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Influence of LDL-Cholesterol Lowering on Cardiovascular Outcomes in Patients With Diabetes Mellitus Undergoing Coronary Revascularization

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ABSTRACT

BACKGROUND Elevated low-density lipoprotein cholesterol (LDL-C) is associated with increased cardiovascular events, especially in high-risk populations.

OBJECTIVES This study sought to evaluate the influence of LDL-C on the incidence of cardiovascular events either following a coronary revascularization procedure (percutaneous coronary intervention [PCI] or coronary artery bypass grafting [CABG]) or optimal medical therapy alone in patients with established coronary heart disease and type 2 diabetes (T2DM).

METHODS Patient-level pooled analysis of 3 randomized clinical trials was undertaken. Patients with T2DM were categorized according to the levels of LDL-C at 1 year following randomization. The primary endpoint was major adverse cardiac or cerebrovascular events ([MACCE] the composite of all-cause mortality, nonfatal myocardial infarction, and nonfatal stroke).

RESULTS A total of 4,050 patients were followed for a median of 3.9 years after the index 1-year assessment. Patients whose 1-year LDL-C remained ≥100 mg/dl experienced higher 4-year cumulative risk of MACCE (17.2% vs. 13.3% vs. 13.1% for LDL-C between 70 and <100 mg/dl and LDL-C <70 mg/dl, respectively; $p = 0.016$). When compared with optimal medical therapy alone, patients with PCI experienced a MACCE reduction only if 1-year LDL-C was <70 mg/dl (hazard ratio: 0.61; 95% confidence interval: 0.40 to 0.91; $p = 0.016$), whereas CABG was associated with improved outcomes across all 1-year LDL-C strata. In patients with 1-year LDL-C ≥70 mg/dl, patients undergoing CABG had significantly lower MACCE rates as compared with PCI.

CONCLUSIONS In patients with coronary heart disease with T2DM, lower LDL-C at 1 year is associated with improved long-term MACCE outcome in those eligible for either PCI or CABG. When compared with optimal medical therapy alone, PCI was associated with MACCE reductions only in those who achieved an LDL-C <70 mg/dl.
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ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass grafting

CHD = coronary heart disease

CI = confidence interval

HR = hazard ratio

LDL-C = low-density lipoprotein cholesterol

MACCE = major adverse cardiac or cerebrovascular events

MI = myocardial infarction

non-HDL-C = non-high-density lipoprotein cholesterol

OMT = optimal medical therapy

PCI = percutaneous coronary intervention

T2DM = type 2 diabetes

Lipid abnormalities, including high levels of low-density lipoprotein cholesterol (LDL-C), are commonly present in patients with type 2 diabetes mellitus (T2DM), particularly in those with concomitant coronary heart disease (CHD) (1,2). In these patients, the atherogenic lipid phenotype is characterized by small, dense LDL particles where apolipoprotein B-containing particles contribute to a more rapid development and progression of coronary atherosclerosis (3). Current clinical practice guidelines recommend aggressive LDL-C reductions in patients with T2DM, and especially in those with established CHD (4,5). In this high-risk secondary prevention population, higher LDL-C levels are generally associated with higher incident rates of cardiovascular events, when compared with individuals with T2DM who have no demonstrable CHD (6).

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The principles of guideline-directed management of patients with CHD with T2DM include intensive lifestyle changes coupled with aggressive, multifaceted secondary prevention, often referred to as optimal medical therapy (OMT), together with the choice of the most appropriate revascularization strategy, if suitable, according to patients' preferences, clinical conditions, and current evidence (7). In patients with T2DM and stable CHD in need of a coronary revascularization procedure, coronary artery bypass grafting (CABG) added to OMT is proven to reduce the rates of major adverse cardiac or cerebrovascular events (MACCE) when compared with OMT alone (8) or percutaneous coronary intervention (PCI) plus OMT (9). Nevertheless, achieving guideline-recommended targets for cholesterol, glycemic, and blood pressure control is a challenging task in this population, and efforts should be made in this direction (10). Notwithstanding these recommendations, little is known about the impact of LDL-C reduction in the years following a revascularization procedure in patients with T2DM. This study combines patient-level data from 3 large randomized trials of coronary revascularization. Our principal objectives were to investigate the influence of LDL-C levels at 1 year of follow-up on the incidence of long-term MACCE following a coronary revascularization procedure in patients with T2DM, to assess whether there was a graded effect of achieved LDL-C on outcomes after 1 year, and whether there was a possible differential effect of LDL-C reduction according to the assigned intervention strategy (e.g., revascularization with PCI, CABG, or OMT alone).

METHODS

PATIENT POPULATION. The current analysis combined individual patient-level information from 3 U.S. Government funded trials: BARI 2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) (8), COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) (11), and FREEDOM (Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multi-vessel Disease) (9). BARI-2D and FREEDOM enrolled only patients with CHD and T2DM, whereas COURAGE also enrolled patients without T2DM. Thus, only patients with T2DM in the COURAGE trial were considered for this pooled analysis (34% of the whole trial population). Patients with LDL-C <20 mg/dl and triglycerides >400 mg/dl both at baseline and 1 year were excluded from the analyses.

Patients were enrolled between 1999 and 2010 and were assigned to OMT versus PCI + OMT (COURAGE), PCI + OMT versus CABG + OMT (FREEDOM), and OMT versus revascularization either with PCI + OMT or CABG + OMT (BARI 2D). Target LDL-C achievement varied somewhat among the trials; in BARI-2D the LDL-C goal was <100 mg/dl, in COURAGE between 60 and 85 mg/dl, and in FREEDOM <70 mg/dl (8,9,11). These recommendations were in accordance with applicable clinical guidelines during the conduct of these trials (12,13). In all trials, at least 90% of the patients were prescribed statins at 1 year (10). Regarding control of other risk factors, all trials had a blood pressure target of <130/80 mm Hg and glycated hemoglobin <7%. At 1 year, at least 80% of the patients in all 3 trials were prescribed with a beta-blocker and a renin-angiotensin system inhibitor and more than 90% of the patients were on aspirin (10). Deidentified data were extracted from each

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dataset and the University of Pittsburgh Graduate School of Public Health, Epidemiology Data Center merged these into a single patient-level dataset. More details about the pooling method were published previously (10,14). This study was approved by the University of Pittsburgh Institutional Review Board.

STATISTICAL METHODS. Patients from the 3 previously mentioned trials were categorized according to their levels of LDL-C achieved after the first year of follow-up (<70 mg/dl; between 70 and <100 mg/dl; and ≥100 mg/dl) and this was the primary independent variable for this analysis. Consequently, the "time zero" for all time-to-event analyses in this report was the time of the 1-year assessment and only patients who survived and remained in the trial for their 1-year follow-up visit were included in this study. Baseline and key 1-year patient characteristics were compared across the trials, based on 1-year LDL-C levels, using the Kruskal-Wallis test for continuous variables and the chi-square statistics for categorical variables.

The primary outcome in this analysis was the 4-year rate of the MACCE composite: all-cause mortality, nonfatal myocardial infarction (MI), or nonfatal stroke. Subsequent revascularization was also ascertained as a secondary endpoint. Four-year cumulative event rates were compared using Kaplan-Meier estimates, log-rank statistics, and Cox proportional hazards models. Two regression models were created: the first was adjusted for original trial (considering that each trial enrolled populations with different risk profiles and compared different interventions), the randomly assigned intervention strategy, and baseline LDL-C. The second model was also adjusted for other baseline variables shown to be clinically meaningful for this population (age, sex, geographic region, body mass index, history of smoking, hypertension, MI, renal dysfunction, prior revascularization procedure, presence of angina, use of insulin, and heart failure). All time-to-event outcomes were censored 4 years after the 1-year assessment. Patients with 1-year LDL-C <70 mg/dl were used as the reference group when computing hazard ratios (HR) by 1-year achieved LDL-C level. The combined effect of the assigned intervention and 1-year LDL-C levels on clinical endpoints was evaluated in survival analyses. The proportionality assumption for the Cox models was assessed in all analyses using time-dependent covariates proportionality tests.

Sensitivity analyses were performed according to non-high-density lipoprotein cholesterol (non-HDL-C) levels, defined as LDL-C + triglycerides/5 (but only among patients with triglycerides <350 mg/dl where the Friedewald equation could be used). The non-HDL-C strata were defined as <100 mg/dl, between 100 and <130 mg/dl, and ≥130 mg/dl. Sensitivity analyses were also performed treating 1-year LDL-C levels as a continuous variable, without prespecified LDL-C categories. The visual inspection of the locally estimated scatterplot smoothing (LOESS) plot was used to indicate the appropriateness to model MACCE as a function of continuous 1-year LDL-C levels. A p value of 0.05 was used to determine statistical significance in all comparisons. All analyses were performed using SAS version 9.3 software (SAS Institute, Cary, North Carolina).

RESULTS

BASELINE CHARACTERISTICS. Among the 5,034 patients comprising the pooled cohort derived from the 3 trials (COURAGE, n = 766; BARI 2D, n = 2,368; FREEDOM, n = 1,900), 341 were excluded for having triglycerides >400 mg/dl, 15 were excluded for having LDL-C <20 mg/dl (at baseline or 1 year), and 628 did not have lipid measurements available. A total of 4,050 patients (80%) had valid LDL-C measurements at pre-randomization baseline and 1 year and this constitutes the study population (COURAGE, n = 637; BARI 2D, n = 2,044; FREEDOM, n = 1,369).

Pre-randomization baseline variables according to 1-year LDL-C categories are summarized in **Table 1**, together with selected 1-year variables. Mean pre-randomization baseline age for the whole cohort was 62.8 ± 8.8 years and 27.0% were female. Mean 1-year LDL-C in the whole population was 83.1 ± 29.1 mg/dl. At 1 year, 1,398 patients (34.5%) had LDL-C levels <70 mg/dl (mean LDL-C: 55.8 ± 10.3 mg/dl), 1,711 (42.2%) had LDL-C between 70 and <100 mg/dl (mean LDL-C: 83.4 ± 8.3 mg/dl), and 941 (23.2%) had LDL-C ≥100 mg/dl (mean LDL-C: 123.0 ± 25.8 mg/dl). A total of 1,348 (33.3%) patients were assigned to the OMT group, 990 (24.4%) to CABG + OMT, and 1,712 (42.3%) to PCI + OMT. **Table 2** describes LDL-C levels at pre-randomization baseline and 1 year according to the assigned intervention strategy. No difference was observed in the mean values of LDL-C attained at 1 year across the 3 intervention groups (p = 0.93).

MACCE RATES ACCORDING TO LDL-C LEVELS ACHIEVED AT 1-YEAR. The median follow-up in the pooled cohort was 3.9 years (Q1 to Q3: 3.0 to 4.0) after the 1-year assessment (a median of 4.6 [Q1 to Q3: 3.7 to 5.0] years after enrollment). **Figure 1** illustrates the Kaplan-Meier event rate curves after the 1-year assessment as compared with the referent 1-year

TABLE 1 Baseline and 1-Year Patient Characteristics According to 1-Year LDL-C Levels

	Total (N = 4,050)	LDL-C <70 (n = 1,398)	70 ≤LDL-C <100 (n = 1,711)	LDL-C ≥100 (n = 941)	p Value
Clinical trial					
BARI 2D - PCI STRATA	34.2 (1,385)	29.8 (417)	38.3 (656)	33.2 (312)	<0.0001
BARI 2D - CABG STRATA	16.3 (659)	15.8 (221)	16.7 (286)	16.2 (152)	
COURAGE	15.7 (637)	16.2 (227)	15.6 (267)	15.2 (143)	
FREEDOM	33.8 (1,369)	38.1 (533)	29.3 (502)	35.5 (334)	
Age, yrs	62.8 ± 8.8	63.9 ± 8.6	62.8 ± 8.9	61.1 ± 8.9	<0.0001
Female	27.0 (1,093)	22.8 (319)	26.7 (456)	33.8 (318)	<0.0001
Race					
White	73.3 (2,970)	76.2 (1,065)	73.8 (1,263)	68.2 (642)	<0.0001
Black	12.5 (508)	8.6 (120)	13.1 (224)	17.4 (164)	
Asian	5.4 (218)	6.7 (93)	5.5 (94)	3.3 (31)	
Other (non-White/Black/Asian)	8.7 (354)	8.6 (120)	7.6 (130)	11.1 (104)	
Hispanic ethnicity	19.6 (792)	16.6 (232)	18.8 (322)	25.3 (238)	<0.0001
Country					
United States	47.3 (1,916)	45.4 (635)	49.0 (839)	47.0 (442)	<0.0001
Canada	20.0 (811)	24.8 (347)	19.0 (325)	14.8 (139)	
Other (non-United States/Canada)	32.7 (1,323)	29.8 (416)	32.0 (547)	38.3 (360)	
Baseline BMI, kg/m^2	30.9 ± 5.7	30.8 ± 5.5	30.8 ± 5.7	31.1 ± 6.0	0.4945
1-yr BMI, kg/m^2	30.9 ± 5.8	30.6 ± 5.6	30.9 ± 5.7	31.4 ± 6.3	0.0815
Baseline smoking status					
Never	36.3 (1,468)	34.8 (486)	34.9 (597)	41.0 (385)	0.0019
Former	49.9 (2,018)	52.6 (735)	50.5 (863)	44.7 (420)	
Current	13.9 (562)	12.7 (177)	14.6 (250)	14.4 (135)	
Current smoker at 1 yr	8.7 (352)	7.6 (106)	8.7 (147)	10.6 (99)	0.0004
History of hypertension	82.8 (3,325)	83.3 (1,155)	82.6 (1,399)	82.4 (771)	0.8225
History of dyslipidemia	76.6 (3,082)	71.1 (988)	77.9 (1,325)	82.2 (769)	<0.0001
History of heart failure	12.7 (513)	13.9 (194)	11.7 (200)	12.7 (119)	0.1927
Prior MI	29.9 (1,199)	29.1 (404)	30.2 (510)	30.5 (285)	0.7336
History of PAD	16.9 (684)	16.4 (229)	16.7 (286)	18.0 (169)	0.6048
History of COPD	5.4 (219)	4.9 (69)	5.4 (93)	6.1 (57)	0.4993
History of renal dysfunction	4.1 (166)	5.2 (72)	3.0 (51)	4.6 (43)	0.0076
Prior PCI	12.5 (504)	10.4 (145)	14.2 (242)	12.4 (117)	0.0065
Prior CABG	5.2 (211)	5.1 (71)	5.6 (96)	4.7 (44)	0.5630
Angina at baseline					
No angina	15.6 (631)	16.8 (235)	15.8 (271)	13.3 (125)	0.1157
Stable, CCS I/atypical	28.6 (1,159)	28.4 (397)	28.9 (494)	28.5 (268)	
Stable, CCS II	34.0 (1,377)	35.0 (489)	33.7 (576)	33.2 (312)	
Stable, CCS III	14.5 (586)	13.4 (187)	14.0 (240)	16.9 (159)	
CCS IV or unstable	7.3 (295)	6.4 (90)	7.5 (129)	8.1 (76)	
No angina at 1 yr	75.6 (3,046)	75.3 (1,048)	77.2 (1,315)	73.0 (683)	0.1513
Diabetes treated with insulin	34.5 (1,399)	34.8 (486)	33.0 (564)	37.1 (349)	0.0995
Baseline HbA_{1c}, %	7.6 ± 1.6	7.4 ± 1.5	7.6 ± 1.6	7.9 ± 1.8	<0.0001
1-yr HbA_{1c}, %	7.2 ± 1.4	7.0 ± 1.3	7.2 ± 1.4	7.5 ± 1.6	<0.0001
Baseline eGFR, ml/min/m^2	79.0 ± 23.1	77.9 ± 23.1	79.8 ± 22.8	79.4 ± 23.6	0.0649
Baseline systolic BP, mm Hg	132.9 ± 19.8	132.4 ± 19.3	133.1 ± 19.6	133.3 ± 20.9	0.7840
1-yr systolic BP, mm Hg	129.9 ± 17.8	128.0 ± 16.7	129.9 ± 17.8	132.6 ± 18.9	<0.0001
Baseline diastolic BP, mm Hg	75.0 ± 11.2	73.8 ± 10.9	75.1 ± 11.0	76.5 ± 11.8	<0.0001
1-yr diastolic BP, mm Hg	73.4 ± 10.4	71.8 ± 9.8	73.4 ± 10.2	76.0 ± 11.1	<0.0001
Baseline LDL-C, mg/dl	98.0 ± 35.3	85.9 ± 31.7	99.9 ± 33.9	112.5 ± 36.8	<0.0001
1-yr LDL-C, mg/dl	83.1 ± 29.1	55.8 ± 10.3	83.4 ± 8.3	123.0 ± 25.8	<0.0001
Baseline HDL-C, mg/dl	40.6 ± 11.1	39.2 ± 10.7	41.1 ± 11.1	41.7 ± 11.3	<0.0001
1-yr HDL-C, mg/dl	41.7 ± 11.4	40.3 ± 11.0	41.9 ± 10.6	43.4 ± 12.9	<0.0001
Baseline triglycerides, mg/dl	161.5 ± 76.7	159.0 ± 74.6	159.8 ± 77.1	168.3 ± 78.6	0.0076
1-yr triglycerides, mg/dl	143.4 ± 69.3	137.6 ± 70.2	137.7 ± 65.4	162.5 ± 71.4	<0.0001
LVEF, %	60.8 ± 11.8	61.3 ±11.7	60.5 ± 11.9	60.6 ± 11.5	0.1144
LVEF <50%	14.3 (568)	13.7 (188)	15.1 (254)	13.6 (126)	0.4492

Continued on the next page

TABLE 1 Continued

	Total (N = 4,050)	LDL-C <70 (n = 1,398)	70 ≤LDL-C <100 (n = 1,711)	LDL-C ≥100 (n = 941)	p Value
Proximal LAD disease	26.9 (1,091)	29.5 (412)	24.4 (418)	27.7 (261)	0.0055
Presence of total occlusion	36.0 (1,455)	36.1 (504)	36.1 (617)	35.5 (334)	0.9455
Number of diseased vessels					
1	24.6 (998)	22.2 (310)	27.2 (465)	23.7 (223)	0.0056
2	30.3 (1,225)	30.9 (432)	30.6 (523)	28.7 (270)	
3	45.1 (1,826)	46.9 (655)	42.3 (723)	47.6 (448)	

Values are % (n) or mean ± SD. LDL-C levels in mg/dl.

BARI 2D = Bypass Angioplasty Revascularization Investigation 2 Diabetes; BMI = body mass index; BP = blood pressure; CABG = coronary artery bypass grafting; CCS = Canadian Cardiovascular Society; COPD = chronic obstructive pulmonary disease; COURAGE = Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation; eGFR = estimated glomerular filtration rate; FREEDOM = Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease; HbA_{1c} = glycosylated hemoglobin; HDL-C = high-density lipoprotein cholesterol; LAD = left anterior descending artery; LDL-C = low-density lipoprotein cholesterol; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PAD = peripheral arterial disease; PCI = percutaneous coronary intervention.

achieved LDL-C levels. Patients with 1-year LDL-C ≥100 mg/dl experienced higher 4-year cumulative risk of MACCE compared with those with 1-year LDL-C between 70 and <100 mg/dl and those with LDL-C <70 mg/dl (17.2% vs. 13.3% and 13.1%, respectively; p = 0.016).

In analyses adjusted for trial, intervention strategy and baseline LDL-C, when comparing with patients with 1-year LDL-C <70 mg/dl, MACCE rates were higher in patients with 1-year LDL-C ≥100 mg/dl (HR: 1.46; 95% confidence interval [CI]: 1.15 to 1.85; p = 0.002) and similar in those with 1-year LDL-C between 70 and <100 mg/dl (HR: 1.07; 95% CI: 0.86 to 1.32; p = 0.54) (**Table 3**). Similar results were found in the second multivariable model, which also included key baseline risk factors (**Table 3**). Supplemental Table 1 further depicts cumulative event rates in each 1-year LDL-C stratum.

In a sensitivity analysis, 1-year LDL-C was treated as a continuous variable. When adjusting for trial, intervention strategy, and baseline LDL-C category, the risk of MACCE increased 4% with each 10 mg/dl increase in the 1-year LDL-C at any given time over the 4-year follow-up period (HR: 1.04; 95% CI: 1.01 to 1.07; p = 0.017). Similar results were found when further adjusting for key baseline risk factors (Supplemental Table 2). In a second sensitivity analysis, the 3,894 patients with triglycerides ≤350 mg/dl (96% of the study population) were categorized according to their non-HDL-C levels and the results were similar to our main results (Supplemental Table 3).

MACCE RATES ACCORDING TO RANDOMIZED INTERVENTION STRATEGY AND LDL-C LEVELS. The **Central Illustration** shows the 4-year cumulative risk of MACCE according to achieved 1-year LDL-C and the assigned intervention strategy. Compared with OMT, CABG was associated with lower rates of MACCE, regardless of 1-year LDL-C strata (1-year LDL-C <70 mg/dl, HR: 0.42; 95% CI: 0.24 to 0.73; p = 0.002; 1-year LDL-C between 70 and <100 mg/dl, HR: 0.52; 95% CI: 0.33 to 0.84; p = 0.007; 1-year LDL-C ≥100 mg/dl, HR: 0.52; 95% CI: 0.30 to 0.92; p = 0.025). When comparing PCI with OMT, PCI patients with 1-year LDL-C <70 mg/dl experienced lower rates of MACCE (HR: 0.61; 95% CI: 0.40 to 0.91; p = 0.016), which was not observed with cholesterol levels between 70 and <100 mg/dl (HR: 1.07; 95% CI: 0.76 to 1.50; p = 0.71) or ≥100 mg/dl (HR: 0.99; 95% CI: 0.66 to 1.51; p = 0.98). When comparing CABG with PCI, CABG led to significantly lower rates of MACCE for those with 1-year LDL-C between 70 and <100 mg/dl (HR: 0.49; 95% CI: 0.31 to 0.79; p = 0.003) and 1-year LDL-C ≥100 mg/dl (HR: 0.53; 95% CI: 0.30 to 0.91; p = 0.022), whereas no statistical difference was observed in patients with 1-year LDL-C <70 mg/dl (HR: 0.69; 95% CI: 0.42 to 1.13; p = 0.141) (**Table 4**). Results were similar in a sensitivity analysis according to non-HDL-C levels (Supplemental Table 4).

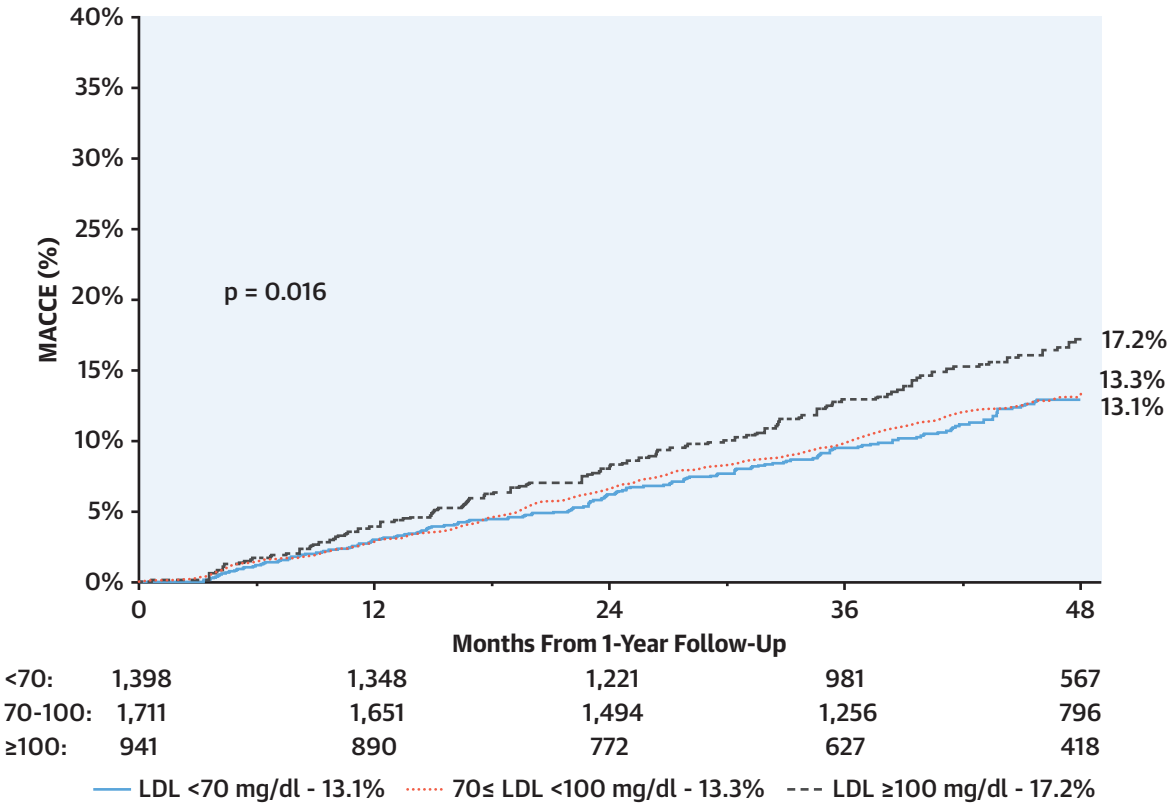
TABLE 2 LDL-C Levels at Baseline and 1 Year, According to Assigned Intervention Strategy

Cholesterol Levels, mg/dl	Total (N = 4,050)	CABG + OMT (n = 990)	OMT (n = 1,348)	PCI + OMT (n = 1,712)	p Value
Mean baseline LDL-C	98.0 ± 35.3	96.6 ± 36.5	102.2 ± 35.4	95.5 ± 34.3	<0.0001
Baseline LDL-C					<0.0001
LDL-C <70	21.3 (861)	25.3 (250)	16.2 (218)	23.0 (393)	
70 ≤LDL-C <100	36.2 (1,466)	33.6 (333)	36.6 (494)	37.3 (639)	
LDL-C ≥100	42.5 (1,723)	41.1 (407)	47.2 (636)	39.7 (680)	
Mean 1-yr LDL-C	83.1 ± 29.1	82.8 ± 32.1	83.0 ± 26.5	83.3 ± 29.3	0.9298
1-yr LDL-C					0.0042
LDL-C <70	34.5 (1,398)	36.7 (363)	31.7 (427)	35.5 (608)	
70 ≤LDL-C <100	42.2 (1,711)	39.3 (389)	46.4 (626)	40.7 (696)	
LDL-C ≥100	23.2 (941)	24.0 (238)	21.9 (295)	23.8 (408)	

Values are mean ± SD or % (n).

OMT = optimal medical therapy; other abbreviations as in **Table 1**.

FIGURE 1 Unadjusted Survival Curves, According to 1-Year LDL-C Group



Curves are shown for the 4-year rates of the composite of all-cause mortality, nonfatal myocardial infarction, and stroke. LDL-C = low-density lipoprotein cholesterol; MACCE = major adverse cardiac or cerebrovascular events (all-cause mortality, nonfatal myocardial infarction, and nonfatal stroke).

SUBSEQUENT REVASCULARIZATION RATES. In analyses adjusted for trial, intervention strategy, and baseline LDL-C, no differences in subsequent revascularization were observed when comparing patients with 1-year LDL-C between 70 and <100 mg/dl with LDL-C <70 mg/dl (HR: 1.11; 95% CI: 0.91 to 1.35; p = 0.30), whereas a nonsignificant trend was observed when comparing 1-year LDL-C ≥100 mg/dl

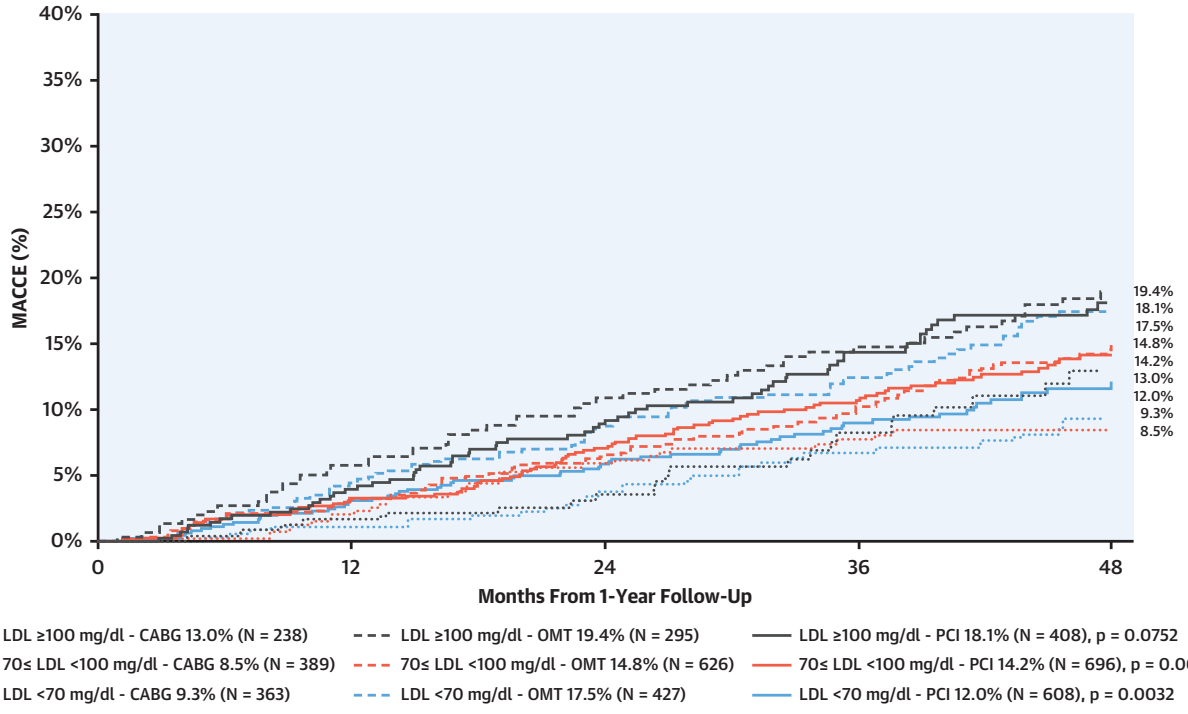
TABLE 3 HR for Clinical Endpoints According to 1-Year LDL-C Levels

	70 ≤LDL-C <100 mg/dl			LDL-C ≥100 mg/dl		
	HR	95% CI	p Value	HR	95% CI	p Value
Model adjusted for trial, intervention strategy, and baseline LDL-C*						
MACCE	1.07	0.86–1.32	0.54	1.46	1.15–1.85	0.002
Revasc	1.11	0.91–1.35	0.30	1.24	0.99–1.56	0.066
Model adjusted for trial, intervention strategy, baseline LDL-C, and other baseline prognostic factors†						
MACCE	1.10	0.89–1.36	0.40	1.52	1.19–1.93	<0.001
Revasc	1.11	0.91–1.35	0.31	1.24	0.98–1.57	0.068

*HR adjusted for trial, assigned intervention strategy, and baseline LDL-C, according to 1-year LDL-C levels (reference group: patients with 1-year LDL-C <70 mg/dl). †Fully adjusted HR, according to 1-year LDL-C levels (reference group: patients with 1-year LDL-C <70 mg/dl). This model was adjusted for trial, assigned intervention strategy, baseline LDL-C, and other key baseline variables (age, sex, geographic region, body mass index, history of smoking, hypertension, myocardial infarction, renal dysfunction, prior revascularization procedure, presence of angina, use of insulin, heart failure).

CI = confidence interval; HR = hazard ratio; MACCE = major adverse cardiac or cerebrovascular events (all-cause mortality, nonfatal myocardial infarction, and nonfatal stroke); Revasc = subsequent revascularization; other abbreviation as in Table 1.

CENTRAL ILLUSTRATION **4-Year Major Adverse Cardiac or Cerebrovascular Events Rates by 1-Year Low-Density Lipoprotein Cholesterol and Assigned Intervention Strategy**



Farkouh, M.E. et al. J Am Coll Cardiol. 2020;76(19):2197–207.

Compared with OMT, CABG was associated with lower rates of MACCE, regardless of 1-year LDL-C strata. When comparing PCI with OMT, PCI was associated with lower rates of MACCE only if 1-year LDL-C was <70 mg/dl. When comparing CABG with PCI, CABG led to significantly lower rates of MACCE for those with 1-year LDL-C between 70 and <100 mg/dl (hazard ratio: 0.49; 95% confidence interval: 0.31 to 0.79; p = 0.003) and 1-year LDL-C ≥100 mg/dl (hazard ratio: 0.53; 95% confidence interval: 0.30 to 0.91; p = 0.022), whereas no statistical difference was observed in patients with 1-year LDL-C <70 mg/dl. CABG or C = coronary artery bypass grafting; LDL-C = low-density lipoprotein cholesterol; MACCE = major adverse cardiac or cerebrovascular events (all-cause mortality, nonfatal myocardial infarction, and nonfatal stroke); OMT or O = optimal medical therapy alone; PCI or P = percutaneous coronary intervention.

with <70 mg/dl (HR: 1.24; 95% CI: 0.99 to 1.56; p = 0.066). Similar results were seen in the second multivariable model, which also included other key baseline risk factors (Figure 2, Table 3).

When compared with both OMT and PCI patients, CABG was associated with lower rates of subsequent revascularization in all 1-year LDL-C strata. There was no difference in subsequent revascularization rates observed when comparing PCI with OMT in any of the 1-year LDL-C strata (Table 4).

DISCUSSION

This pooled analysis of 3 large federally funded revascularization clinical trials of patients with stable CHD including >4,000 patients with T2DM showed that patients with LDL-C ≥100 mg/dl after 1 year following a revascularization procedure were at increased risk for MACCE. LDL-C levels have a differential influence in cardiovascular outcomes depending on the revascularization strategy. When compared with OMT alone, patients randomized to CABG had lower rates of MACCE at any 1-year LDL-C level, whereas PCI patients were only able to experience a MACCE reduction if 1-year LDL-C levels were <70 mg/dl. This reinforces the need for LDL-C control to take full advantage of the benefits of a revascularization procedure, particularly for PCI. Patients with 1-year LDL-C levels >70 mg/dl experienced lower rates of MACCE when undergoing CABG compared with PCI, whereas patients with 1-year LDL-C <70 mg/dl had similar rates of MACCE with CABG or PCI.

Our results are in accordance with the recently published 2018 American Heart Association/American College of Cardiology Guidelines on the Management

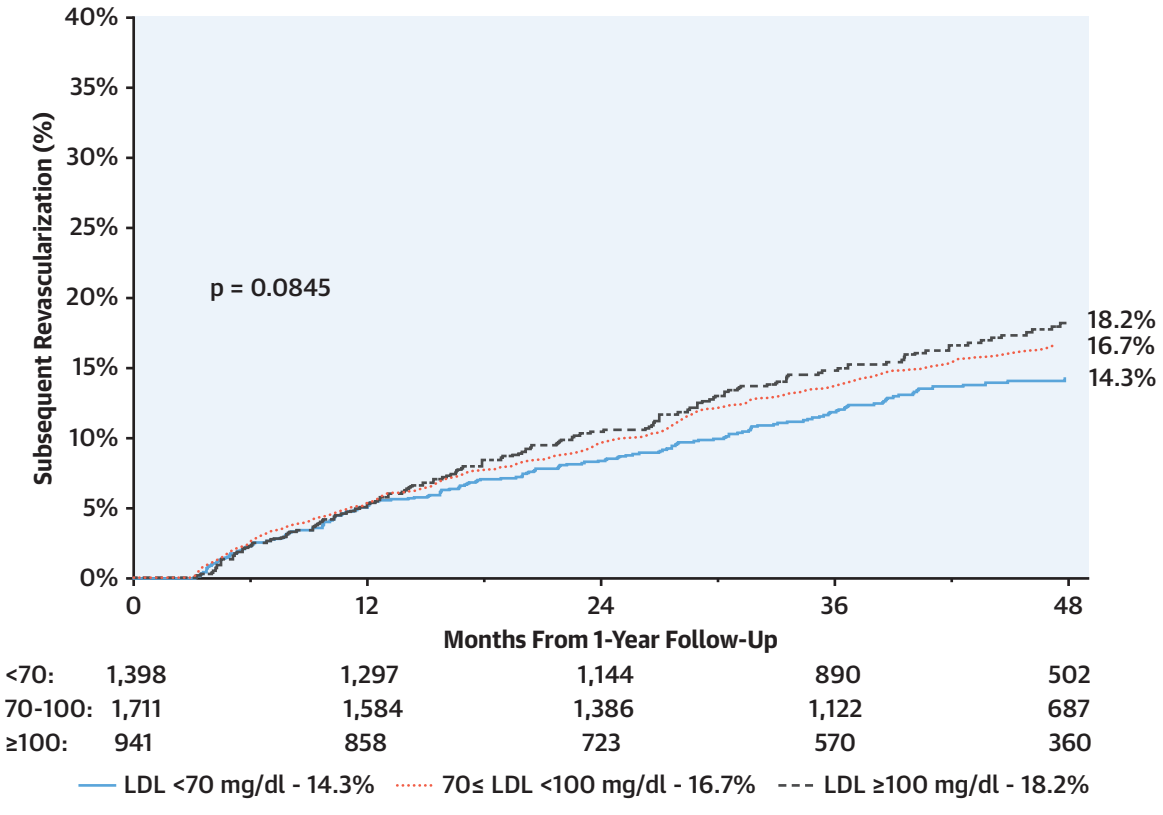
TABLE 4 Trial-Adjusted HR for MACCE and Subsequent Revascularization According to Assigned Intervention Strategy and 1-Year LDL-C Strata

	LDL-C <70 mg/dl			70 ≤LDL-C <100 mg/dl			LDL-C ≥100 mg/dl		
	HR	95% CI	p Value	HR	95% CI	p Value	HR	95% CI	p Value
MACCE									
CABG vs. OMT	0.42	0.24-0.73	0.002	0.52	0.33-0.84	0.007	0.52	0.30-0.92	0.025
PCI vs. OMT	0.61	0.40-0.91	0.016	1.07	0.76-1.50	0.71	0.99	0.66-1.51	0.98
CABG vs. PCI	0.69	0.42-1.13	0.141	0.49	0.31-0.79	0.003	0.53	0.30-0.91	0.022
Revasc									
CABG vs. OMT	0.43	0.24-0.77	0.005	0.25	0.14-0.42	<0.001	0.36	0.19-0.70	0.003
PCI vs. OMT	0.80	0.56-1.14	0.220	0.85	0.63-1.15	0.29	1.07	0.72-1.58	0.75
CABG vs. PCI	0.54	0.32-0.91	0.022	0.29	0.17-0.48	<0.001	0.34	0.18-0.63	<0.001

Abbreviations as in Tables 1 to 3.

of Blood Cholesterol (4). According to these guidelines, our analysis comprises a combination of high-risk and very-high-risk patients who should be prescribed high-intensity statin and other LDL-C-lowering therapies with a target LDL-C of at least 70 mg/dl. This is particularly important in patients who underwent revascularization with PCI, because no MACCE benefit was observed in these patients with 1-year LDL-C levels >70 mg/dl. In a previous analysis by Mancini et al. (14) with the same cohort of

FIGURE 2 Unadjusted Survival Curves, According to 1-Year LDL-C Group



Curves are shown for the 4-year rates of subsequent revascularization. Abbreviation as in Figure 1.

patients, CABG, when compared with OMT and PCI, was associated with reduced MACCE rates in patients with T2DM. In the present analysis, we extended these findings and suggest that the CABG superiority over PCI for MACCE may be only observed when LDL-C ≥70 mg/dl. Apart from the revascularization strategy, other evidence should also be considered when deciding on the optimal LDL-C goal for a specific patient, particularly in light of recently reported concerns of increased risk of hemorrhagic stroke in women with LDL-C <70 mg/dl (15), even though the absolute rates of this isolated event are extremely low and statins are associated with lower rates of other cardiovascular outcomes, such as overall stroke and peripheral artery disease (5).

It is important to note that in our study, compared with patients with 1-year LDL-C <70 mg/dl, only those with 1-year LDL-C >100 mg/dl experienced a significant increase in long-term cardiovascular risk. This observation may prompt interest in a possible heterogeneity regarding baseline (or, in our study, 1 year) lipid levels and cardiovascular benefit derived from lipid-lowering therapies. In the ODYSSEY-OUTCOMES trial, alirocumab, compared with placebo and on top of high-intensity statin therapy, led to reduced rates of cardiovascular events in the long term among patients with a recent acute coronary syndrome. This benefit seemed to be more pronounced in the subgroup of patients with baseline LDL-C levels >100 mg/dl (16). Similarly, a meta-analysis of 34 randomized trials reported significant reductions in all-cause and cardiovascular mortality associated with lipid-lowering therapy only when the baseline LDL-C was >100 mg/dl (17). Reductions in MI, coronary revascularization, and MACCE were also more pronounced in these patients (17). Taken together with our results, these studies might suggest that the threshold of 100 mg/dl of LDL-C may be a marker of coronary atherosclerotic plaque instability, which requires further investigation (18).

Previous studies have investigated the role of LDL-C lowering in the coronary revascularization setting. The LIPS (Lescol Intervention Prevention Study) showed a benefit of fluvastatin versus placebo in reducing long-term cardiovascular events among patients undergoing elective PCI (19). More recently, an analysis of the J-DESsERT (Japan Drug-Eluting Stents Evaluation: a Randomized Trial) demonstrated that PCI patients who were able to achieve OMT targets at the time of the procedure had lower rates of 24-month target vessel failure (7% vs. 10%; p = 0.03) (20). In a post hoc analysis of the SYNTAX (Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery) trial, the use of statin therapy, compared with no statins, was related to lower 5-year rates of MACCE, following both the CABG (HR: 0.32; 95% CI: 0.23 to 0.45; p < 0.001) and PCI arms (HR: 0.51; 95% CI: 0.36 to 0.72; p < 0.001) (21). Reducing LDL-C after a revascularization procedure was associated with lower rates of cardiovascular events in all these reports, which is consistent with our observations.

Other evidence also supports LDL-C reduction specifically in the post-CABG setting. In the POST CABG (Post Coronary Artery Bypass Graft) trial, reducing LDL-C to levels <100 mg/dl, compared with usual care, led to a reduction in atherosclerosis progression in saphenous-vein grafts (27% vs. 39%; p < 0.001) and in repeat revascularization (6.5% vs. 9.2%; p = 0.03), during 4.3 years of post-operative follow-up (22,23). After a follow-up of 7.5 years, patients assigned to the lower LDL-C group experienced a reduction in the composite of cardiovascular death, nonfatal MI, stroke, and repeat revascularization (30.6% vs. 40.2%; p = 0.001) (24). A post hoc analysis of the CASCADE (Clopidogrel after Surgery for Coronary Artery Disease) trial showed that graft patency at 12 months post-CABG was higher in patients with 1-year LDL-C <100 mg/dl, compared with patients with 1-year LDL-C >100 mg/dl (96.5% vs. 83.3%; p = 0.03) (25). According to an American Heart Association Scientific Statement, these analyses and additional evidence (26,27) justify the recommendation for routine prescription of statin therapy in post-CABG patients (28). CABG is capable of bypassing multiple lesions, whereas PCI is a focal intervention, targeted to a specific lesion (29). Although this rationale may justify the differential effect of LDL-C control in CABG versus PCI patients, our results do not imply or support a less stringent LDL-C control in CABG patients because LDL-C control is associated with lower rates of cardiovascular events in the overall population with T2DM and CHD (5), including those submitted to a coronary revascularization procedure.

STUDY LIMITATIONS. This is a pooled analysis of 3 large clinical trials, designed to evaluate the effects of LDL-C reduction in a specific group of patients (patients with T2DM assigned to an intervention strategy) and not to define LDL-C thresholds in the general population. Although patients were randomized to the revascularization strategy, they were not specifically randomized to CABG or PCI (except in the FREEDOM trial) and they were not randomized either to different LDL-C targets. Therefore, additional confounders may influence the association between cardiovascular outcomes and both the choice of

revascularization procedure and the LDL-C control rate. This was partially mitigated by the multivariable analysis, but data on an important variable, adherence to prescribed therapy, are not available. The therapeutic interventions to reduce LDL-C during the first year of follow-up (lifestyle changes, medications, and doses) were not systematically analyzed. In addition, events from the first year were excluded from this report and the occurrence of immortal time bias must be considered. Finally, medical technology has evolved in the last decade. Advances in PCI, such as newer generations of drug-eluting stents, intracoronary imaging and invasive physiologic guidance, and new medical therapy for T2DM (e.g., sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide-1 receptor agonists) may likewise influence these findings, including the potential relative mitigation of the beneficial effects of aggressive lipid lowering.

CONCLUSIONS

This individual patient-level pooled analysis of 3 large randomized trials evaluating coronary revascularization in patients with T2DM clarifies the importance of LDL-C control in the first year post-procedure. Patients with LDL-C ≥100 mg/dl at 1 year had higher rates of MACCE and subsequent revascularization, when compared with patients with LDL-C <70 mg/dl. Additionally, LDL-C-lowering seems to be particularly important in patients with T2DM undergoing PCI, because when compared with OMT alone, MACCE reductions in this group were observed only with 1-year LDL-C levels <70 mg/dl. Thus, optimal LDL-C control may be pivotal to achieving optimal outcomes following PCI, which warrants further studies. By contrast, CABG was superior to OMT regardless of the LDL-C level attained and superior to PCI if 1-year LDL-C levels were >70 mg/dl.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients with T2DM undergoing coronary revascularization, control of blood levels of LDL-C improves prognosis, particularly among those undergoing PCI.

TRANSLATIONAL OUTLOOK: Additional studies are needed to compare various strategies for lowering LDL-C levels in patients with T2DM undergoing revascularization.

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KEY WORDS coronary artery disease, coronary revascularization, diabetes, lipids

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