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Low-Density Lipoprotein Cholesterol Levels and Neoatherosclerosis After STEMI

A Secondary Analysis of the CONNECT Randomized Clinical Trial

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IMPORTANCE Neoatherosclerosis represents a major cause of late stent failure and results in cardiac events after drug-eluting stent (DES) implantation. Achieving secondary preventive low-density lipoprotein cholesterol (LDL-C) target levels can reduce plaque progression in native coronary arteries; however, its association with neoatherosclerosis formation remains unclear.

OBJECTIVE To determine whether achieving guideline-endorsed LDL-C levels after DES implantation is associated with reduced risk of long-term neoatherosclerosis formation.

DESIGN, SETTING, AND PARTICIPANTS This is a post hoc analysis of the CONNECT randomized clinical trial conducted at 7 sites in Switzerland and Japan that had randomized 239 patients with ST-segment elevation myocardial infarction (STEMI) to percutaneous coronary intervention (PCI) with biodegradable- or durable-polymer everolimus-eluting stents between June 2017 and June 2020. The prevalence of neoatherosclerosis was assessed with optical coherence tomography (OCT) 3 years after primary PCI. Data analysis for this post hoc analysis was conducted from September 2024 to October 2025.

INTERVENTION Patients with STEMI received primary PCI with DES, and statin therapy was recommended according to country-specific guidelines.

MAIN OUTCOMES AND MEASURES The prevalence of neoatherosclerosis 3 years after primary PCI was compared between patients with vs without achievement of guideline-endorsed target LDL-C levels. A multivariable predictor analysis was performed to determine whether on-treatment LDL-C levels were associated with occurrence of neoatherosclerosis.

RESULTS Among 178 patients (mean [SD] age, 63.4 [10.9] years; 27 [15%] female) who underwent OCT at 3 years, 98 patients (55%) achieved the target LDL-C level and 80 patients (45%) did not. The mean (SD) on-treatment LDL-C levels for these groups were 48 (13) and 87 (37) mg/dL, respectively (to convert to millimoles per liter, multiply by 0.0259). The prevalence of neoatherosclerosis was lower in patients who achieved the target LDL-C level as compared with patients who did not (7 patients [7%] vs 15 patients [19%], respectively; odds ratio for those who did not achieve the LDL-C target level, 3.00; 95% CI, 1.19-8.24; $P = .02$). On-treatment LDL-C level (per 25-mg/dL increase) emerged as an independent determinant of neoatherosclerosis at 3 years in multivariable logistic regression analysis (odds ratio, 1.46; 95% CI, 1.09-2.01; $P = .01$).

CONCLUSIONS AND RELEVANCE On-treatment LDL-C level emerged as an independent predictor of neoatherosclerosis 3 years after DES implantation for STEMI. Neoatherosclerosis was less frequent among patients who achieved the guideline-recommended on-treatment LDL-C level, underscoring the importance of LDL-C lowering in preventing neoatherosclerosis formation.

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Neoatherosclerosis is histologically characterized by the accumulation of lipid-laden macrophage foam cells, necrotic cores, and calcification in the neointimal tissue of the stented coronary segment.[1,2] It represents a major mechanism leading to late stent failure after drug-eluting stent (DES) implantation, including stent thrombosis and in-stent restenosis.[3-5] The criterion standard for the diagnosis of neoatherosclerosis in vivo is by optical coherence tomography (OCT).[6] Previous retrospective studies suggested that neoatherosclerosis is associated with procedure-related (eg, stent type, strut apposition, underlying plaque type) and patient-related (diabetes, kidney failure) factors and on-treatment serum low-density lipoprotein cholesterol (LDL-C) level.[7-9]

For secondary prevention in patients with acute coronary syndrome, the target LDL-C level is set at less than 55 mg/dL (to convert to millimoles per liter, multiply by 0.0259) in the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) guidelines[10] and less than 70 mg/dL in the Japan Atherosclerosis Society (JAS) guidelines.[11] However, the effects of achieving guideline-endorsed target LDL-C levels and the use of high-intensity statin therapy on neoatherosclerosis formation after DES implantation remain unclear. As 50% of cardiovascular events following primary percutaneous coronary intervention (PCI) occur in relation to the implanted stent and neoatherosclerosis is reportedly one of the dominant drivers of these events, a better understanding of these associations is warranted.

We conducted a secondary analysis of the CONNECT (A Randomized Comparison of Long-Term Vascular Healing Between Biodegradable Polymer vs Durable Polymer Everolimus Eluting Stents in Acute ST-Elevation Myocardial Infarction) randomized clinical trial to investigate the association of achieving guideline-endorsed target LDL-C levels and long-term neoatherosclerosis formation following current-generation DES implantation.

Key Points

Question Does achieving guideline-recommended low-density lipoprotein cholesterol (LDL-C) levels help prevent neoatherosclerosis after drug-eluting stent implantation in patients with ST-segment elevation myocardial infarction (STEMI)?

Findings In this secondary analysis of the CONNECT randomized clinical trial, neoatherosclerosis was less frequent in patients who achieved guideline-endorsed LDL-C levels and received high-intensity statin therapy. On-treatment LDL-C level emerged as an independent determinant of neoatherosclerosis.

Meaning Achieving guideline-recommended LDL-C levels through intensive lipid-lowering therapy may help prevent neoatherosclerosis formation and prevent late stent failure in patients with STEMI.

Methods

Study Population

The CONNECT trial (ClinicalTrials.org identifier: NCT03440801) was a prospective, multicenter, open-label, assessor-blind, randomized clinical trial investigating the prevalence of neoatherosclerosis in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary PCI who have received a biodegradable- vs durable-polymer everolimus-eluting stent (the trial protocol appears in Supplement 1 and the statistical analysis plan in Supplement 2). The trial was conducted at 7 centers in 2 countries (Switzerland and Japan). The main results of the CONNECT trial have been reported previously.[12] Briefly, patients 18 years or older were eligible for the study if they presented with STEMI for primary PCI within 24 hours of symptom onset with a culprit lesion that qualified for DES implantation. Major exclusion criteria were hemodynamic instability, left ventricular ejection fraction of 20% or less, mechanical complications of acute myocardial infarction, myocardial infarction secondary to stent thrombosis or in-stent restenosis, known chronic kidney disease (estimate glomerular filtration rate <30 mL/min/1.73 m^2), life expectancy less than 3 years, and culprit lesions not suitable for OCT imaging. This post hoc analysis of the CONNECT trial included 178 patients who underwent OCT imaging for the culprit lesion of STEMI 3 years following primary PCI. All patients provided written informed consent, and the study was approved by the ethical committee at each site. We followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines for reporting of the study results. Data analysis for this post hoc analysis was conducted from September 2024 to October 2025.

Difference of the LDL-C Level Target Between Countries and Definitions of High-Intensity Statin Therapy

High-intensity treatment with statins was recommended to achieve guideline-endorsed target LDL-C levels at the time of the enrollment period. Because of the difference in the target LDL-C levels between the 2019 ESC/EAS guidelines for the management of dyslipidemias and the 2017 JAS guidelines for the prevention of atherosclerotic cardiovascular diseases, the target LDL-C level was defined as less than 55 mg/dL in Swiss patients and less than 70 mg/dL in Japanese patients.[10,11] High-intensity statin treatment was defined as atorvastatin, at least 40 mg/d, or rosuvastatin, at least 20 mg/d, in Swiss patients and as atorvastatin, at least 20 mg/d, rosuvastatin, at least 10 mg/d, or pitavastatin, 4 mg/d, in Japanese patients according to the maximum allowable dose of statins in country-specific clinical practice.[13,14]

Laboratory Analyses

Blood samples for biochemical analyses were obtained at baseline (before or immediately after primary PCI) and at 3-year follow-up. Laboratory analyses were conducted at each site according to local standards. The LDL-C level was either directly measured or calculated using the Friedewald formula.

Acquisition and Analysis of OCT Image

OCT images were analyzed at the OCT core laboratory of Bern University Hospital, Bern, Switzerland, by experienced analysts unaware of LDL-C levels. Neoatherosclerosis was defined as the presence of atherosclerotic change, comprising a

Table 1. Baseline Clinical and Procedural Characteristics Stratified by Whether Patients Achieved the Guideline-Recommended Target LDL-C Level

Characteristic	Overall (N = 178)	LDL-C target[a]		*P* value
		Achieved (n = 98)	Not achieved (n = 80)	
Age, mean (SD), y	63.4 (10.9)	64.0 (11.3)	62.5 (10.3)	.36
Sex, No. (%)				
Female	27 (15)	15 (15)	12 (15)	>.99
Male	151 (85)	83 (85)	68 (85)	
BMI, mean (SD)	26.3 (3.9)	26.2 (4.1)	26.4 (3.6)	.71
Cardiovascular risk factors and medical history, No. (%)				
Diabetes, receiving oral medication or insulin	22 (12)	14 (14)	8 (10)	.49
Hypertension	89 (50)	54 (55)	35 (44)	.18
Dyslipidemia	80 (45)	41 (42)	39 (49)	.37
Current smoker	72 (40)	36 (37)	36 (45)	.14
Family history of coronary artery disease	35 (20)	19 (19)	16 (20)	>.99
Kidney failure[b]	22 (12)	14 (14)	8 (10)	.49
Previous myocardial infarction	4 (2)	1 (1)	3 (4)	.33
Previous PCI	9 (5)	3 (3)	6 (8)	.30
Previous coronary artery bypass surgery	1 (1)	1 (1)	0	>.99
History of stroke	5 (3)	5 (5)	0	.07
History of peripheral artery disease	4 (2)	2 (2)	2 (3)	>.99
Medication regularly taken at home prior to index PCI, No. (%)				
Antithrombotic therapy				
Aspirin	13 (7)	5 (5)	8 (10)	.25
P2Y12 inhibitor	3 (2)	2 (2)	1 (1)	>.99
Dual antiplatelet therapy	0	0	0	>.99
Statin treatment	23 (13)	15 (15)	8 (10)	.37
Statin intensity[c]				
High	6 (3)	2 (2)	4 (5)	.11
Low or moderate	17 (10)	13 (13)	4 (5)	
Biochemical findings at baseline, mean (SD)				
Creatinine, mg/dL	0.87 (0.25)	0.89 (0.27)	0.86 (0.21)	.52
Total cholesterol, mg/dL	194 (47)	179 (41)	211 (46)	<.001
HDL-C, mg/dL	46 (13)	46 (12)	47 (14)	.44
LDL-C, mg/dL	124 (37)	114 (35)	137 (37)	<.001
Triglycerides, mg/dL	133 (105)	136 (108)	131 (102)	.76
HbA_{1c}, % of total hemoglobin	6.08 (1.11)	6.05 (1.03)	6.12 (1.21)	.70
Peak creatine kinase, U/L	2271 (2092)	2359 (2194)	2165 (1971)	.54
Clinical presentation				
LVEF, mean (SD), %	50 (11)	52 (11)	47 (10)	.01
Symptom onset to balloon time, mean (SD), min	213 (364)	216 (309)	208 (375)	.34

(continued)

fibroatheroma, fibrocalcific plaques, or macrophage accumulations, within the neointima of a stented segment with a longitudinal extension of more than 1 mm at 3 years. Fibroatheromas were characterized as a signal-poor region displaying high attenuation (to differentiate from layered neointima) with diffuse borders and a lateral extension of at least 1 quadrant. Macrophage accumulations were defined as lines or dots with strong signal attenuation producing a shadow with a sharply delineated lateral border.[6,15-17] Representative examples of OCT features of neoatherosclerosis are shown in eFigure 1 in Supplement 3. Details on acquisition and analysis of OCT images are provided in the eMethods in Supplement 3.

Study End Point

Primary analysis of this substudy was to compare the prevalence of neoatherosclerosis 3 years after DES implantation, stratified by whether patients achieved the target LDL-C level. For secondary analysis, the prevalence of neoatherosclerosis

Table 1. Baseline Clinical and Procedural Characteristics Stratified by Whether Patients Achieved the Guideline-Recommended Target LDL-C Level (continued)

Characteristic	Overall (N = 178)	LDL-C target[a]		*P* value
		Achieved (n = 98)	Not achieved (n = 80)	
Angiographic and procedural characteristics of primary PCI				
Infarct-related coronary artery, No. (%)				
Left main	1 (1)	1 (1)	0	.24
LAD	80 (45)	38 (39)	42 (53)	
LCX	22 (12)	14 (14)	8 (10)	
RCA	75 (42)	45 (46)	30 (38)	
TIMI flow grade, No. (%)				
Before PCI				
0 or 1	104 (59)	60 (61)	44 (56)	.74
2	57 (32)	30 (31)	27 (34)	
3	16 (9)	8 (8)	8 (10)	
After PCI				
0 or 1	0	0	0	>.99
2	2 (1)	1 (1)	1 (1)	
3	176 (99)	97 (99)	79 (99)	
Assigned stent group, No. (%)				
BP-EES	88 (49)	41 (42)	47 (59)	.04
DP-EES	90 (51)	57 (58)	33 (41)	
Stents implanted in culprit lesion, mean (SD), No.	1.29 (0.52)	1.24 (0.48)	1.34 (0.57)	.30
Stent diameter, mean (SD), mm	3.09 (0.48)	3.10 (0.49)	3.09 (0.48)	.92
Total stent length, mean (SD), mm	32.3 (17.0)	31.5 (16.9)	33.2 (17.2)	.26
Maximal implantation pressure, mean (SD), atm	15 (3)	15 (3)	15 (4)	.67
Postdilation	110 (63)	55 (57)	55 (69)	.16
Intracoronary imaging after PCI[d]	174 (98)	95 (97)	79 (99)	.79

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BP-EES, biodegradable-polymer everolimus-eluting stent; DP-EES, durable-polymer everolimus-eluting stent; HbA_{1c}, hemoglobin A_{1c}; HDL-C, high-density lipoprotein cholesterol; LAD, left anterior descending; LCX, left circumflex; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; P2Y12, P2Y purinergic receptor 12; RCA, right coronary artery; TIMI, thrombolysis in myocardial infarction.

SI conversion factors: To convert creatine kinase to microkatals per liter, multiply by 0.0167; creatinine to micromoles per liter, multiply by 88.4; triglycerides to millimoles per liter, multiply by 0.0113; HbA_{1c} to proportion of total hemoglobin, multiply by 0.01; total cholesterol, HDL-C, and LDL-C to millimoles per liter, multiply by 0.0259.

[a] The guideline-recommended target LDL-C level was less than 55 mg/dL for Swiss patients and less than 70 mg/dL for Japanese patients.

[b] An estimated glomerular filtration rate less than 60 mL/min/1.73 m^2, calculated with the Cockcroft-Gault formula, indicated kidney failure.

[c] High-intensity statins were defined as atorvastatin, at least 40 mg/d, or rosuvastatin, at least 20 mg/d, in Swiss patients and as rosuvastatin, at least 10 mg/d, atorvastatin, at least 20 mg/d, or pitavastatin, 4 mg/d, in Japanese patients. Lower doses and other statins were defined as low or moderate intensity.

[d] Imaging was by optical coherence tomography or intravascular ultrasonography.

was compared in relation to on-treatment LDL-C level as well as to the intensity of statin therapy at 3-year follow-up.

Statistical Analysis

Continuous variables are presented as mean (SD), and categorical variables are presented as count (percentage). Clinical characteristics, procedural characteristics, medication, and biomarker variables were compared between LDL-C groups (target LDL-C level achieved vs not achieved) using *t* test, Fisher exact test, or Wilcoxon rank sum test as appropriate. OCT end points at follow-up were compared between LDL-C groups using logistic, linear, binomial, or quantile regressions depending on the end point. Raw values per group are presented as count (percentage), mean (SD), or median (IQR). The between-group comparison for each end point was extracted from the model and presented as odds ratio (95% CI), mean difference (95% CI), or median difference (95% CI). Multivariable logistic regression analysis was performed to investigate the determinants of neoatherosclerosis formation with the following variables: stent type, diabetes, kidney failure, and on-treatment LDL-C level. Statistical tests were 2-sided, and $P < .05$ indicated statistical significance. All statistical analyses were performed using R version 4.4.1 (R Foundation).

Results

Achievement of Target LDL-C Levels and Medication Use at 3-Year Follow-Up

Among 239 patients enrolled in the CONNECT trial, 178 patients (mean [SD] age, 63.4 [10.9] years; 27 [15%] female) underwent follow-up angiography with OCT imaging for culprit lesions at 3 years, of whom 98 patients (55%; 39 of 91 [43%] in Switzerland and 59 of 87 [68%] in Japan) achieved the guideline-endorsed target LDL-C levels, while 80 patients (45%; 52 [57%] in Switzerland and 28 [32%] in Japan) did not (eFigure 2 in

Table 2. Medication and Biomarkers at 3-Year Follow-Up Stratified by Whether Patients Achieved the Guideline-Recommended Target LDL-C Level

Medication or biomarker	Overall (N = 178)	LDL-C target[a]		P value
		Achieved (n = 98)	Not achieved (n = 80)	
Medication at 3 y, No. (%)				
Aspirin	98 (55)	47 (48)	51 (64)	.049
P2Y12 inhibitor	83 (47)	53 (54)	30 (38)	.03
Prasugrel	16 (9)	12 (12)	4 (5)	.12
Ticagrelor	10 (6)	4 (4)	6 (8)	.35
Clopidogrel	57 (32)	37 (38)	20 (25)	.08
Any dual antiplatelet therapy	15 (8)	7 (7)	8 (10)	.59
Oral anticoagulant	9 (5)	5 (5)	4 (5)	>.99
Statin treatment	164 (92)	97 (99)	67 (84)	<.001
Statin intensity[b]				
High	142 (80)	87 (89)	55 (69)	<.001
Low or moderate	22 (12)	10 (10)	12 (15)	
Type of statin				
Rosuvastatin	148 (83)	89 (91)	59 (74)	<.001
Atorvastatin	14 (8)	8 (8)	6 (8)	
Other statin	2 (1)	0	2 (2)	
Ezetimibe	86 (48)	50 (51)	36 (45)	.45
ACE inhibitor	57 (32)	28 (29)	29 (36)	.33
Angiotensin II receptor antagonist	91 (51)	59 (60)	32 (40)	.01
β-Blocker	116 (66)	71 (72)	47 (59)	.06
Biomarkers at 3 y				
HbA_{1c}, median (IQR), % of total hemoglobin	5.9 (5.6-6.3)	5.9 (5.5-6.4)	5.9 (5.6-6.3)	.60
Total cholesterol, mean (SD), mg/dL	139 (37)	119 (19)	162 (38)	NA[c]
HDL-C, mean (SD), mg/dL	49 (11)	47 (11)	50 (12)	.16
LDL-C, mean (SD), mg/dL	65 (33)	48 (13)	87 (37)	NA[c]
Triglycerides, median (IQR), mg/dL	112 (83-177)	105 (81-164)	121 (93-182)	.06

Abbreviations: ACE, angiotensin-converting enzyme; HbA_{1c}, hemoglobin A_{1c}; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NA, not applicable; P2Y12, P2Y purinergic receptor 12.

SI conversion factors: To convert HbA_{1c} to proportion of total hemoglobin, multiply by 0.01; total cholesterol, HDL-C, and LDL-C to millimoles per liter, multiply by 0.0259; triglycerides to millimoles per liter, multiply by 0.0113.

[a] The guideline-recommended target LDL-C level was less than 55 mg/dL for Swiss patients and less than 70 mg/dL for Japanese patients.

[b] High-intensity statins were defined as atorvastatin, at least 40 mg/d, or rosuvastatin, at least 20 mg/d, in Swiss patients and as rosuvastatin, at least 10 mg/d, atorvastatin, at least 20 mg/d, or pitavastatin, 4 mg/d, in Japanese patients. Lower doses and other statins were defined as low or moderate intensity.

[c] No statistical comparison was performed because the grouping was itself based on LDL-C values.

Supplement 3). Mean (SD) LDL-C levels were 48 (13) mg/dL in patients who achieved the target LDL-C level and 87 (37) mg/dL in those who did not. Baseline clinical and procedural characteristics are summarized in **Table 1**. Patients who achieved the target LDL-C level, compared with those who did not, had lower mean (SD) baseline levels of total cholesterol (179 [41] vs 211 [46] mg/dL [to convert to millimoles per liter, multiply by 0.0259]; $P < .001$) and LDL-C (114 [35] vs 137 [37] mg/dL; $P < .001$). The mean (SD) left ventricular ejection fraction at baseline was greater for those who achieved the target LDL-C level than for those who had not (52% [11%] vs 47% [10%]; $P = .01$). No significant procedural differences were observed, except for a higher frequency of durable-polymer everolimus-eluting stent use in patients who achieved the target LDL-C level compared with those who did not (57 of 98 patients [58%] vs 33 of 80 patients [41%]; $P = .04$). At discharge, 164 patients (92%) received high-intensity statin therapy, without significant differences between groups (eTable 1 in Supplement 3).

Medication and biomarkers at 3-year follow-up are shown in **Table 2**. The flow of the proportion of patients with statin therapy is illustrated in eFigure 3 in Supplement 3. At 3 years, the use of high-intensity statin therapy was higher in patients who achieved the target LDL-C level compared with those who did not (87 [89%] vs 55 [69%]; $P < .001$), whereas the use of ezetimibe did not differ (50 [51%] vs 36 [45%]; $P = .45$). Other lipid-lowering medication use was rare (overall, 4 patients received eicosapentaenoic acid, 1 received fibrates, and 2 received evolocumab). The proportion of patients using aspirin was lower in those who achieved the target LDL-C level than in those who did not (47 [48%] vs 51 [64%]; $P = .049$), while the proportion receiving P2Y purinergic receptor 12 (P2Y12) inhibitors was higher (53 [54%] vs 30 [38%]; $P = .03$). Higher P2Y12 inhibitor use in the group of patients who had achieved the target LDL-C level are explained by more frequent use of P2Y12 inhibitor monotherapy in Japan (eTable 2 in Supplement 3) and a higher proportion of Japanese patients achieving the target LDL-C level in view of the lower threshold compared with that in Switzerland.

On-Treatment LDL-C Levels and Neoatherosclerosis

In total, neoatherosclerosis was identified in 22 patients (12%) at 3-year follow-up. Comparisons of OCT findings between groups are shown in **Table 3**. The prevalence of neoatherosclerosis was lower in patients who achieved the target LDL-C level compared with those who did not (7 patients [7%] vs 15 patients [19%]; odds ratio for those who did not achieve the LDL-C target level, 3.00; 95% CI, 1.19-8.24; $P = .02$) (**Figure 1**A). Stratified by the achieved level of LDL-C irrespective of country-specific target recommendations, neoatherosclerosis was found in 5 of 64 patients (8%) with an LDL-C level below 55 mg/dL, 7 of 61 patients (11%) with a level of 55 to less than 70 mg/dL, and 10 of 53 patients (19%) with a level of 70 mg/dL or higher ($P = .22$) (Figure 1B). A logistic regression curve showing the prevalence of neoatherosclerosis in relation to on-treatment LDL-C level is shown in **Figure 2**. Detailed OCT findings applying the same cutoff levels (55 mg/dL and 70 mg/dL) for all patients are provided in eTable 3 and eTable 4 in Supplement 3. Further stratifications and country-specific results are

Table 3. OCT Findings at 3 Years Stratified by Whether Patients Achieved the Guideline-Recommended Target LDL-C Level

OCT finding at 3 y	Overall (N = 178)	LDL-C target[a] Achieved (n = 98)	LDL-C target[a] Not achieved (n = 80)	OR or difference (95% CI)[b]	*P* value
Cross-sections analyzed per lesion, mean (SD), No.	77.43 (36.39)	74.99 (34.54)	80.41 (38.54)	5.42 (−5.40 to 16.24)	.32
Primary end point					
Presence of neoatherosclerosis, No. (%)[c]	22 (12.4)	7 (7.1)	15 (18.8)	3.00 (1.19 to 8.24)	.02
Lesions with fibroatheroma >1 mm, No. (%)	18 (10.1)	5 (5.1)	13 (16.2)	3.61 (1.29 to 11.69)	.02
Lesions with fibrocalcific plaque >1 mm, No.	0	0	0	NA	NA
Lesions with macrophage accumulations >1 mm, No. (%)	7 (3.9)	2 (2.0)	5 (6.2)	3.20 (0.67 to 22.78)	.17
Any neoatherosclerosis in ≥1 frame, No. (%)	24 (13.5)	8 (8.2)	16 (20.0)	2.81 (1.16 to 7.31)	.03
Lesions with fibroatheroma in ≥1 frame, No. (%)	18 (10.1)	5 (5.1)	13 (16.2)	3.61 (1.29 to 11.69)	.02
Lesions with fibrocalcific plaque in ≥1 frame, No.	0	0	0	NA	NA
Lesions with macrophage accumulations in ≥1 frame, No. (%)	11 (6.2)	3 (3.1)	8 (10.0)	3.52 (0.98 to 16.49)	.07
Minimal cap thickness, mean (SD), μm[d]	96.01 (55.09)	109.62 (40.67)	90.78 (60.34)	−18.85 (−81.40 to 43.70)	.53
Length of fibroatheroma, mean (SD), mm[d]	3.38 (2.14)	2.88 (1.25)	3.57 (2.42)	0.69 (−1.75 to 3.13)	.56
Maximal lipid arc, mean (SD), degrees[d]	180.03 (75.17)	173.77 (54.26)	182.43 (83.67)	8.66 (−77.66 to 94.98)	.83
Maximal angle extension of macrophages, mean (SD), degrees[e]	81.55 (43.50)	80.80 (40.55)	81.84 (47.25)	1.03 (−69.19 to 71.25)	.97
Analysis at lesion level					
Minimal luminal area, mean (SD), mm^2	4.94 (2.47)	5.08 (2.62)	4.78 (2.29)	−0.29 (−1.03 to 0.44)	.43
Minimal stent area, mean (SD), mm^2	6.24 (2.40)	6.35 (2.55)	6.10 (2.20)	−0.25 (−0.96 to 0.47)	.50
Analysis at cross-section level					
Mean luminal area, mean (SD), mm^2	7.05 (2.78)	7.16 (3.00)	6.92 (2.50)	−0.24 (−1.07 to 0.58)	.56
Mean stent area, mean (SD), mm^2	7.93 (2.77)	7.99 (2.94)	7.85 (2.57)	−0.15 (−0.97 to 0.68)	.73
Mean neointimal area, mean (SD), mm^2	0.93 (0.65)	0.89 (0.62)	0.99 (0.69)	0.10 (−0.09 to 0.30)	.30
Mean malapposed area, mean (SD), mm^2	0.06 (0.18)	0.06 (0.15)	0.06 (0.21)	0.00 (−0.05 to 0.06)	.86
Mean neointimal thickness, mean (SD), μm	130.92 (70.07)	127.32 (68.12)	135.34 (72.59)	8.02 (−12.84 to 28.88)	.45
Mean malapposition distance, mean (SD), μm[f]	235.60 (140.96)	259.60 ± 154.78	203.84 (114.88)	−55.76 (−118.69 to 7.18)	.08
Analysis at strut level					
Uncovered struts, mean (SD), %	4.29 (6.27)	4.61 (6.91)	3.90 (5.41)	−0.71 (−2.54 to 1.12)	.45[g]
Malapposed struts, mean (SD), %	1.11 (2.64)	1.16 (2.81)	1.04 (2.42)	−0.12 (−0.90 to 0.65)	.76[g]
Neointimal healing score, median (IQR), points	0.10 (0.02 to 0.34)	0.10 (0.02 to 0.34)	0.10 (0.02 to 0.33)	0.002 (−0.073 to 0.077)	.96

Abbreviations: LDL-C, low-density lipoprotein cholesterol; NA, not applicable; OCT, optical coherence tomography; OR, odds ratio.

[a] The guideline-recommended target LDL-C level was less than 55 mg/dL for Swiss patients and less than 70 mg/dL for Japanese patients.

[b] Values for categorical variables are presented as OR (95% CI), extracted from logistic models. Values for continuous variables are presented as between-group difference (95% CI), extracted from linear models (or quantile regression for healing score).

[c] Defined as fibroatheroma or fibrocalcific plaques, or as macrophage accumulations within the neointima of a stented segment with a longitudinal extension in at least 3 frames, eg, of at least 1 mm.

[d] Only in patients with fibroatheroma (n = 18).

[e] Only in patients with macrophage accumulations (n = 11).

[f] Only in patients with malapposition (n = 79).

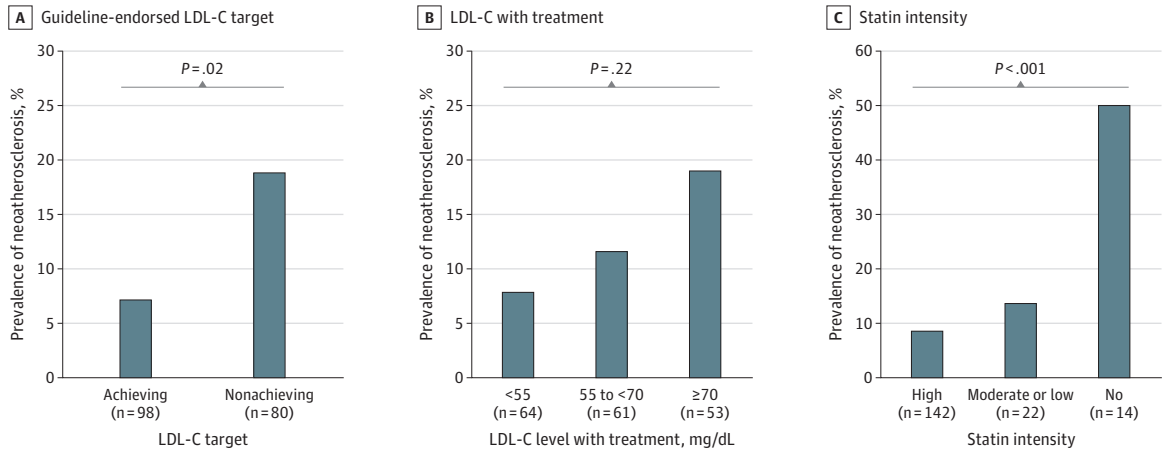
[g] *P* values are from binomial regressions.

shown in eFigure 4 and eFigure 5 in Supplement 3. The proportion of patients with in-stent fibroatheroma was significantly lower in those who achieved the target LDL-C level compared with those who did not (5 patients [5%] vs 13 patients [16%]; *P* = .02), while the proportion of patients with in-stent macrophages was comparable between the groups (2 patients [2%] vs 5 patients [6%]; *P* = .17). No significant differences were observed in minimum lumen area or mean neointimal area.

Lipid-Lowering Therapy and Neoatherosclerosis

At the 3-year follow-up, 142 patients (80%; 81% among Swiss patients and 78% among Japanese patients) were receiving high-intensity statin therapy, 22 patients (12%) were receiving low- or moderate-intensity statin therapy, and 14 patients (8%) were not receiving statins. Mean (SD) LDL-C levels were 59 (20) mg/dL in patients with high-intensity statin therapy, 66 (28) mg/dL in patients with low- or moderate-intensity statin therapy, and 128 (64) mg/dL in those not receiving statins (*P* < .001). The prevalence of neoatherosclerosis was significantly lower in patients receiving statin therapies compared with those not receiving such therapy (12 of 142 patients [8%] receiving high-intensity statin therapy vs 3 of 22 patients [14%] receiving low- or moderate-intensity statin therapy vs 7 of 14 patients [50%] without statins; *P* < .001) (Figure 1C). OCT findings stratified by whether patients were or were not receiving high-intensity statin therapy, country-specific results, and a sensitivity analysis comparing the prevalence of neoatherosclerosis between patients with vs without intensive lipid-lowering therapy, defined as either high-intensity

Figure 1. Prevalence of Neoatherosclerosis by On-Treatment Low-Density Lipoprotein Cholesterol (LDL-C) Level and Statin Therapy at 3 Years



Prevalence of neoatherosclerosis at 3 years in patients with or without achievement of guideline-endorsed target LDL-C levels (A), stratified by on-treatment LDL-C levels less than 55 mg/dL, 55 to less than 70 mg/dL, and 70 mg/dL or higher (B), and stratified by the intensity of statin therapy (C). The target LDL-C levels were defined as less than 55 mg/dL for Swiss patients and less than 70 mg/dL for Japanese patients. High-intensity statin therapy was defined as atorvastatin, at least 40 mg/d, or rosuvastatin, at least 20 mg/d, in Swiss patients and as rosuvastatin, at least 10 mg/d, atorvastatin, at least 20 mg/d, or pitavastatin, 4 mg/d, in Japanese patients. Lower doses and other statins were defined as low or moderate intensity. Neoatherosclerosis was defined as the presence of a fibroatheroma or fibrocalcific plaques, or of macrophage accumulations within the neointima of a stented segment with a longitudinal extension of more than 1 mm in optical coherence tomography at 3 years. To convert LDL-C to millimoles per liter, multiply by 0.0259.

statin therapy or therapy with moderate-intensity statin plus ezetimibe, are provided in eTable 5, eFigure 6, and eFigure 7 in Supplement 3.

Determinants of Neoatherosclerosis

Patients with neoatherosclerosis, compared with those without neoatherosclerosis, had higher mean (SD) hemoglobin A_{1c} levels at baseline (6.52% [1.35%] vs 6.01% [1.06%]; to convert to proportion of total hemoglobin, multiply by 0.01; $P = .048$), whereas other baseline clinical characteristics and biochemical findings as well as procedural characteristics, including stent type, did not differ between patients with and without neoatherosclerosis (eTable 6 in Supplement 3). At 3 years, the mean (SD) on-treatment LDL-C level was significantly higher in patients with neoatherosclerosis than in those without neoatherosclerosis (83 [43] mg/dL vs 63 [30] mg/dL; $P = .005$), and patients with neoatherosclerosis were less likely to be receiving high-intensity statin therapy (12 patients [55%] with neoatherosclerosis vs 130 patients [83%] without neoatherosclerosis; $P < .001$) (eTable 7 in Supplement 3). In a multivariable logistic regression model, only the LDL-C level at the 3-year follow-up emerged as an independent determinant of neoatherosclerosis formation (per 25-mg/dL increase: odds ratio, 1.46; 95% CI, 1.09-2.01; $P = .01$), while diabetes status, kidney failure, and stent type were not (eTable 8 in Supplement 3).

Discussion

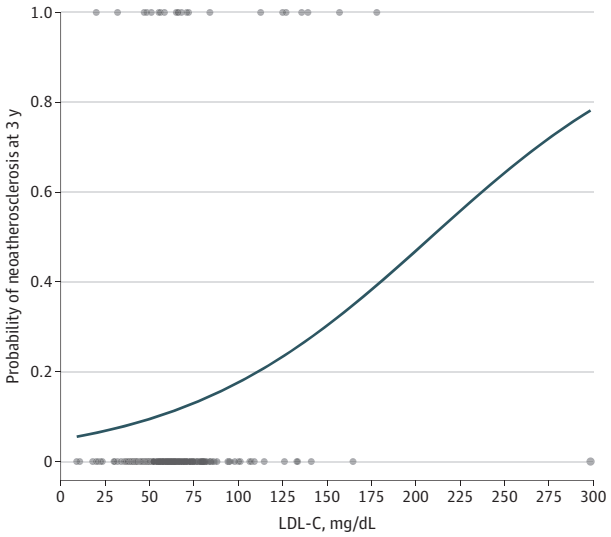
This is the first report, to our knowledge, to demonstrate the association between the on-treatment LDL-C level and the occurrence of neoatherosclerosis after newer-generation DES implantation. The key findings of the present study are as follows: (1) on-treatment LDL-C level emerged as independent predictor of neoatherosclerosis; (2) the prevalence of neoatherosclerosis was significantly lower in patients who achieved guideline-endorsed target LDL-C levels than in those who did not; and (3) patients treated with high-intensity statin therapy exhibited a lower risk of neoatherosclerosis formation compared with those receiving less-intense statin treatment.

These findings were obtained in the context of modern PCI using imaging guidance in most cases and newer-generation DES implantation. While the type of stent (ie, biodegradable- vs durable-polymer DES) was not associated with neoatherosclerosis formation, the on-treatment LDL-C level was. These findings are clinically relevant as neoatherosclerosis represents one of the key drivers of stent-related adverse outcomes throughout long-term follow-up, and our data suggest that the achievement of a target LDL-C level may prevent its occurrence. While early stent failures are frequently related to mechanical problems, there is a continued risk of delayed stent-related major adverse cardiac events of approximately 1% to 2% per year without attenuation over time.[18,19] This continued risk is largely associated with neoatherosclerosis owing to very late stent thrombosis (ie, induced by rupture of neointimal fibroatheroma) and restenosis (ie, caused by increasing atheroma inside the stent).[8,20] Collectively, our analysis suggests that the benefit associated with intensive lipid-lowering therapy is not limited to the untreated coronary arteries but importantly includes stented segments.

LDL-C Levels and Neoatherosclerosis Formation

Neoatherosclerosis is defined as the development of new atherosclerosis within the neointima of a stented segment, and the underlying pathophysiological mechanisms (ie, the migration of macrophages and lymphocytes, and the accumu-

Figure 2. Probability of Neoatherosclerosis by On-Treatment Low-Density Lipoprotein Cholesterol (LDL-C) Level



The logistic regression curve illustrates the association between on-treatment LDL-C level and the probability of neoatherosclerosis at 3 years. Each dot at 0 or 1 indicates a patient either without or with neoatherosclerosis, respectively, at 3 years. To convert LDL-C to millimoles per liter, multiply by 0.0259.

lation of oxidized LDL-C into the neointimal layer) are similar to those leading to atherosclerosis in native coronary arteries.[21] Indeed, a long-term clinical study suggested that the development of neoatherosclerosis was associated with progression of native coronary atherosclerosis.[22] However, while native atherosclerosis requires decades to develop, formation of atheroma in stented segments is accelerated by 10 to 20 times, mainly due to the impaired endothelial function triggered by stent implantation–related endothelial denudation and delayed endothelial recovery due to the antiproliferative effect of the eluted drug of the DES or persisting inflammation.[5] As such, neoatherosclerosis may serve as an in vivo model of accelerated atherosclerosis, and its observation allows for the detection of the protective effects of therapeutic interventions at shorter follow-up duration.

Assuming similar underlying pathophysiological mechanisms for both entities, it has been suggested that therapeutic strategies that attenuate atherosclerosis progression might also suppress neoatherosclerosis formation.[22] Our study found that, similar to its effects on native coronary arteries, a lower on-treatment LDL-C level was associated with a lower prevalence of atherosclerotic changes in the in-stent neointima. Furthermore, the logistic regression curve in Figure 2 suggests that the probability of neoatherosclerosis continues to decrease with further reductions in achieved LDL-C levels—even below 55 mg/dL, mirroring the near-linear association observed between plaque regression and on-treatment LDL-C levels in native coronary arteries.[23,24] Given this association, it is not surprising that patients receiving high-intensity statin therapy at 3-year follow-up exhibited a lower prevalence of neoatherosclerosis compared with those treated with less-intensive regimens.

Although the effect of LDL-C levels on neoatherosclerosis formation may vary depending on factors such as the duration of stent placement and stent type, the association between on-treatment LDL-C levels and neoatherosclerosis has been reported in several retrospective studies.[7,8,25] Previous prospective studies were inconclusive. In 2 studies with long-term follow-up, on-treatment LDL-C levels were not associated with the prevalence of neoatherosclerosis 5 years after implantation of bare-metal stents and first-generation DESs, but mean on-treatment LDL-C levels in those studies were far higher (>90 mg/dL and >100 mg/dL) than the target LDL-C levels outlined in current guidelines and achieved in our patient cohort.[22,26] On the other hand, a recent Japanese study found higher on-treatment LDL-C levels in patients with neoatherosclerosis 1 year after second-generation DES implantation for acute coronary syndrome as compared with those without neoatherosclerosis (mean [SD] LDL-C level, 94 [36] vs 72 [19] mg/dL, all in statin-treated patients), but non–HDL-C and lipoprotein (a) levels appeared to be stronger predictors.[27] However, that study was limited by a small sample size (N = 83) and the short follow-up duration of only 1 year, a time point at which neoatherosclerosis is about to start building up.[6,8]

Association Between Achieving Guideline-Endorsed Target LDL-C Levels and Neoatherosclerosis Formation

To our knowledge, no previous studies have addressed the association between guideline-endorsed target LDL-C levels and neoatherosclerosis formation. This study not only demonstrated a lower incidence of neoatherosclerosis in patients who achieved guideline-recommended target LDL-C levels but also found the lowest rates of neoatherosclerosis in patients treated with high-intensity statins. While the exploratory nature of this nonrandomized analysis does not allow for definitive conclusion about causality, our findings suggest that intensive lipid-lowering therapy may prevent and mitigate accelerated atherosclerotic changes in the stented neointima, similar to its effects on native coronary artery plaques. Indeed, the LINK-IT (Lesional Evaluation of High-Risk Patients With Neoatherosclerosis Treated With Rosuva-Statin and Eicosapentaenoic Acid) trial[28] found that in patients with evidence of neoatherosclerosis, the intervention group (rosuvastatin, 10 mg/d, plus eicosapentaenoic acid, 1800 mg/d) showed no increase in lipid index and a decrease in macrophage grade after 1 year, while the comparator group (rosuvastatin, 2.5 mg/d) showed an increased lipid index and no change in macrophage grade.

Achievement of Target LDL-C Levels and Patient Adherence

Despite highly prevalent use of statin therapy (92%) and common use of ezetimibe at 3 years in the present study, only 55% of patients achieved the guideline-endorsed target LDL-C levels. A partial explanation is that the CONNECT trial commenced before the widespread availability of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, with only 2 patients receiving evolocumab at the 3-year follow-up. Contemporary data, however, suggest that nonachievement of target LDL-C levels continues to be a concern despite broader availability of PCSK9 inhibitors.[29]

Patients' adherence to statins in secondary prevention is limited for various reasons, including the perception that stents entirely resolve their coronary artery disease.[30,31] Explaining to patients that statins are relevant to keep their stent open by mitigating thrombosis or restenosis may be particularly effective in improving adherence to intensive lipid-lowering therapy and may even motivate interventional cardiologists to highlight the benefit of statins to their patients. The LDL-C level should be monitored from the early post-PCI period and at regular intervals thereafter, with intensification of lipid-lowering therapy when guideline-endorsed targets are not achieved.

Limitations

This study has several limitations. First, LDL-C levels were assessed only at the 3-year follow-up; thus, the cumulative exposure to LDL-C over time (eg, area under the LDL-C curve) remains unknown. Similarly, the imaging protocol provides only a point prevalence of OCT-detected neoatherosclerosis at 3 years and, by design, cannot capture its onset, progression, or peak occurrence. As a result, temporal relationships between changes in the LDL-C level and the development of neoatherosclerosis cannot be established. Moreover, the nonrandomized nature of this secondary analysis, the modest sample size, and the presence of concomitant therapies limit causal inference, and residual confounding cannot be excluded. Ultimately, definitive assessment of whether intensive LDL-C–lowering therapies (eg, PCSK9 inhibitors) prevent neoatherosclerosis will require dedicated randomized trials. Second, the study pooled patients from countries where different guideline-endorsed LDL-C targets and different definitions of high-intensity statin therapy apply. This discrepancy may explain why patients do not receive uniform oral therapy, potentially affecting both the achievement of guideline-endorsed target LDL-C levels and the occurrence of neoatherosclerosis. Third, ESC guidelines lowered the secondary prevention target level of LDL-C from less than 70 mg/dL to less than 55 mg/dL in 2019. Therefore, in Swiss patients enrolled before 2019, lipid-lowering therapy was initiated aiming for levels below 70 mg/dL, and it is unclear whether their targets were revised after the publication of the new recommendations in 2019. However, the recommendation to prescribe therapy with high-intensity statin remained unchanged throughout the study period in all patients. Fourth, the frequency of patients with diabetes was low. It remains unknown whether the findings also apply to this subgroup. Fifth, biodegradable-polymer everolimus-eluting stents were significantly more frequent in patients achieving target LDL-C levels. As no study-related LDL-C level measurements were done between baseline and 3 years, it is unlikely that knowledge of the stent type would have biased the lipid-lowering therapy. No significant difference in the statin therapy between stent-type groups was detected,[12] and the stent type was not an independent predictor for neoatherosclerosis in multivariate analysis. Finally, biochemical analyses were not conducted by a central laboratory but at each site locally, and the LDL-C level was either measured directly or calculated using the Friedewald formula.

Conclusions

In this secondary analysis of the CONNECT randomized clinical trial, on-treatment LDL-C level emerged as an independent predictor of neoatherosclerosis 3 years after DES implantation for STEMI. Neoatherosclerosis was less frequent in patients who achieved on-treatment guideline-endorsed target LDL-C levels, suggesting the importance of LDL-C lowering in preventing neoatherosclerosis formation. Intensive lipid-lowering therapy may inhibit neoatherosclerosis formation and therefore presumably prevent late stent failure, but this requires confirmation in adequately designed studies. Informing patients on this relevant association may further help to improve adherence to intensive lipid-lowering therapy and improve stent-related outcomes.

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