were not available. All-cause mortality is, however, not affected by adjudication bias and is endorsed in the Academic Research Consortium-2 statement as the most unbiased method to report deaths in coronary intervention studies.[31] Lastly, no follow-up concerning hsCRP or LDL-C concentrations was available for the current cohort.

Conclusions

In this large-scale analysis of statin-treated patients who underwent PCI for a non-MI, inflammation quantified by an hsCRP ≥2 mg/L was the main driver for adverse clinical outcomes after 1-year follow-up. This was irrespective of baseline LDL-C concentrations. These data underscore previous results with regard to the role of inflammation in patients with ASCVD, particularly CAD, and emphasize the importance of residual inflammatory risk in individuals undergoing PCI.

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The graphical abstract was designed using BioRender.

Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

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Data Availability

The data underlying this article will be shared on reasonable request with the corresponding author.

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Ethical Approval

The study was conducted in compliance with the Declaration of Helsinki and was approved by the research ethics committee and the institutional review board at Mount Sinai Hospital, NY, USA. All patients provided written informed consent before inclusion in the study.

Pre-registered Clinical Trial Number

Not applicable.

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