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CLINICAL RESEARCH
Thrombosis and antithrombotic treatment

LDL cholesterol levels and in-hospital bleeding in patients on high-intensity antithrombotic therapy: findings from the CCC-ACS project

Qing Yang[1]*, Dongdong Sun[1], Chongzhe Pei [1], Yuhong Zeng[2], Zhuoqun Wang[1], Ziping Li[1], Yongchen Hao[2], Xiwen Song[1], Yongle Li[1], Gang Liu[3], Yida Tang [4], Sidney C. Smith, Jr [5] Yaling Han[6], Yong Huo [7], Junbo Ge[8], Changsheng Ma [2], Gregg C. Fonarow [9], Louise Morgan[10], Jing Liu [2], Jun Liu[2], Mengge Zhou[2], Dong Zhao [2], Yujie Zhou[2]*, and Xin Zhou [1]*; on behalf of the CCC-ACS Investigators[†]

[1]Department of Cardiology, Tianjin Medical University General Hospital, 154 Anshan Road, Heping District, Tianjin 300052, China; [2]Departments of Epidemiology and Cardiology, Beijing Anzhen Hospital, Capital Medical University, the Key Laboratory of Remodeling-Related Cardiovascular Diseases, Ministry of Education, Beijing Municipal Key Laboratory of Clinical Epidemiology, Beijing Institute of Heart, Lung and Blood Vessel Diseases, No.2 Anzhen Road, Chaoyang District, Beijing 100029, China; [3]Heart Center, the First Hospital of Hebei Medical University, 89 Donggang Road, Shijiazhuang 050000, Hebei, China; [4]Department of Cardiology, Peking University Third Hospital, 49 Huayuanbei Road, Haidian District, Beijing 100191, China; [5]Division of Cardiology, University of North Carolina at Chapel Hill, 6031 Burnett-Womack Building, Chapel Hill, NC 27599-7075, USA; [6]Department of Cardiology, General Hospital of Northern Theater Command, 83 Wenhua Road, Shenhe District, Shenyang 110801, Liaoning, China; [7]Department of Cardiology, Peking University First Hospital, 8 Xishiku Street, Xicheng District, 100034 Beijing, China; [8]Department of Cardiology, Shanghai Institute of Cardiovascular Diseases, Zhongshan Hospital, Fudan University, 180 Fenglin Road, 200032 Shanghai, China; [9]Division of Cardiology, David Geffen School of Medicine at University of California, Los Angeles, 100 UCLA Medical Plaza, Los Angeles, CA 90095, USA; and [10]International Quality Improvement Department, American Heart Association, 7272 Greenville Ave, Dallas, TX 75231, USA

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Aims Emerging evidence has linked cholesterol metabolism with platelet responsiveness. We sought to examine the dose–response relationship between low-density lipoprotein cholesterol (LDL-C) and major in-hospital bleeds in acute coronary syndrome (ACS) patients.

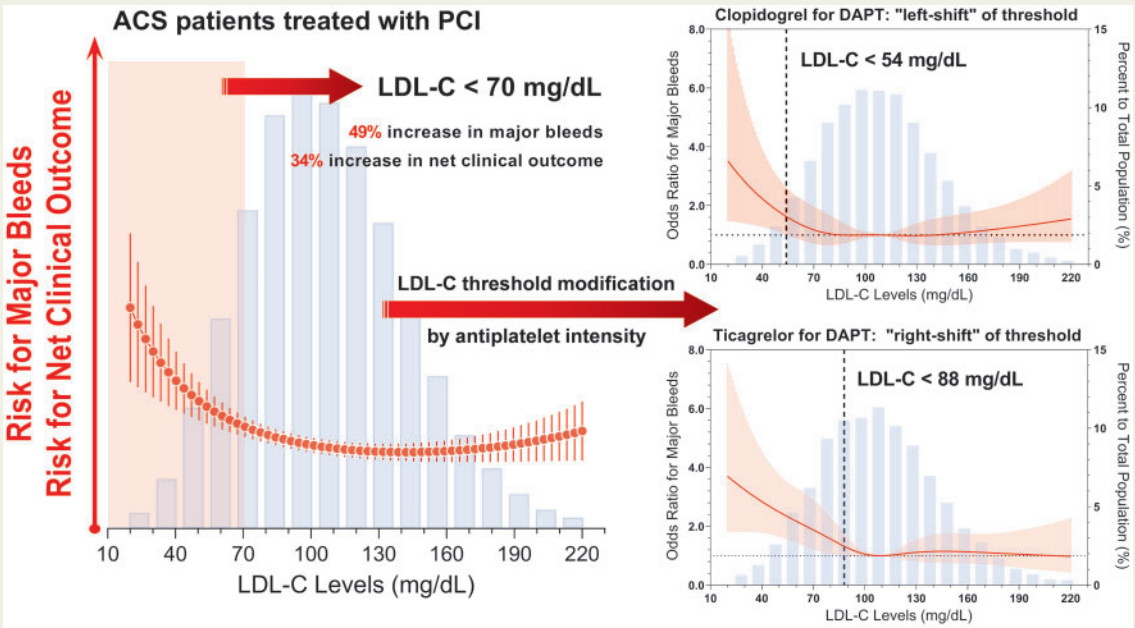
Methods and results Among 42 378 ACS patients treated with percutaneous coronary intervention (PCI) enrolled in 240 hospitals in the Improving Care for Cardiovascular Disease in China-ACS project from 2014 to 2019, a total of 615 major bleeds, 218 ischaemic events, and 337 deaths were recorded. After controlling for baseline variables, a non-linear relationship was observed for major bleeds, with the higher risk at lower LDL-C levels. No dose–response relationship was identified for ischaemic events and mortality. A threshold value of LDL-C <70 mg/dL was associated with an increased risk for major bleeds (adjusted odds ratio: 1.49; 95% confidence interval: 1.21–1.84) in multivariable-adjusted logistic regression models and in propensity score-matched cohorts. The results were consistent in multiple sensitivity analyses. Among ticagrelor-treated patients, the LDL-C threshold for increased bleeding risk was observed at <88 mg/dL, whereas for clopidogrel-treated patients, the threshold was <54 mg/dL. Across a full spectrum of LDL-C levels, the treatment effect size associated with ticagrelor vs. clopidogrel on major bleeds favoured clopidogrel at lower LDL-C levels, but no difference at higher LDL-C levels.

Conclusions In a nationwide ACS registry, a non-linear association was identified between LDL-C levels and major in-hospital bleeds following PCI, with the higher risk at lower levels. As the potential for confounding may exist, further studies are warranted.

Trial registration ClinicalTrials.gov Identifier: NCT02306616

* Corresponding authors. Tel: +86-10-64456489, Email: azzyj12@163.com (Y.Z.); Tel: +86-22-60362163, Email: cardio-yq@tmu.edu.cn (Q.Y.); Tel: +86-22-60363095, Email: xinzhou@tmu.edu.cn (X.Z.)
† A complete list of CCC-ACS Investigators is given in the supplementary material online, *Table S8*.

Graphical Abstract



The nonlinear association between admission LDL-C levels and in-hospital major bleeds in patients treated with percutaneous coronary intervention for acute coronary syndrome in the CCC-ACS project.

Keywords Low-density lipoprotein cholesterol • Acute coronary syndrome • Percutaneous coronary intervention • Bleeding • Antiplatelet therapy

Introduction

During the past two decades, there has been a substantial reduction in acute coronary syndrome (ACS) related mortality and ischaemic events due to the introduction of timely percutaneous coronary intervention (PCI) and more intensive antithrombotic treatment. Meanwhile, efforts have also been focused on the prevention of the concomitant increase in bleeding events,[1] which is the most common non-cardiac complication of PCI and is associated with a poor prognosis. In order to improve clinical outcomes, the need to recognize patients with high bleeding risk,[2] as well as the implementation of appropriate strategies to reduce bleeding complications, are warranted in this population.

An overwhelming body of evidence demonstrates the net benefit of a long-term low-density lipoprotein cholesterol (LDL-C) lowering strategy to reduce atherosclerotic cardiovascular disease (ASCVD) events. On the other hand, some observational studies from East Asian and Western populations have reported an association between hypercholesterolaemia and a reduced bleeding risk in patients on antiplatelet therapy.[3–6] Moreover, in a data-driven analysis based on the ISAR-REACT (Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment) 3 trial, the authors found that low cholesterol levels were an independent predictor of major bleeding at 30 days after PCI.[7] Notably, a recent basic study showed that plasma proprotein convertase subtilisin/kexin 9 (PCSK9) directly enhances platelet activation and thrombosis by binding to platelet CD36.[8] Therefore, emerging evidence implies a potential mechanistic link between cholesterol metabolism and platelet responsiveness.

For ACS patients, the current American Heart Association guideline recommends the use of a maximally tolerated statin dose to lower LDL-C levels by ≥50% or the addition of non-statins to maximally tolerated statin therapy when LDL-C ≥70 mg/dL[9]; the European Society of Cardiology guideline recommends the initiation of aggressive LDL-C lowering, regardless of the initial LDL-C values, to reach a 50% LDL-C reduction from baseline and an LDL-C goal of <55 mg/dL.[10] Notably, with the application of PCSK9 inhibitors, these LDL-C lowering goals are currently achievable during ACS hospitalization.[11,12] Acute coronary syndrome patients undergoing PCI are at high risk for in-hospital bleeding complications due to the concomitant administration of high-intensity antiplatelet and anticoagulant medications.[13,14] Given the evidence linking cholesterol metabolism and platelet responsiveness,[3–8] we therefore sought to examine the dose–response relationships between LDL-C, bleeding risk, and the net clinical outcome in ACS patients in contemporary practice in the Improving Care for Cardiovascular Disease in China-Acute Coronary Syndrome (CCC-ACS) project,[15] which provides an opportunity to investigate these associations in a large sample size.

Methods

Study design and population

As a collaborative initiative of the American Heart Association and the Chinese Society of Cardiology to improve the quality of care for ACS patients, the CCC-ACS project is an ongoing nationwide quality improvement project initiated in November 2014 involving 150 tertiary hospitals in China. From 2017, the CCC-ACS project was extended to 82 secondary hospitals and another 8 tertiary hospitals. Detailed information on the study design has been published previously.[15] The CCC-ACS project was approved by the institutional review board of Beijing Anzhen Hospital, with a waiver for informed consent. This study is registered at ClinicalTrials.gov (unique identifier: NCT02306616) and complies with the Declaration of Helsinki. From November 2014 to July 2019, a total of 104 516 ACS patients were enrolled. Among the 90.2% of patients without missing LDL-C values, 89.5% of the LDL-C values were obtained within 24 h of first medical contact. We focused our analysis on participants diagnosed with ACS on admission and treated with PCI during the index hospitalization. The inclusion and exclusion criteria are shown in *Figure 1*. The final analytic sample consisted of 42 378 ACS patients.

Study variables

The study variables included diagnosis on admission [ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction, and unstable angina], demographics (age, sex, body mass index, and smoking), medical history (hypertension, diabetes, dyslipidaemia, myocardial infarction, PCI, coronary artery bypass grafting, heart failure, atrial fibrillation, renal failure, ischaemic stroke, haemorrhagic stroke, and peripheral vascular disease), clinical variables [peak level of creatine kinase MB isoform (CK-MB), serum levels of LDL-C, high-density lipoprotein cholesterol and triglycerides, levels of systolic and diastolic blood pressure, heart rate, Killip class, estimated glomerular filtration rate (eGFR), baseline haemoglobin, and platelet counts], pre-hospital medications in the past 2 weeks [aspirin, $P2Y_{12}$ inhibitors, statins, β-blockers, angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs), aldosterone antagonists, oral anticoagulants, proton pump inhibitors (PPIs)], dual antiplatelet therapy (DAPT) status within 24 h of first medical contact [(i) DAPT intensity: non-loading DAPT (DAPT was not in loading dose), single-loading DAPT (one of DAPT in loading dose), and both-loading DAPT (DAPT both in loading dose); (ii) $P2Y_{12}$ inhibitor used: ticagrelor vs. clopidogrel], post-PCI anticoagulation [unfractionated heparin, low molecular weight heparin (LMWH; doses were converted to enoxaparin-equivalent dose divided by body weight), and others], platelet glycoprotein IIb/IIIa inhibitor use during hospitalization, other in-hospital medications within 24 h of first medical contact (statins, β-blockers, ACEIs/ARBs, aldosterone antagonists, oral anticoagulants, and PPIs) and route for PCI (radial route or not). The definitions of the above study variables are shown in the Supplementary material online, *Table S1*. Information concerning platelet counts, PPIs and LMWH doses was available among the patients enrolled after July 2017. The handling of missing values was performed using the sequential regression multiple imputation method as described in detail in the Supplementary material online, *Table S2*.

Definition of in-hospital outcomes

The CCC-ACS project routinely collected bleeding data as a part of core in-hospital outcomes. Data collected included fatal bleeding, haemorrhagic stroke, bleeding in vital organs/locations (intracranial, spinal canal, retroperitoneal, pericardial, and intra-ocular with compromised vision), gastrointestinal bleeding, bleeding requiring clinical intervention (requiring pressors, surgery, or intravenous vasoactive agents), haemoglobin drop related to bleeding (the admission level minus the nadir level), and bleeding requiring blood transfusion and the total amount of transfusion. Based on this information, we defined a composite of major bleeds using the following three major bleeding definitions (shown in detail in the Supplementary material online): (i) Bleeding Academic Research Consortium (BARC) type 3b–3c and type 5; (ii) Thrombolysis In Myocardial Infarction (TIMI) major bleeding; and (iii) PLATelet inhibition and patient Outcomes (PLATO) life-threatening major bleeding. Coronary artery bypass grafting related bleeding (BARC type 4) was excluded. In-hospital haemorrhagic stroke was defined as an acute episode of focal or global cerebral or spinal dysfunction caused by parenchymal, subarachnoid, or intraventricular Haemorrhage detected by computed tomography or magnetic resonance imaging. Procedure-related/peri-procedural bleeding was defined as bleeds occurring within the first 48 h following PCI, and bleeds after this period were defined as non-procedure-related/non-peri-procedural bleeding.[16] Other study outcomes included in-hospital mortality, ischaemic events (defined as re-infarction, in-stent thrombosis, and ischaemic stroke), as well as the net clinical outcome (defined as any occurrence of major bleed, ischaemic event, and mortality).

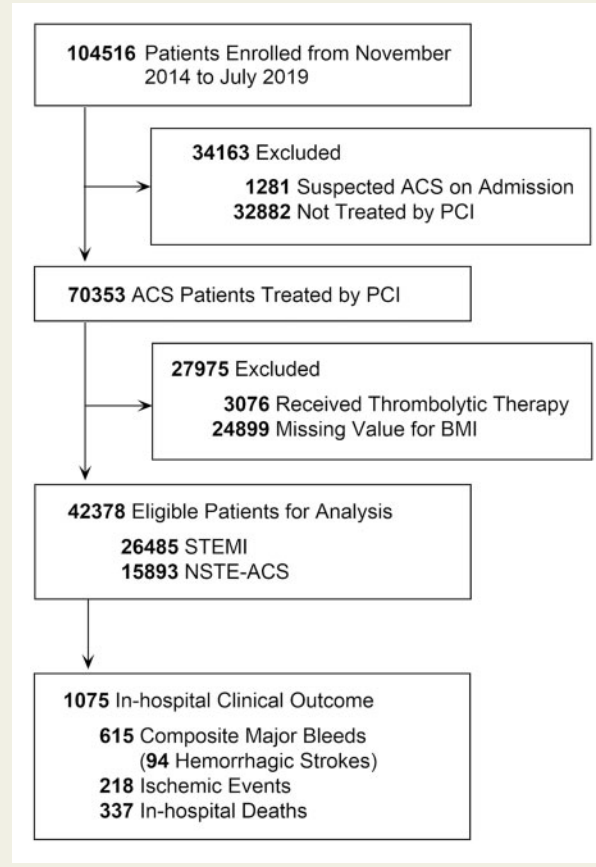


Figure 1 Study flow diagram. ACS, acute coronary syndrome; BMI, body mass index; NSTE-ACS, non-ST-elevation acute coronary syndrome; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

Statistical analysis

Detailed statistical methods are provided in the Supplementary material online. The linearity between LDL-C levels and study outcomes

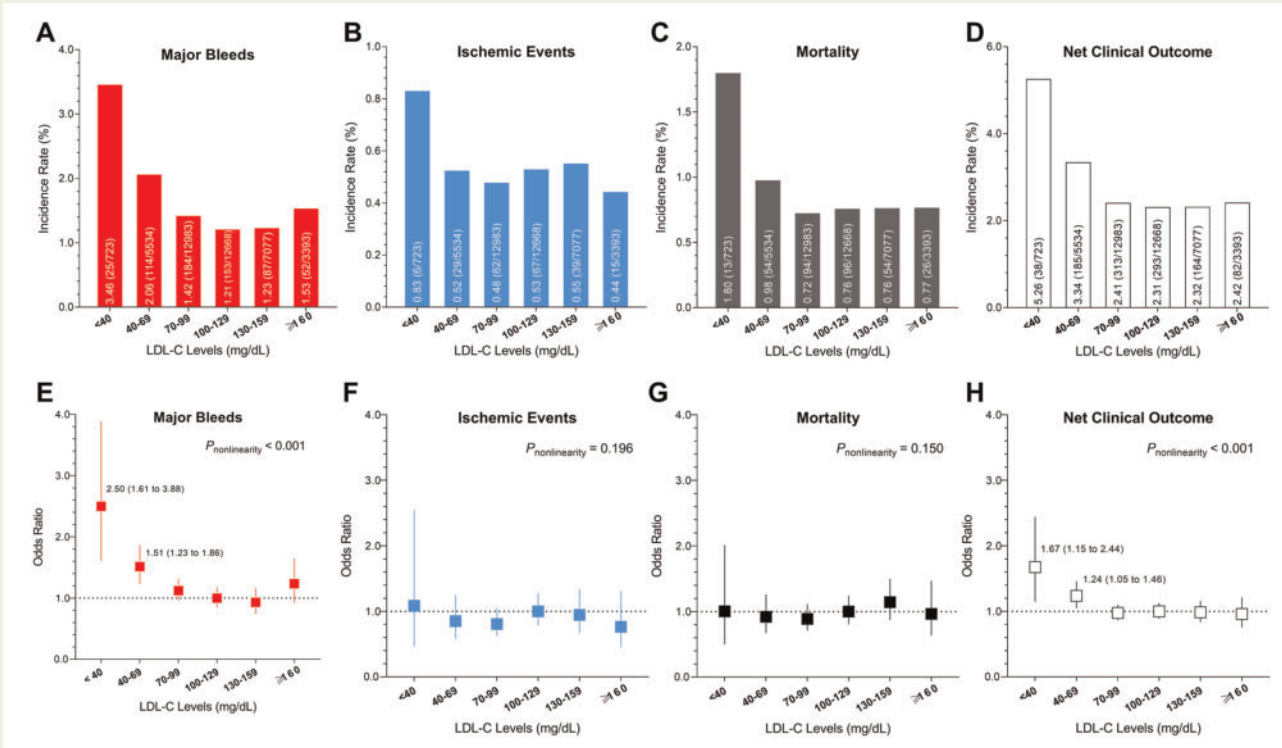


Figure 2 In-hospital major bleeds, ischaemic events, mortality, and the net clinical outcome according to six LDL-C categories. (*A–D*) Incidence by LDL-C categories. The numbers in parentheses indicate cases and total patients in each LDL-C category. (*E–H*) Adjusted odds ratios (OR) and 95% confidence intervals in six LDL-C categories by using the floating absolute risk method. The reference was set at LDL-C 100∼129 mg/dL. Covariate adjustment was performed using the variables mentioned in the methods section. Major bleeds were defined as the composite of BARC type 3b–3c and type 5, TIMI major bleeding and PLATO life-threatening major bleeding. The net clinical outcome was defined as any occurrence of major bleed, an ischaemic event or mortality. BARC, Bleeding Academic Research Consortium; PLATO, PLATelet inhibition and patient Outcomes; TIMI, Thrombolysis In Myocardial Infarction.

was assessed by Box-Tidwell transformation. The non-linear association was further evaluated by using restricted cubic splines in logistic regression models. We estimated the associations between LDL-C < 70 mg/dL and study outcomes with high LDL-C (≥70 mg/dL) as the reference in the following four models: (i) univariable logistic regression models; (ii) multivariable-adjusted logistic regression models; (iii) multivariable-adjusted logistic regression models with 1000 bootstrapping replications performed for internal validation; and (iv) propensity score-matched analyses (matching specifications are shown in Supplementary material online, *Table S3*; covariates balance before and after propensity score-matching are presented as absolute standardized differences in love plots and are shown in Supplementary material online, *Figures S1–S4*). For multivariable logistic regressions, the covariates mentioned above were used for adjustment, unless otherwise specified. We used marginal effects to examine the impact of exposures of interest on bleeding risk and the net clinical outcome across a full spectrum of LDL-C levels (20–220 mg/dL). To further examine the impact of ticagrelor vs. clopidogrel on major bleeding risk and the net clinical outcome across LDL-C levels, we performed an analysis based on a 1:1 propensity score-matched sample by using multivariable fractional polynomial interactions. We used Stata (version 15.1, StataCorp, College Station, TX, USA) and R (version 3.6.1) for analysis. A two-tailed $P < 0.05$ was considered statistically significant.

Results

A total of 615 major bleeds (including 94 haemorrhagic strokes), 218 ischaemic events, and 337 deaths were recorded during a median hospital stay of 8 days (interquartile range: 6–11 days).

Associations between LDL-C and in-hospital major bleeds, ischaemic events, mortality, and the net clinical outcome

In general, with a stepwise increase of 30 mg/dL in the LDL-C categories from <40 to ≥ 160 mg/dL, there was a decreasing trend for major bleeds, ischaemic events and death, as well as for the net clinical outcome (*Figure 2A–D*). After covariate adjustment, a non-linear pattern was only observed for major bleeds and for the net clinical outcome with a consistent increase in risk at LDL-C < 70 mg/dL (*Figure 2E–H*; Supplementary material online, *Figures S5–S7*). Further analyses using restricted cubic splines in logistic regression revealed a consistent increase in BARC-, TIMI-defined major bleeds, and PLATO life-threatening major bleeds, and the net clinical outcome at low LDL-C levels (<70 mg/dL, *Figure 3*; Supplementary material online, *Figures S8–S10*).

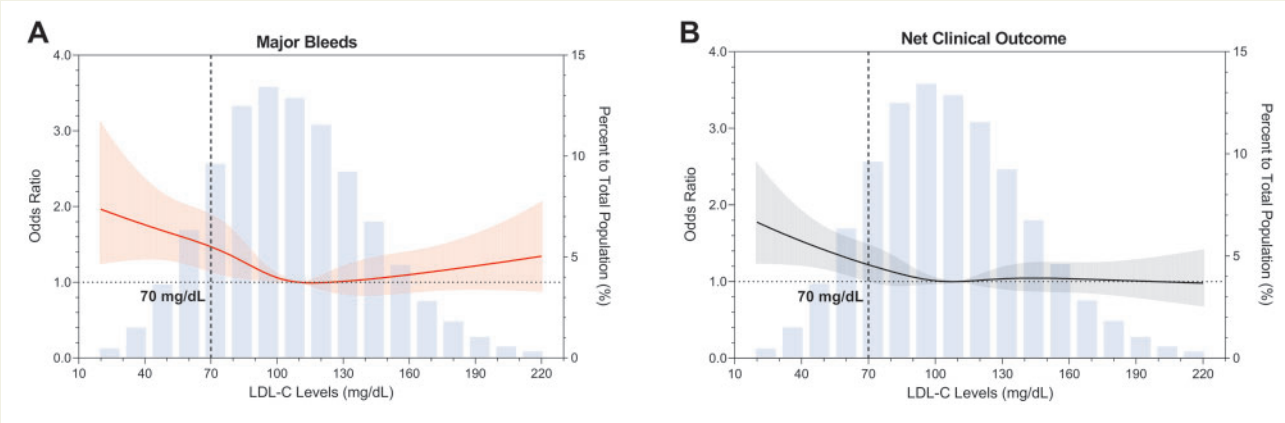


Figure 3 Restricted cubic spline plots for major bleeds and the net clinical outcome by LDL-C levels after covariate adjustment. The background histograms (light blue colour) represent the per cent of the density distribution of LDL-C in the study population (right *y*-axis). Heavy central lines represent the estimated adjusted odds ratios, with shaded ribbons denoting 95% confidence intervals. The vertical dotted lines indicate the threshold value of LDL-C at 70 mg/dL. The horizontal dotted lines represent the odds ratio of 1.0. The reference point was set at the lowest risk for bleeding in each plot (LDL-C level at 110 mg/dL). (*A*) Restricted cubic spline plot for major in-hospital bleeds. (*B*) Restricted cubic spline plot for the net clinical outcome, which was defined as any occurrence of major bleed, an ischaemic event, or mortality.

Table 1 shows the comparisons of clinical information in patients with LDL-C < 70 mg/dL vs. ≥ 70 mg/dL. Acute coronary syndrome patients with LDL-C < 70 mg/dL were more likely to have an advanced age, less likely to present with STEMI, more likely to have a higher prevalence of MI and a PCI history and other cardiovascular comorbidities, and to have a higher prevalence of pre-hospital cardiovascular medications. Notably, for in-hospital treatment, patients with LDL-C < 70 mg/dL received less potent antithrombotic therapy (loading dose DAPT, ticagrelor use, post-PCI anticoagulation, and glycoprotein IIb/IIIa inhibitor use).

In multivariable-adjusted logistic regression models, LDL-C < 70 mg/dL was associated with an increased major bleeding risk [odds ratio (OR): 1.49; 95% confidence interval (CI): 1.21–1.84, $P < 0.001$], as well as with the net clinical outcome (OR: 1.34, 95% CI: 1.14–1.58, $P < 0.001$), accounting for a 0.63% and 0.76% increase in absolute risk differences, respectively (Model 2 in *Table 2*). These findings were consistent as assessed by bootstrapping validation (Model 3 in *Table 2*) and in a propensity score-matched sample (Model 4 in *Table 2*). Notably, despite numerical increases in crude incidences for ischaemic events and mortality in patients with LDL-C < 70 mg/dL, no statistical significance was found as compared with those with LDL-C ≥ 70 mg/dL (*Table 2*).

Further covariate-adjusted analyses concerning more specific bleeding types revealed that LDL-C < 70 mg/dL was associated with 59% and 58% increases in non-procedure-related major bleeds and gastrointestinal major bleeds, respectively (Supplementary material online, *Table S4*). No association was observed between LDL-C < 70 mg/dL and procedure-related major bleeds and total gastrointestinal bleeds.

Association between LDL-C and haemorrhagic stroke

With a stepwise increase of 30 mg/dL in the LDL-C categories from <40 to ≥160 mg/dL, there was a linear negative correlation between LDL-C and haemorrhagic stroke incidence (Supplementary material online, *Figure S11*). After covariate adjustment, for every 30 mg/dL increase in LDL-C, the risk for haemorrhagic stroke was decreased by 20% (OR: 0.80, 95% CI: 0.66–0.97; $P = 0.021$; Supplementary material online, *Figure S11*).

Sensitivity analyses

As shown in *Figure 4*, sensitivity analyses revealed that LDL-C < 70 mg/dL was consistently associated with an increased risk of major bleeding and the net clinical outcome (Supplementary material online, *Tables S5 and S6*). Additionally, the *E*-values for the associations between LDL-C < 70 mg/dL and major bleeding risk derived from covariate-adjusted and propensity score-matched analyses (derived from Models 2 and 4 in *Table 2*) were 2.34 and 2.73, respectively. These *E*-values indicate that an unmeasured confounder with the same associations with both the exposure (LDL-C < 70 mg/dL) and outcome (major bleeds) might negate the current findings.

Subgroup analyses

Figure 5 shows the impact of high-intensity antithrombotic therapy, i.e. ticagrelor vs. clopidogrel, glycoprotein IIb/IIIa inhibitor use, and post-PCI anticoagulation, on the adjusted probabilities for major bleeds and the net clinical outcome. Interestingly, antiplatelet therapy intensity, especially ticagrelor, modified the dose–response relationship between LDL-C and major bleeds: at lower LDL-C levels, but not higher levels, ticagrelor was associated with increased probabilities of bleeding (*Figure 5B*). Notably, there was a linear negative association between glycoprotein IIb/IIIa inhibitor-related bleeding probability and LDL-C levels (*Figure 5C*), as well as for the net clinical outcome (*Figure 5G*). Post-PCI anticoagulation was also associated with an augmentation of increased bleeding risk at lower LDL-C levels (*Figure 5D*).

In a 1:1 propensity score-matched sample, across a full spectrum of LDL-C levels, the treatment effect size associated with ticagrelor

Table 1 Patient characteristics

Characteristics	Total ($n = 42\,378$)	LDL-C levels (mg/dL)		P
		<70 ($n = 6257$)	≥70 ($n = 36\,121$)	
Age, years	61.7 ± 11.9	63.4 ± 11.8	61.5 ± 11.9	<0.001
Male sex, *n* (%)	33 092 (78.1)	5002 (79.9)	28 090 (77.8)	<0.001
Smoking, *n* (%)	20 578 (48.6)	2873 (45.9)	17 705 (49.0)	<0.001
Body weight, kg	68.8 ± 11.1	68.3 ± 11.2	68.9 ± 11.1	<0.001
Body mass index, kg/m^2	24.5 ± 3.3	24.3 ± 3.4	24.5 ± 3.3	<0.001
Acute coronary syndrome subtypes, *n* (%)				
STEMI	26 485 (62.5)	3384 (54.1)	23 101 (64.0)	<0.001
NSTEMI	10 012 (23.6)	1561 (24.9)	8451 (23.4)	
Unstable angina	5881 (13.9)	1312 (21.0)	4569 (12.6)	
Hospital stay (days)	8 (6–11)	8 (6–11)	8 (6–11)	0.517
Previous history, *n* (%)				
Myocardial infarction	3002 (7.1)	867 (13.9)	2135 (5.9)	<0.001
PCI	3492 (8.2)	1094 (17.5)	2398 (6.6)	<0.001
Coronary artery bypass grafting	137 (0.32)	36 (0.58)	101 (0.28)	<0.001
Diabetes	9351 (22.1)	1646 (26.3)	7705 (21.3)	<0.001
Dyslipidaemia	3697 (8.7)	629 (10.1)	3068 (8.5)	<0.001
Hypertension	21 918 (51.7)	3417 (54.6)	18 501 (51.2)	<0.001
Heart failure	429 (1.0)	103 (1.6)	326 (0.90)	<0.001
Renal failure	511 (1.2)	126 (2.0)	385 (1.1)	<0.001
Atrial fibrillation	692 (1.6)	155 (2.5)	537 (1.5)	<0.001
Ischaemic stroke	2807 (6.6)	522 (8.3)	2285 (6.3)	<0.001
Haemorrhagic stroke	255 (0.60)	51 (0.82)	204 (0.57)	0.021
Peripheral vascular disease	364 (0.86)	81 (1.30)	283 (0.78)	<0.001
SBP, mmHg	130.7 ± 22.9	128.6 ± 22.0	131.1 ± 23.1	<0.001
DBP, mmHg	78.6 ± 14.3	76.4 ± 13.7	78.9 ± 14.3	<0.001
Heart rate, b.p.m.	76.7 ± 15.1	75.3 ± 15.2	76.9 ± 15.1	<0.001
Killip class, *n* (%)				
I	31 151 (73.5)	4485 (71.7)	26 666 (73.8)	0.002
II	8222 (19.4)	1274 (20.4)	6948 (19.2)	
III	1756 (4.1)	290 (4.6)	1466 (4.1)	
IV	1249 (3.0)	208 (3.3)	1041 (2.9)	
Five-fold elevated TnI/TnT, *n* (%)[a]	19 415 (50.4)	2455 (43.1)	16 960 (51.7)	<0.001
LDL-C, mg/dL	107.0 ± 37.7	54.8 ± 11.5	116.0 ± 33.0	<0.001
HDL-C, mg/dL	42.2 ± 15.5	40.8 ± 19.4	42.2 ± 14.8	<0.001
TG, mg/dL	133 (93–196)	112 (78–174)	136 (96–199)	<0.001
eGFR, mL/min/1.73 m^2	85.8 ± 22.5	83.4 ± 23.7	86.2 ± 22.2	<0.001
Haemoglobin on admission, g/L	138.5 ± 19.4	134.4 ± 20.6	139.2 ± 19.1	<0.001
Platelet count, 10^9/L[b]	216.4 ± 66.5	198.8 ± 64.0	219.5 ± 66.4	<0.001
Pre-hospital medications in the past 2 weeks, *n* (%)				
Aspirin	9398 (22.2)	2175 (34.8)	7223 (20.0)	<0.001
$P2Y_{12}$ inhibitor	7034 (16.6)	1604 (25.6)	5430 (15.0)	<0.001
Statin	7428 (17.5)	1803 (28.8)	5625 (15.6)	<0.001
Oral anticoagulants	92 (0.22)	27 (0.43)	65 (0.18)	0.001
β-blocker	4008 (9.46)	971 (15.5)	3037 (8.41)	<0.001
ACEI/ARB	4387 (10.4)	881 (14.1)	3506 (9.71)	<0.001
Aldosterone antagonist	468 (1.10)	112 (1.79)	356 (0.99)	<0.001
Proton pump inhibitor[b]	693 (4.05)	149 (5.79)	544 (3.74)	<0.001
DAPT status in the first 24 hours of medical contact, *n* (%)				
Non-loading DAPT	2936 (6.93)	597 (9.54)	2339 (6.48)	<0.001
Single-loading DAPT	15 512 (36.6)	2762 (44.1)	12 750 (35.3)	
Both-loading DAPT	23 930 (56.5)	2898 (46.3)	21 032 (58.2)	
Ticagrelor as $P2Y_{12}$ inhibitor	13 383 (31.6)	1776 (28.4)	11 607 (32.1)	<0.001

Continued

Table 1 *Continued*

Characteristics	Total (n = 42 378)	LDL-C levels (mg/dL)		P
		<70 (n = 6257)	≥70 (n = 36 121)	
Anticoagulation therapy following PCI, *n* (%)				
Unfractionated heparin	1889 (4.46)	250 (4.00)	1639 (4.54)	0.059
LMWH	29 059 (68.6)	4078 (65.2)	24 981 (69.2)	<0.001
Other	850 (2.01)	104 (1.66)	746 (2.07)	0.036
LMWH dosing (mg/kg/day)[b]	1.31 (1.12–1.54)	1.33 (1.14–1.54)	1.31 (1.12–1.54)	0.012
In-hospital glycoprotein IIb/IIIa inhibitor	14 543 (34.3)	1824 (29.2)	12 719 (35.2)	<0.001
Other in-hospital medications in the first 24 hours of medical contact, *n* (%)				
Statin	40 287 (95.1)	5923 (94.7)	34 364 (95.1)	0.114
Oral anticoagulant	241 (0.57)	43 (0.69)	198 (0.55)	0.173
β-blocker	24 070 (56.8)	3533 (56.5)	20 538 (56.9)	0.571
ACEI/ARB	20 319 (47.9)	2872 (45.9)	17 447 (48.3)	<0.001
Aldosterone antagonist	5704 (13.5)	824 (13.2)	4880 (13.5)	0.483
Proton pump inhibitor[b]	11 099 (64.9)	1567 (60.9)	9532 (65.6)	<0.001
PCI route, *n* (%)				
Radial	39 822 (94.0)	5882 (94.0)	33 940 (94.0)	0.908
Non-radial	2556 (6.03)	375 (6.00)	2181 (6.04)	

[a]Information based on 38 521 participants with either TnI or TnT measurement on admission.
[b]Information based on 17 107 participants enrolled after July 2017.
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; DAPT, dual antiplatelet therapy; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LMWH, low molecular weight heparin; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; STEMI, ST-elevation myocardial infarction; TG, triglycerides; TnI, troponin I; TnT, troponin T.

vs. clopidogrel significantly increased the risks for major bleeding at lower LDL-C levels but not at higher levels (*Figure 6*). Moreover, in this matched cohort, the intensity of $P2Y_{12}$ inhibition modified the threshold value of LDL-C for increased bleeding risk: as revealed by restricted cubic splines, the threshold value for clopidogrel-treated patients was <54 mg/dL, whereas for ticagrelor-treated patients, the value increased to <88 mg/dL (*Graphical abstract*). Despite a small increase at lower LDL-C levels, no statistical difference was observed in terms of the treatment effect size of ticagrelor vs. clopidogrel for the net clinical outcome (*Figure 6*).

Additional analyses showed that neither pre-hospital nor in-hospital statin therapy had a significant impact on major bleeds (Supplementary material online, *Figures S12 and S13*). Notably, in-hospital statin therapy showed an LDL-C-independent reduction in the net clinical outcome (Supplementary material online, *Figure S13*). Advanced age (≥65 years) did not modify the dose–response relationship between LDL-C and major bleeding, except for an increase in the net clinical outcome at higher LDL-C levels (Supplementary material online, *Figure S14*). Among those with BMI <25 kg/m^2, females and STEMI (Supplementary material online, *Figures S15–S17*), the risks for bleeds and the net clinical outcome all slightly increased across a full spectrum of LDL-C levels. Hypertension history was associated with a slight increase in the study outcomes across LDL-C levels (Supplementary material online, *Figure S18*).

Based on ACS patients enrolled after July 2017, we had an opportunity to evaluate the impact of PPI use (pre-hospital and in-hospital), post-PCI LMWH dose and platelet counts. The information for this subgroup is shown in *Table 1*. We found a linear positive association between LDL-C and platelet counts (Supplementary material online, *Figure S19*). After adjusting for platelet counts, the association between LDL-C and major bleeds remained statistically significant in this subgroup (Supplementary material online, *Table S7*). Moreover, in a propensity score-matched cohort after incorporating PPI use, post-PCI LMWH dose and platelet counts (Supplementary material online, *Figure S4* and *Table S3*), the associations between low LDL-C and bleeding risk and the net clinical outcome remained stable (*Figure 4* and Supplementary material online, *Tables S5 and S6*).

Discussion

In this nationwide ACS registry, the relationships between LDL-C levels and major in-hospital bleeds, and the net clinical outcome exhibited a non-linear association, with higher risks with lower LDL-C levels after controlling for baseline covariates. As no clear dose–response relationship was found between LDL-C levels and ischaemic events and mortality, the low LDL-C-related higher risk for the net clinical outcome was mainly driven by an increase in major bleeds. The threshold value for the increased risk of adverse outcomes in this population was observed at LDL-C < 70 mg/dL. Notably, the use of potent antiplatelet medications (i.e. ticagrelor) was associated with an augmentation of low LDL-C-related bleeding risk (*Graphical abstract*). To our knowledge, this is the first report specifically addressing the relationship between LDL-C levels and bleeding risk under the background of high-intensity antithrombotic therapy. This finding would have important implications for current ACS management

Table 2 Associations of LDL-C < 70 mg/dL and major in-hospital bleeds, ischaemic events, mortality, and the net clinical outcome after percutaneous coronary intervention for acute coronary syndrome

	Odds ratio and 95% confidence interval		Absolute risk difference and 95% confidence interval	
	LDL-C < 70 vs. LDL-C ≥ 70 mg/dL	*P*-value	LDL-C < 70 vs. LDL-C ≥ 70 mg/dL	*P*-value
Model 1				
Composite major bleeds	1.70 (1.41 to 2.06)	<0.001	0.90% (0.52% to 1.29%)	<0.001
BARC type 3b–3c and type 5 major bleeds	1.53 (1.24 to 1.90)	<0.001	0.60% (0.26% to 0.94%)	0.001
TIMI major bleeds	1.53 (1.21 to 1.93)	0.001	0.50% (0.19% to 0.81%)	0.004
PLATO life-threatening major bleeds	1.76 (1.44 to 2.15)	<0.001	0.87% (0.51% to 1.24%)	<0.001
Ischaemic events	1.10 (0.77 to 1.59)	0.590	0.05% (-0.15% to 0.25%)	0.603
Mortality	1.44 (1.10 to 1.88)	0.008	0.32% (-0.05% to 0.59%)	0.019
Net clinical outcome	1.53 (1.32 to 1.78)	<0.001	1.21% (0.72% to 1.69%)	<0.001
Model 2				
Composite major bleeds	1.49 (1.21 to 1.84)	<0.001	0.63% (0.26% to 0.99%)	<0.001
BARC type 3b–3c and type 5 major bleeds	1.50 (1.20 to 1.88)	<0.001	0.55% (0.20% to 0.91%)	0.002
TIMI major bleeds	1.57 (1.23 to 2.01)	0.001	0.53% (0.19% to 0.86%)	0.002
PLATO life-threatening major bleeds	1.56 (1.25 to 1.94)	<0.001	0.63% (0.28% to 0.98%)	<0.001
Ischaemic events	0.90 (0.61 to 1.33)	0.609	-0.05% (-0.24% to 0.14%)	0.598
Mortality	1.14 (0.85 to 1.55)	0.383	0.10% (-0.13% to 0.33%)	0.401
Net clinical outcome	1.34 (1.14 to 1.58)	<0.001	0.76% (0.30% to 1.22%)	0.001
Model 3				
Composite major bleeds	1.49 (1.20 to 1.85)	<0.001	0.63% (0.25% to 1.01%)	0.001
BARC type 3b–3c and type 5 major bleeds	1.50 (1.19 to 1.90)	<0.001	0.55% (0.19% to 0.92%)	0.001
TIMI major bleeds	1.57 (1.22 to 2.02)	<0.001	0.53% (0.19% to 0.86%)	0.002
PLATO life-threatening major bleeds	1.56 (1.24 to 1.95)	<0.001	0.63% (0.27% to 1.00%)	<0.001
Ischaemic events	0.90 (0.61 to 1.33)	0.607	-0.05% (-0.23% to 0.13%)	0.595
Mortality	1.14 (0.84 to 1.55)	0.389	0.10% (-0.14% to 0.34%)	0.407
Net clinical outcome	1.34 (1.14 to 1.59)	0.001	0.76% (0.29% to 1.23%)	0.001
Model 4				
Composite major bleeds	1.67 (1.33 to 2.10)	<0.001	0.87% (0.45% to 1.29%)	<0.001
BARC type 3b–3c and type 5 major bleeds	1.68 (1.30 to 2.18)	<0.001	0.70% (0.33% to 1.07%)	<0.001
TIMI major bleeds	1.87 (1.40 to 2.49)	<0.001	0.68% (0.34% to 1.02%)	<0.001
PLATO life-threatening major bleeds	1.78 (1.39 to 2.26)	<0.001	0.88% (0.48% to 1.28%)	<0.001
Ischaemic events	1.12 (0.73 to 1.71)	0.607	0.06% (-0.16% to 0.28%)	0.614
Mortality	1.24 (0.91 to 1.68)	0.179	0.20% (-0.10% to 0.51%)	0.193
Net clinical outcome	1.46 (1.22 to 1.75)	<0.001	1.09% (0.55% to 1.63%)	<0.001

Model 1 was crude analysis without adjustment. Model 2 was adjusted by the covariates listed in the methods section. Model 3 was adjusted by the covariates listed in the methods section with 1000 bootstrapping replications performed. Model 4 was based on univariable logistic regression models in a 1:2 propensity score-matched sample (matching specifications were shown in Supplementary material online, *Table S3*).
BARC, Bleeding Academic Research Consortium; PLATO, PLATelet inhibition and patient Outcomes; TIMI, Thrombolysis In Myocardial Infarction.

strategies, especially for East Asian countries, considering the relatively low cholesterol levels in the general East Asian population,[17–19] compared with Caucasians.[20]

LDL-C levels and bleeding risk following percutaneous coronary intervention

Our findings should be interpreted in the context of a specific clinical scenario, i.e. ACS hospitalization following PCI, in which bleeding complications exceed the ischaemic events.[14] To the best of our knowledge, previous studies based on East Asians[3,4] and Westerners,[5,6] identified hypercholesterolaemia as an independent predictor of a reduced bleeding risk following PCI in outpatient settings. On the other hand, another study showed that a low cholesterol level was associated with an 85% increased risk for major bleeding at 30 days after PCI.[7] Based on the current paradigm for ASCVD prevention, i.e. 'lower is better; for LDL-C reduction, all of the authors of these studies were cautious about their findings, which may have led to the questioning of LDL-C lowering sacrificing the net clinical outcome improvement. However, these findings provide a

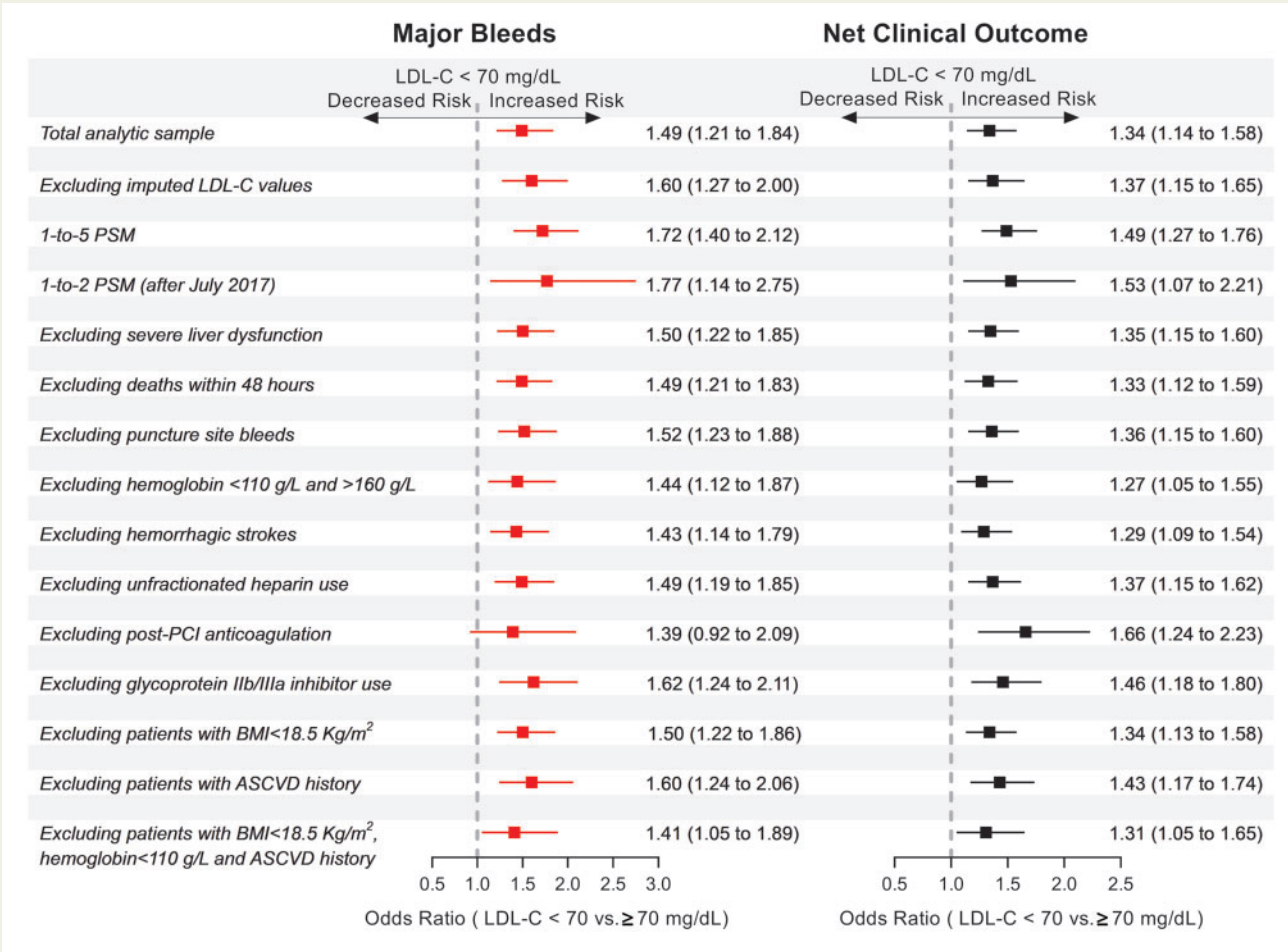


Figure 4 Sensitivity analyses of LDL-C < 70 mg/dL and risks for major bleeds and the net clinical outcome. All analyses were performed with logistic regression models after adjustment for variables listed in the methods section, except for propensity score-matched cohorts. Atherosclerotic cardiovascular disease history was defined as any of the following conditions: myocardial infarction, atherosclerotic cardiovascular disease, CABG, atrial fibrillation, heart failure, ischaemic stroke or peripheral artery disease. ASCVD, atherosclerotic cardiovascular disease; CABG, coronary artery bypass grafting; PSM, propensity score-matching.

unique opportunity to better understand the role of cholesterol in the pathogenesis of bleeding complications while undergoing high-intensity antithrombotic therapy.

The magnitude of LDL-C lowering and clinical outcomes in the acute phase of acute coronary syndrome

In terms of statin therapy, we did not find an increase in bleeding risk among patients who received either pre-hospital or in-hospital statin. The following issues should be taken into account when interpreting these findings. First, high-intensity statins are rarely prescribed in China due to the lack of convincing evidence of a benefit. Second, the LDL-C lowering effect of statins is achieved by long-term adherence, whereas for ACS patients, even high-intensity statin therapy only achieved a <20% reduction in LDL-C at discharge.[11,12] For more intensive LDL-C lowering by PCSK9 inhibitors, significant reductions in ASCVD, i.e. the divergence of survival curves, could only be achieved after ~6 months,[21,22] which helps to explain the lack of a dose–response relationship between LDL-C and ischaemic events in the present study. Interestingly, we confirmed an LDL-C-independent reduction in the net clinical outcome by in-hospital statins, possibly due to its well-known anti-inflammatory capacity.

With the advent and application of PCSK9 inhibitors, the currently recommended LDL-C lowering goal (<55 mg/dL) for ACS patients is achievable even before discharge.[11,12] Although in these small trials, no increase in bleeding events was reported, it should be noted that scattered reports from a series of ODYSSEY trials,[23–26] as well as from the DESCARTES trial (Durable Effect of PCSK9 Antibody Compared with Placebo Study),[27] consistently reported a numerically higher incidence of anaemia in the PCSK9 inhibition arm, with a prevalence of 1.2–2.4%. One should keep in mind that the incidence of major in-hospital bleeds following PCI is only 1–2% (1.45% in the present study). Therefore, further studies with sufficient power are warranted to elucidate the impact of aggressive LDL-C lowering and the risk of bleeding.

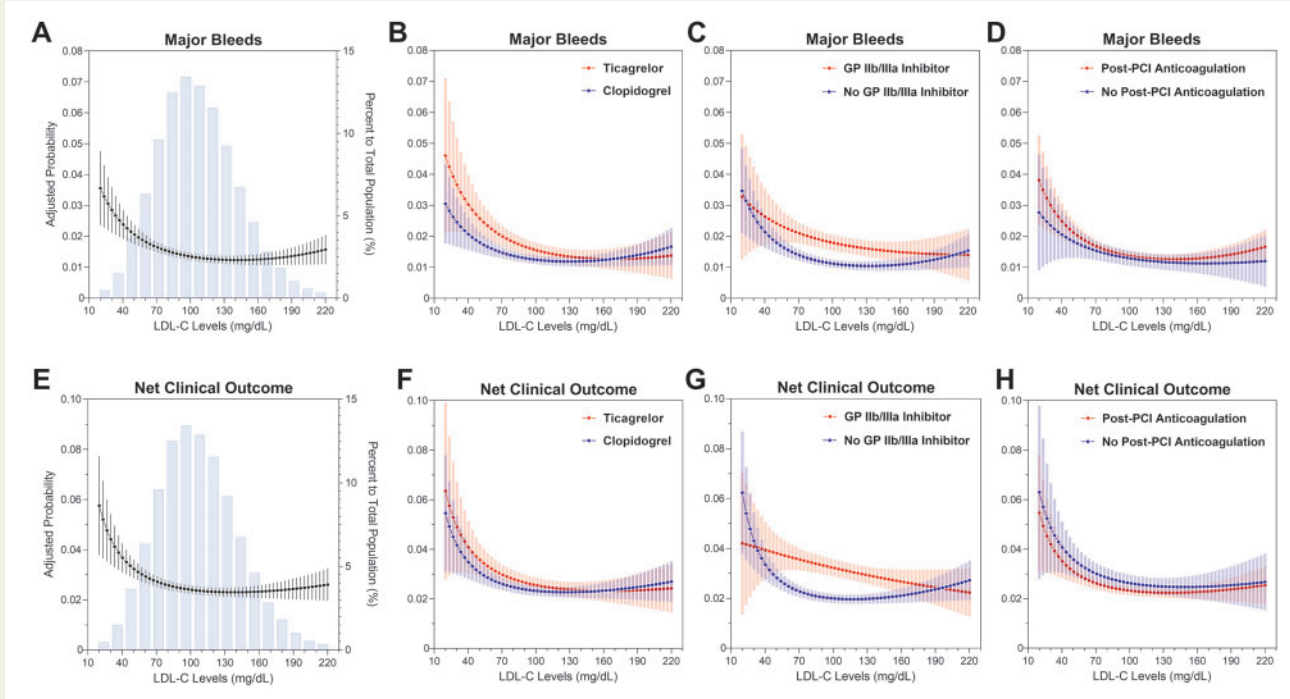


Figure 5 Marginal effects of high-intensity antithrombotic therapy on major bleeds and the net clinical outcome across a full spectrum of LDL-C levels (20–220 mg/dL) in covariate-adjusted logistic regression models. Heavy lines represent estimated probabilities for major bleeds and the net clinical outcome, with thin lines/shaded ribbons denoting 95% confidence intervals. The background blue histograms in Panel A and Panel E represent the per cent of the density distribution of LDL-C in the study population (right *y*-axis). Panels A to D show the marginal effects of high-intensity antithrombotic therapy on major bleeds across LDL-C levels. Panels E to H show the marginal effects of high-intensity antithrombotic therapy on the net clinical outcome across LDL-C levels.

LDL-C levels and haemorrhagic stroke

In our ACS population, we confirmed the negative correlation between LDL-C levels and haemorrhagic stroke as reported in previous long-term cohort studies.[28–30] The clinical significance in these two scenarios may be different. First, haemorrhagic stroke following PCI is more likely to occur within 48 h,[13] and the cumulative incidence (0.24% in the present study) was dramatically higher than those reported in long-term cohort studies (0.80–1.60% during 9–20 years[28–30]). Second, haemorrhagic stroke in those long-term cohorts was mainly confined to participants with hypertension and associated with pathological alterations in the cerebral vasculature,[28,30] whereas both higher and lower blood pressure levels were associated with increased risk for haemorrhagic stroke after ACS (Supplementary material online, *Figure S20*). Third, a recent Mendelian randomization study showed that lower LDL-C is causally associated with intra-cerebral haemorrhage in the Chinese population.[28] This finding helps to explain the observations that the positive findings were mainly from China and other East Asian studies, whereas only a numerically higher number of intracranial haemorrhages, with no statistical significance, was reported in aggressive LDL-C lowering trials with participants mainly from Western populations.[31,32] Notably, the interpretation of low LDL-C-related haemorrhagic stroke in the Chinese population cannot be overstated, considering the substantial net clinical benefit of LDL-C lowering in terms of ASCVD reduction and ischaemic stroke prevention.[28]

Potential mechanisms and clinical implications

Emerging studies provide evidence linking cholesterol metabolism and platelet function. First, low LDL-C levels are metabolically associated with low PCSK9 concentrations. Because PCSK9 enhances platelet activation by binding to platelet CD36,[8] in the context of low LDL-C levels/reduced plasma PCSK9 levels, PCSK9/CD36-mediated downstream cyclooxygenase-1/thromboxane A2 signalling pathways are hampered, thereby augmenting platelet inhibition and impairing haemostasis under the background of high-intensity DAPT. Supportively, LDL-apheresis-induced acute LDL-C reduction, which led to a concomitant ~50% drop in PCSK9 levels,[33] contributed to a significantly reduced shear stress-dependent platelet adhesion.[34] Second, cholesterol, as a key component of platelet membrane lipid rafts, plays an essential role in platelet signalling. For example, *in vitro* cholesterol depletion could directly impair platelet aggregation,[35] whereas hypercholesterolaemia and dysfunction in platelet cholesterol efflux potentiate $P2Y_{12}$ signalling-mediated hyper-reactivity and aggregability.[36,37] Interestingly, our finding that more potent $P2Y_{12}$ inhibition via ticagrelor is associated with an augmentation of bleeding risk only at low LDL-C levels further supports the notion that LDL-C plays an important role in modulating platelet responsiveness. Third, our finding that there is a linear, positive association between LDL-C and platelet counts provides further evidence supporting a pivotal role of cholesterol metabolism in mediating thrombocytopoiesis.[38] In

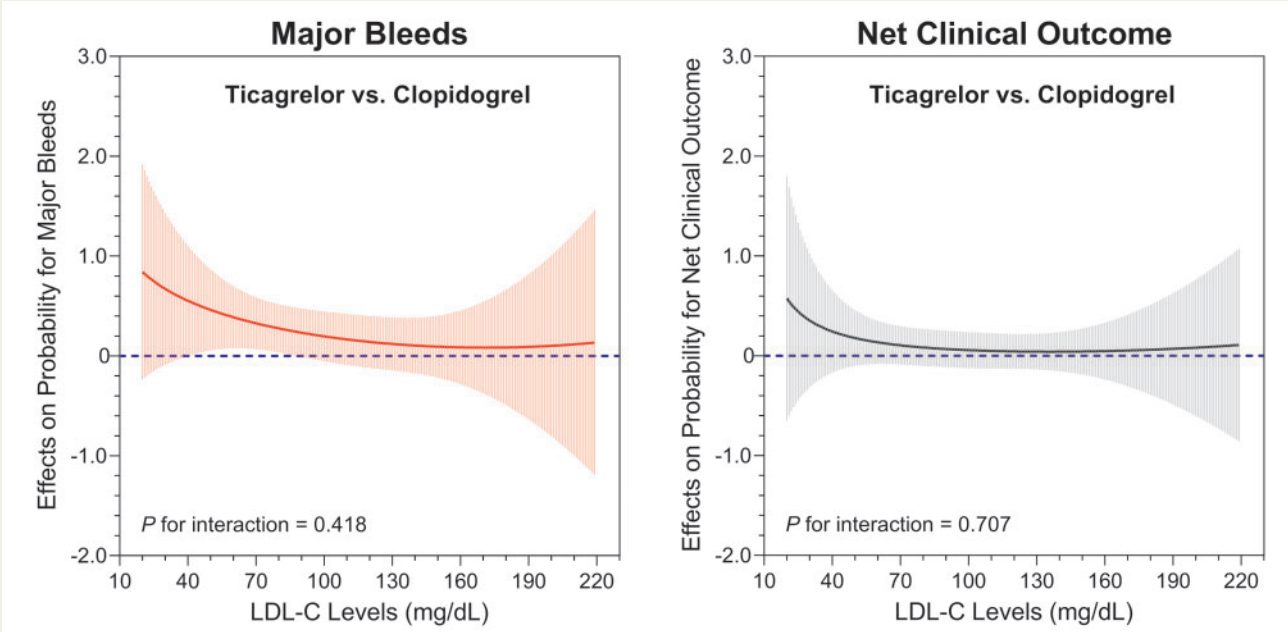


Figure 6 Treatment effect size associated with ticagrelor vs. clopidogrel on major bleeds and on the net clinical outcome according to a full spectrum of LDL-C levels (20–220 mg/dL) in a 1:1 propensity score-matched cohort. Heavy red/black lines represent estimated probabilities for major bleeds and the net clinical outcome, respectively, with shaded ribbons denoting 95% confidence intervals. The blue dotted line at Y = 0 indicates no change in the estimated probability. A positive probability indicates an increased risk, whereas a negative value indicates a reduced risk. The specifications of the sample sizes and propensity score-matching ratios are shown in Supplementary material online, *Table S3*.

addition to currently available evidence focusing on platelet phenotype, a recent study showed that non-haematopoietic deficiency of PCSK9 worsened anaemia in a murine model of sickle cell disease.[39] Its association with increased anaemia incidence among patients receiving PCSK9 inhibition warrants further investigation.

In our study, the proportion of ACS patients with LDL-C < 70 mg/dL was 14.8% (among them 28.8% received pre-admission statins). Similar levels of LDL-C and pre-admission statin use were reported in other East Asian populations and Caucasian ACS patients.[40,41] With the wider application of PCSK9 inhibitors, especially the newly developed siRNA-based approach, a trend for a higher prevalence of patients with LDL-C < 70 mg/dL will be inevitable. Considering our findings that low LDL-C was only associated with non-procedure-related, gastrointestinal major bleeds, which are less likely to be amenable to current bleeding avoidance strategies, future work, such as the adjustment of lipid-lowering intensity and/or the choice of an optimal antiplatelet agent, is required to ensure the safety of patients on antithrombotic therapy.

Strengths and limitations

The major strengths of the present study are the large sample size, coverage, and representativeness of the national population, which provide sufficient power to examine the association between LDL-C and clinical outcomes. Nevertheless, we also acknowledge several limitations. First, as an observational study, we cannot establish a causal relationship between low LDL-C and bleeding risk in the context of high-intensity antithrombotic therapy. Second, despite our efforts to adjust for many important confounders, unmeasured confounders associated with bleeding risk cannot be excluded, i.e. cancer history. However, based on the following reasons, cancer history is unlikely to play a major role in our study: (i) spontaneous low LDL-C is not causally associated with cancer risk[42]; (ii) our sensitivity analysis using *E*-value methodology yielded *E*-values of 2.34–2.73 for the low LDL exposure (<70 mg/dL)-associated major bleeding risk, which implies that the unmeasured confounder (cancer history) should have an association with both major bleeds and low LDL-C exposure equivalent to these values to overcome the effect of low LDL-C exposure. These *E*-values are higher than the reported strength of the associations between cancer history [OR 1.08 (1.03–1.13)] and active cancer [OR 1.92 (1.82–2.04)] with bleeding in patients receiving PCI[43]; (3) our sensitivity analysis after excluding admission haemoglobin <110 and >160 g/L revealed an unchanged strength of association between low LDL-C and major bleeds. Therefore, active cancer is less likely to negate the association between low LDL-C and major bleeds in the present study. We acknowledge that there is still the potential that the residual measured or unmeasured confounding may influence these findings. Third, our patients were all from China. Studies from other populations are necessary to confirm our findings.

Conclusions

In a nationwide registry of patients treated with PCI for ACS in China, a non-linear association was identified between LDL-C and major in-hospital bleeds, with the higher risk at lower LDL-C levels.

This finding provides evidence linking low LDL-C levels to an increased bleeding risk among patients on high-intensity antithrombotic therapy. As the potential for confounding may exist, further studies are warranted.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Conflict of interest: C.G.F. consulted for Amgen, Bayer, Janssen, and Novartis and served on the AHA's Quality Oversight Committee. The other authors declare that there is no conflict of interest.

Data availability

The data, analytic methods, and study materials will be made available for onsite audits by third parties for the purposes of reproducing the results or replicating the procedure.

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