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Low-Density Lipoprotein Cholesterol and Adverse Cardiovascular Events After Percutaneous Coronary Intervention

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ABSTRACT

BACKGROUND After percutaneous coronary interventions (PCIs), patients remain at high risk of developing late cardiovascular events. Although controlling low-density lipoprotein cholesterol (LDL-C) may improve outcomes after PCI, practice guidelines do not have specific recommendations on LDL-C management for this subgroup.

OBJECTIVES The purpose of this study was to evaluate LDL-C testing and levels after PCIs, and to assess the association between LDL-C and longer-term cardiovascular events after PCIs.

METHODS All patients who received their first PCI from October 1, 2011, to September 30, 2014, in Ontario, Canada, were considered for inclusion. Patients who had LDL-C measurement within 6 months after PCI were categorized as: <70 mg/dl, 70 to <100 mg/dl, and ≥100 mg/dl. The primary composite outcome was cardiovascular death, myocardial infarction, coronary revascularization, and stroke through December 31, 2016.

RESULTS Among 47,884 included patients, 52% had LDL-C measured within 6 months of PCI and 57% had LDL-C <70 mg/dl. After a median 3.2 years, the rates of cardiovascular events were 55.2/1,000 person-years for the LDL-C <70 mg/dl group, 60.3/1,000 person-years for 70 to <100 mg/dl, and 94.0/1,000 person-years for ≥100 mg/dl. The adjusted subdistribution hazard ratios for cardiovascular events were 1.17 (95% confidence interval: 1.09 to 1.26) for LDL-C of 70 to <100 mg/dl, and 1.78 (95% confidence interval: 1.64 to 1.94) for LDL-C ≥100 mg/dl when compared with LDL-C <70 mg/dl.

CONCLUSIONS One in 2 patients had LDL-C measured within 6 months after PCI, and only 57% had LDL-C <70 mg/dl. Higher levels of LDL-C were associated with an increased incidence of late cardiovascular events. Improved cholesterol management after PCI should be considered to improve the outcomes of these patients.
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Percutaneous coronary intervention (PCI) is the most utilized cardiac procedure to treat patients with coronary artery disease (CAD). Each year, more than one-half million PCI procedures are performed in the United States (1). Despite improvements in interventional techniques and advancements in adjunctive medical therapy, patients who have undergone PCIs continue to be at high risk of developing cardiovascular events at long-term. A recent report from the National Cardiovascular Data Registry CathPCI registry estimated that 1 in 6 patients had a major adverse cardiovascular event within 1 year of the initial procedure (2). Although the majority of research efforts have focused on improving the procedural or peri-procedural aspects of PCI, a gap in knowledge continues to exist regarding the best management to optimize patient outcomes after PCI at longer-term.

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An area of potential improvement could be the optimization of cholesterol management. Studies have shown a consistent association between lower low-density lipoprotein cholesterol (LDL-C) and better outcomes in patients with CAD (3,4). However, in clinical trials focusing on revascularization and optimal medical therapy for CAD patients, optimization of LDL-C was poor despite feedback mechanisms and tracking programs employed by investigators and providers to enhance attainment of lipid goals (5). Observational studies have also demonstrated suboptimal LDL-C control, poor adherence to statin therapy, and underutilization of high-intensity statins in high-risk CAD patients despite strong endorsement from practice guidelines (6–8). For patients who have undergone PCIs, it is conceivable that they may even be less inclined to manage their cholesterol profile aggressively because they may be free of symptoms and falsely assured that their future risk is low because their lesions are fixed. Practice guidelines provide no formal recommendations regarding when to check cholesterol profiles or what are the optimal targets of LDL-C after PCIs (9–11). Accordingly, we undertook a population-based study to determine LDL-C assessment and LDL-C levels after PCI procedures in a real-world setting. We also examined the relationship between post-PCI LDL-C and subsequent cardiovascular events.

METHODS

DATA SOURCES. The CorHealth Ontario clinical cardiac registry prospectively collects clinical and procedural characteristics on all patients undergoing invasive cardiac procedures in Ontario, Canada, including PCI procedures across 19 regional cardiac centers. Ontario is the most populous province in Canada, with more than 14.6 million residents. This clinical database was linked to provincial laboratory and administrative databases using unique encoded identifiers and analyzed at ICES (formerly known as the Institute for Clinical Evaluative Sciences) (12). ICES is an independent, nonprofit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze health care and demographic data, without consent, for health system evaluation and improvement. The linked databases included: 1) the Ontario Laboratory Information System for laboratory data, which provides information on laboratory data such as cholesterol testing and values in the province; 2) the Registered Persons Database for date of death; 3) Office of the Registrar General for identifying cardiovascular death; 4) the Canadian Institute for Health Information Discharge Abstract Database to capture pre-existing comorbidities and hospitalizations; 5) Statistics Canada census data to assess neighborhood income and rural residence; and 6) Ontario Drug Benefit Database which provides prescription medication use for all patients over the age of 65 years.

STUDY COHORT. Our primary cohort included all Ontario residents undergoing PCI procedures between October 1, 2011, and September 30, 2014. We excluded patients with prior coronary revascularization to include only the patients' first PCI procedure. We then excluded patients with severe comorbid conditions, in whom life expectancy might be limited, or who would have generally been excluded from clinical trials of cholesterol-lowering therapy, such as severe left ventricular dysfunction (left ventricular ejection fraction <20%), severe chronic kidney

ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

CI = confidence interval

LDL-C = low-density lipoprotein cholesterol

MACE = major adverse cardiovascular events

PCI = percutaneous coronary intervention

PCSK9 = proprotein convertase subtilisin/kexin type 9

sHR = subdistribution hazard ratio

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC* author instructions page.

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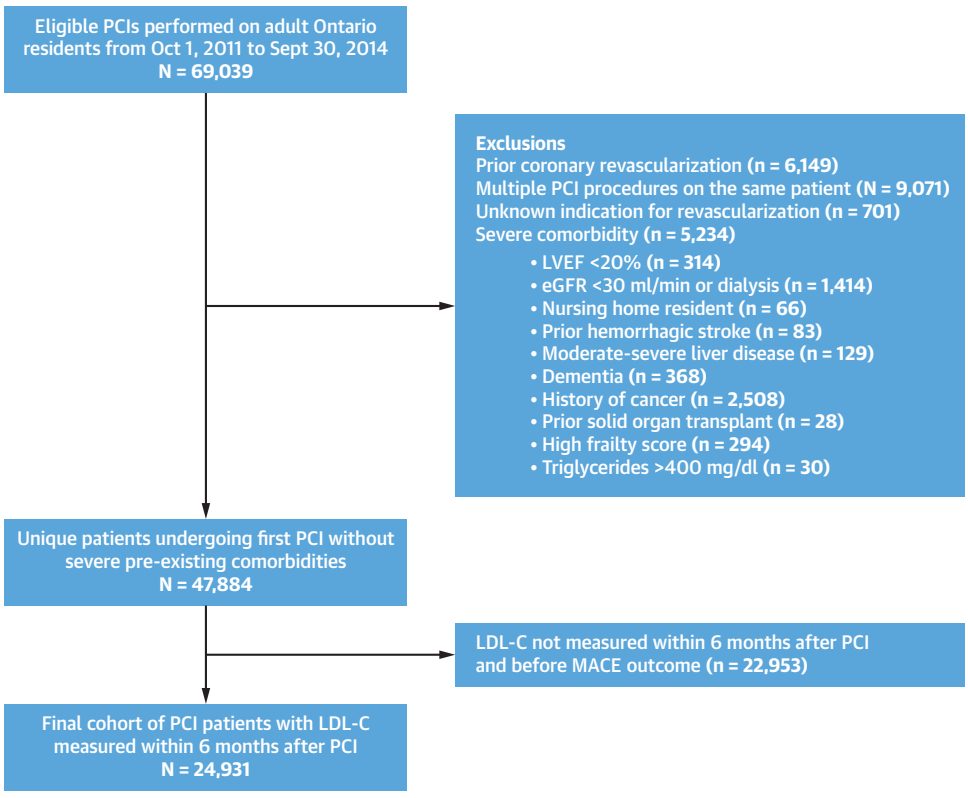
FIGURE 1 Cohort Creation



eGFR = estimated glomerular filtration rate; LDL-C = low-density lipoprotein cholesterol; LVEF = left ventricular ejection fraction; MACE = major adverse cardiovascular events; PCI = percutaneous coronary intervention.

disease defined by an estimated glomerular filtration rate <30 ml/min/1.73 m^2, prior hemorrhagic stroke, moderate-severe liver disease, dementia, cancer history, solid organ transplant recipients, severe frailty (13), and residents of long-term care facilities. Patients with severe hypertriglyceridemia (>400 mg/dl) were also excluded because of the potential inaccuracy of reported LDL-C values (14).

LDL-C MEASUREMENT AFTER PCI. Our main exposure variable was the first LDL-C measurement after PCI, defined as the first available value within 6 months post-procedure. We did not consider cholesterol values if they were obtained on the same day as a cardiovascular event because they were likely obtained secondary to the outcome. No protocols exist in Ontario for post-PCI LDL-C surveillance and initiation of statin therapy. We therefore chose a 6-month period to assess cholesterol measurement based on prior reports showing that PCI patients are evaluated by their specialists and had functional testing in this period (15). We categorized patients into 3 groups based on LDL-C (<70, 70 to <100, and ≥100 mg/dl) in accordance with practice guidelines and clinical studies (16,17).

OUTCOMES OF INTEREST. Our primary outcome was major adverse cardiovascular events (MACE), defined as a composite of cardiovascular death, hospitalization for myocardial infarction, stroke (ischemic or hemorrhagic), or coronary revascularization (PCI or bypass surgery). Assessment of outcomes began at the date of LDL-C measurement for each patient. Secondary outcomes of interest included the first occurrence of each component of our primary outcome. We used validated algorithms to ascertain hospitalizations from the Canadian Institute for Health Information Discharge Abstract Database and cause-specific mortality from the Office of the Registrar General Database until December 31, 2016 (12).

STATISTICAL ANALYSIS. Demographic and clinical characteristics were compared across categories of LDL-C using chi-square tests for categorical variables

TABLE 1 Baseline Characteristics

	All Patients (N = 24,931)	LDL-C Within 6 Months After PCI			p Value
		<70 mg/dl (n = 14,293)	70 to <100 mg/dl (n = 6,880)	≥100 mg/dl (n = 3,758)	
Demographics					
Age, yrs	63 (55–72)	64 (56–73)	63 (55–71)	60 (53–69)	<0.01
Female	6,820 (27.4)	3,623 (25.3)	2,064 (30.0)	1,133 (30.1)	<0.01
Cardiovascular comorbidities					
Previous myocardial infarction	9,530 (38.2)	5,894 (41.2)	2,547 (37.0)	1,089 (29.0)	<0.01
Heart failure	1,445 (5.8)	922 (6.5)	351 (5.1)	172 (4.6)	<0.01
Left ventricular ejection fraction*					
20%–34%	547 (2.2)	320 (2.2)	142 (2.1)	85 (2.3)	<0.01
35%–49%	1,519 (6.1)	858 (6.0)	429 (6.2)	232 (6.2)	
≥50%	6,319 (25.3)	3,593 (25.1)	1,890 (27.5)	836 (22.2)	
Atrial fibrillation/flutter	1,067 (4.3)	673 (4.7)	271 (3.9)	123 (3.3)	<0.01
Peripheral vascular disease	1,096 (4.4)	652 (4.6)	302 (4.4)	142 (3.8)	0.11
Cerebrovascular disease	1,262 (5.1)	750 (5.2)	340 (4.9)	172 (4.6)	0.22
Hypertension	15,774 (63.3)	9,415 (65.9)	4,269 (62.0)	2,090 (55.6)	<0.01
Noncardiovascular comorbidities					
Diabetes	6,530 (26.2)	4,363 (30.5)	1,499 (21.8)	668 (17.8)	<0.01
Active smoker*	6,392 (25.6)	3,299 (23.1)	1,933 (28.1)	1,160 (30.9)	<0.01
Chronic obstructive pulmonary disease	1,563 (6.3)	920 (6.4)	434 (6.3)	209 (5.6)	0.14
Hyperlipidemia	14,729 (59.1)	8,389 (58.7)	4,312 (62.7)	2,028 (54.0)	<0.01
Frailty score	0.94 [0.91–0.96]	1.02 [0.99–1.05]	0.87 [0.83–0.91]	0.75 [0.69–0.80]	<0.01
Procedural characteristics					
Index procedure indication					
Acute coronary syndrome	15,587 (62.5)	9,052 (63.3)	4,021 (58.4)	2,514 (66.9)	<0.01
Stable coronary artery disease	9,344 (37.5)	5,241 (36.7)	2,859 (41.6)	1,244 (33.1)	
Drug-eluting stent implanted	15,813 (63.4)	9,221 (64.5)	4,364 (63.4)	2,228 (59.3)	<0.01
Number of stents implanted					
1	15,263 (61.2)	8,804 (61.6)	4,157 (60.4)	2,302 (61.3)	0.44
2	6,447 (25.9)	3,647 (25.5)	1,812 (26.3)	988 (26.3)	
≥3	3,221 (12.9)	1,842 (12.9)	911 (13.2)	468 (12.5)	
Laboratory measurements					
Serum creatinine, mmol/l	81 (69–95)	81 (70–96)	80 (69–94)	80 (69–94)	<0.01
Time from PCI to serum cholesterol measurement, days	45 (18–88)	49 (24–89)	46 (17–91)	16 (1–17)	<0.01
Cholesterol-lowering therapy†					
Statin therapy					
Any statin	8,242 (77.6)	5,681 (87.2)	2,119 (75.3)	442 (34.1)	<0.01
Low intensity	219 (2.1)	79 (1.2)	77 (2.7)	63 (4.9)	
Moderate intensity	2,880 (27.1)	1,784 (27.4)	891 (31.7)	205 (15.8)	
High intensity	5,143 (48.4)	3,818 (58.6)	1,151 (40.9)	174 (13.4)	
Ezetimibe	707 (6.7)	406 (6.2)	190 (6.8)	111 (8.6)	<0.01
Statin therapy plus ezetimibe	8,406 (79.1)	5,720 (87.8)	2,175 (77.4)	511 (39.4)	<0.01

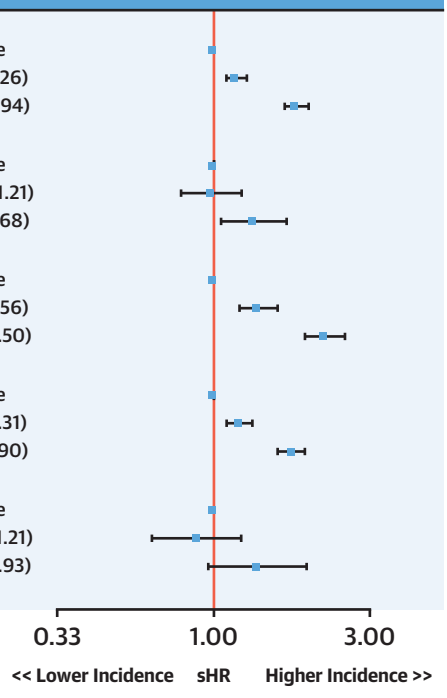
Values are median (interquartile range), n (%), or mean [95% confidence interval]. A full list of baseline characteristics is available in Supplemental Table 1. *Smoking history was missing in 3.9% of the cohort. †Among 10,622 patients over the age of 65 years with baseline medication data in the 90 days prior to LDL-C measurement. Statin intensity was defined in accordance with AHA/ACC Guidelines (9).

IQR = interquartile range; LDL-C = low-density lipoprotein cholesterol; PCI = percutaneous coronary intervention.

and the Kruskal-Wallis test for continuous variables. The association between LDL-C on the cumulative incidence function of each outcome was estimated using a Fine and Gray proportional subdistribution hazards model accounting for the competing risk of noncardiovascular death (18). Models were adjusted for baseline sociodemographic characteristics (age, sex, rural residence, and quintiles of neighborhood income), pre-existing comorbid conditions (myocardial infarction, heart failure, atrial fibrillation, peripheral vascular disease, cerebrovascular disease, diabetes, smoking status, and hypertension), disease severity indexes (frailty score and Charlson comorbidity index), and procedural characteristics (indication for revascularization, drug-eluting stent usage, number of disease epicardial coronary vessels, and

FIGURE 2 The Association Between MACE and Categories of LDL-C After Percutaneous Coronary Intervention

Outcome	LDL-C within 6 Months After PCI	Rate (95% CI) per 1,000 pyrs	Adjusted sHR (95% CI)
Major Adverse Cardiovascular Events	<70 mg/dl	55.2 (53.0-57.4)	Reference
	70 to <100 mg/dl	60.3 (57.1-63.7)	1.17 (1.09-1.26)
	≥100 mg/dl	94.0 (88.3-100.1)	1.78 (1.64-1.94)
Cardiovascular Death	<70 mg/dl	7.7 (7.0-8.5)	Reference
	70 to <100 mg/dl	6.5 (5.6-7.6)	0.99 (0.80-1.21)
	≥100 mg/dl	8.2 (6.8-10.0)	1.33 (1.05-1.68)
Myocardial Infarction	<70 mg/dl	14.8 (13.7-15.9)	Reference
	70 to <100 mg/dl	17.6 (16.0-19.4)	1.37 (1.20-1.56)
	≥100 mg/dl	29.2 (26.2-32.4)	2.18 (1.89-2.50)
Coronary Revascularization	<70 mg/dl	41.0 (39.2-42.9)	Reference
	70 to <100 mg/dl	46.8 (44.0-49.8)	1.20 (1.10-1.31)
	≥100 mg/dl	70.9 (66.0-76.1)	1.73 (1.57-1.90)
Stroke	<70 mg/dl	3.5 (3.0-4.0)	Reference
	70 to <100 mg/dl	3.0 (2.3-3.7)	0.89 (0.65-1.21)
	≥100 mg/dl	3.9 (2.9-5.1)	1.36 (0.97-1.93)



Subdistribution hazard ratios account for the competing risk of noncardiovascular death and are adjusted for baseline predictors detailed in the Methods section. CI = confidence interval; LDL-C = low-density lipoprotein cholesterol; PCI = percutaneous coronary intervention; pyrs = person-years; sHR = subdistribution hazard ratio.

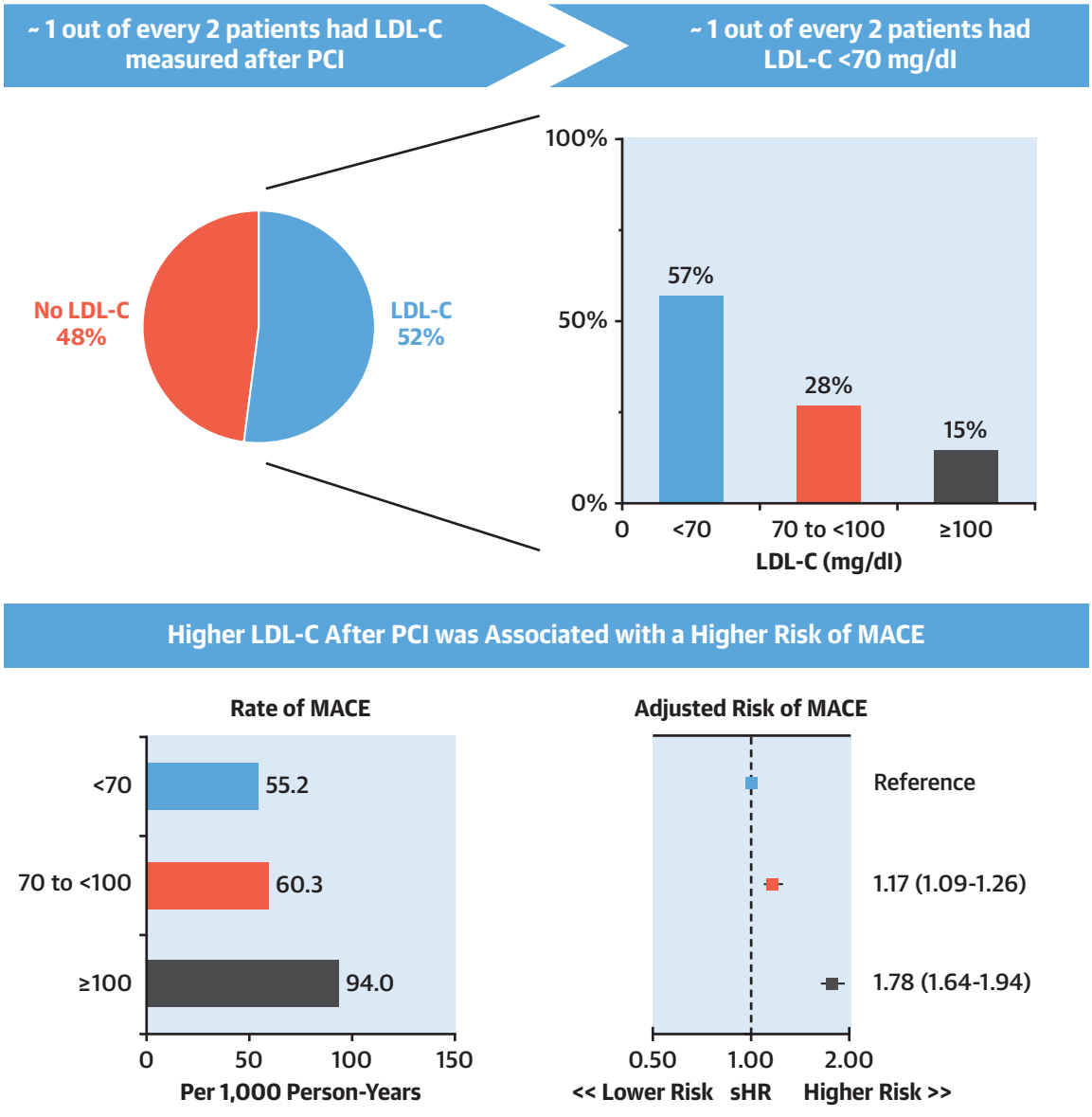
baseline serum creatinine). Effect estimates were reported as subdistribution hazard ratios (sHRs) along with 95% confidence intervals (CIs).

We performed a series of additional analyses to test the robustness of our findings. First, we performed a subgroup analysis to test for interactions between categories of LDL-C at 6 months and indications for initial PCI (acute coronary syndromes [ACS] vs. stable CAD), age (<65 and ≥65 years), and statin use in patients over the age of 65 years. We then assessed the relationship between LDL-C and MACE across the spectrum of LDL-C values without pre-specified LDL-C categories. To do so, we modeled LDL-C as continuous variable in the regression analysis using restricted cubic splines with 5 knots. For each patient in the sample, we estimated the cumulative incidence of MACE at 3 years using the regression equation for each observed value of post-PCI LDL-C ranging up to 200 mg/dl. The average incidence of MACE at 3 years for each LDL-C value was computed. We generated 95% CI using 100 bootstrap resamples. Finally, we performed a sensitivity analysis to test the association between LDL-C measured earlier after PCI (within 3 months rather than 6 months) and our primary outcome. Statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, North Carolina). A 2-sided p value of <0.05 was considered statistically significant. Data usage in this project was authorized under section 45 of Ontario's Personal Health Information Protection Act, and therefore does not require review by a Research Ethics Board.

RESULTS

STUDY COHORT. There were 69,039 eligible PCIs performed on Ontario residents between October 1, 2011, and September 30, 2014. After applying exclusions, there were 47,884 unique patients who had undergone their first PCI procedure during the study period who did not have severe comorbidities and did not reside in a nursing home. In these eligible patients, 24,931 (52%) patients had an LDL-C measurement within 6 months after PCI and constituted the study cohort (Figure 1).

CENTRAL ILLUSTRATION **Long-Term Risk of Major Adverse Cardiovascular Events in Patients Undergoing Percutaneous Coronary Intervention Who Have Low-Density Lipoprotein Cholesterol Assessment Within 6 Months After Percutaneous Coronary Intervention**



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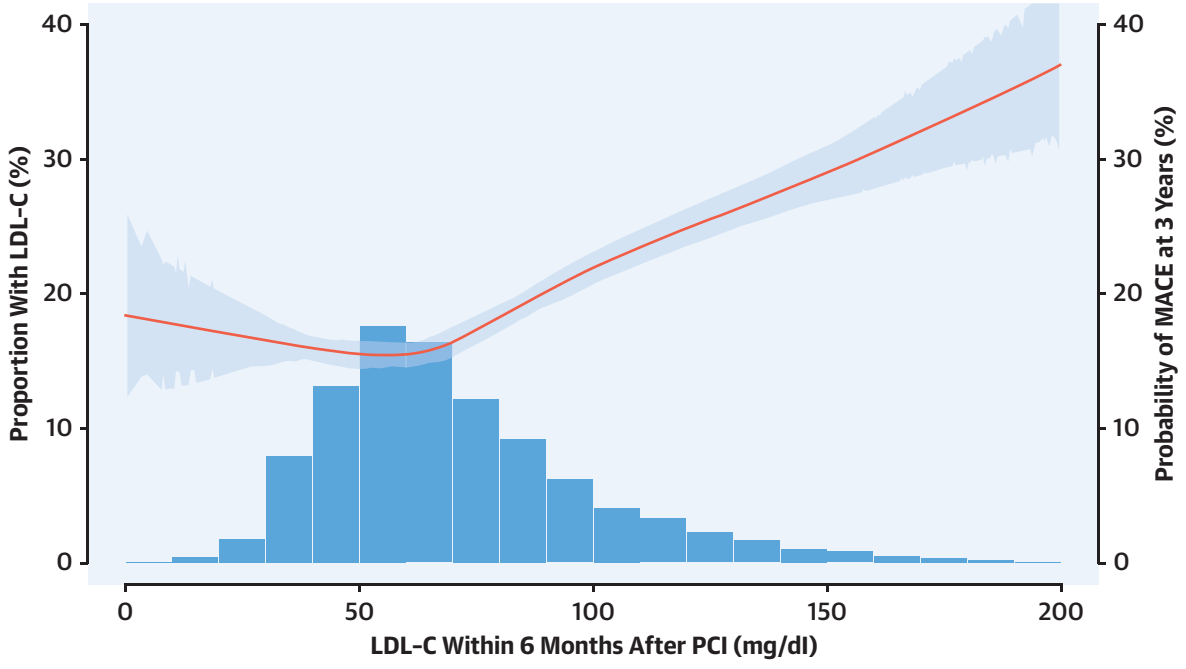
In a population-based cohort of post-PCI patients in Ontario, Canada, 52% had an LDL-C measurement within 6 months after PCI and 57% had an LDL-C <70 mg/dl. After adjustment and a median 3.2 years of follow-up, progressively higher levels of LDL-C were associated with a higher incidence of late MACE. LDL-C = low-density lipoprotein cholesterol; MACE = major adverse cardiovascular events; PCI = percutaneous coronary intervention; sHR = subdistribution hazard ratio.

BASELINE CHARACTERISTICS OF PCI PATIENTS WITH LDL-C MEASUREMENTS. The median age of the study cohort was 63 years, 27% were women, and 62% had an ACS at the time of their index PCI (Table 1, Supplemental Table 1). The median time to LDL-C measurement was 45 days (interquartile range: 18 to 88 days) and the median LDL-C value was 65 mg/dl (interquartile range: 51 to 85 mg/dl).

There were 14,293 (57%) patients with LDL-C <70 mg/dl, 6,880 (28%) with LDL-C 70 to <100 mg/dl, and 3,758 (15%) with LDL-C ≥100 mg/dl. Patients with LDL-C <70 mg/dl were significantly older (64 years vs.

FIGURE 3 The Association Between MACE at 3 Years and LDL-C After Percutaneous Coronary Intervention



The nonlinear relationship for LDL-C and MACE at 3 years **(red line)** is modeled along with 95% confidence intervals **(shaded light blue)**. The association is overlaid on a histogram that depicts the frequency of LDL-C values measured within 6 months after PCI in the cohort. Abbreviations as in Figure 1.

60 years) and had higher rates of cardiovascular comorbidities such as prior myocardial infarction (41% vs. 29%), hypertension (66% vs. 56%), or diabetes (30% vs. 18%) compared with patients with an LDL-C ≥100 mg/dl.

Prescription medication data were available in the 10,622 patients older than 65 years and eligible for the Ontario drug benefit plan. Utilization of statins differed substantially across LDL-C categories. Statins were prescribed in 87% of patients with LDL-C <70 mg/dl, 75% with LDL-C 70 to <100 mg/dl, and 34% with LDL-C ≥100 mg/dl. Among patients who were prescribed statins, the use of high-intensity statin therapy at 59%, 41%, and 13% also differed substantially across the LDL-C groups ($p < 0.01$). Ezetimibe was prescribed in 6% of patients with LDL-C <70 mg/dl, 7% with LDL-C 70 to <100 mg/dl, and 9% with LDL-C ≥100 mg/dl (**Table 1**) ($p < 0.01$). Similar trends of underutilization across categories of LDL-C were seen for other evidence-based cardiac medications such as antiplatelets, renin angiotensin system inhibitors, and beta-blockers. After 3 months, the rates of statin use were lowest in patients with LDL-C ≥100 mg/dl and the difference in statin utilization was greater than the difference in other cardiac medications (Supplemental Table 1).

ASSOCIATION BETWEEN LDL-C CATEGORIES AND MACE AFTER PCI. After a median 3.17 years of follow-up, 4,660 (18.7%) patients experienced a MACE. The rates of MACE increased from 55.2/1,000 person-years for patients with LDL-C <70 mg/dl to 60.3/1,000 person-years for LDL-C 70 to <100 mg/dl to 94.0/1,000 person-years for LDL-C ≥100 mg/dl (Supplemental Table 2). Compared with the LDL-C <70 mg/dl group, the adjusted sHRs for MACE were 1.17 (95% CI: 1.09 to 1.26) for LDL-C of 70 to <100 mg/dl and 1.78 (95% CI: 1.64 to 1.94) for LDL-C ≥100 mg/dl (**Figure 2, Central Illustration**).

A similar trend of progressively higher event rates in patients with higher LDL-C was also observed for each individual component of the MACE outcome. The LDL-C ≥100 mg/dl group had consistently higher adjusted sHRs compared with the LDL-C <70 mg/dl for cardiovascular death (1.33, 95% CI: 1.05 to 1.68), myocardial infarction (2.18, 95% CI: 1.89 to 2.50), coronary revascularization (1.73, 95% CI: 1.57 to 1.90), and stroke (1.36, 95% CI: 0.97 to 1.93).

ASSOCIATION OF MACE WITH LDL-C MODELED AS A CONTINUOUS VARIABLE AFTER PCI. Figure 3 shows the distribution of LDL-C after PCI and the relationship between the cumulative incidence of MACE at 3 years and post-PCI LDL-C. The probability of MACE at

3 years increased with higher post-PCI LDL-C. Although the overall relationship was nonlinear ($p < 0.01$ for nonlinearity), between 70 and 200 mg/dl the association appeared linear, whereas for LDL-C lower than 70 mg/dl, the association appeared attenuated. Furthermore, in the region between 70 and 200 mg/dl, assuming a linear relationship, every 10 mg/dl increase in LDL-C after PCI was associated with approximately a 1.6% higher incidence of MACE at 3 years.

SUBGROUP ANALYSIS. The association between categories of LDL-C and MACE was modified by the indication for revascularization (p for interaction <0.01). The adjusted incidence of MACE associated with higher LDL-C was larger for patients presenting with an ACS compared with patients presenting with stable CAD. For instance, when LDL-C was ≥100 mg/dl, the adjusted sHRs were 1.93 (95% CI: 1.74 to 2.14) in patients with ACS and 1.39 (95% CI: 1.19 to 1.61) for patients with stable CAD (**Table 2**, Supplemental Table 3). The association between LDL-C and MACE was not modified by baseline age above and below 65 years ($p = 0.06$) or statin use in patients over the age of 65 years ($p = 0.89$).

SENSITIVITY ANALYSES. In the 22,953 eligible patients who were excluded because they did not have an LDL-C measured within 6 months after PCI, only 5,654 (25%) had LDL-C checked in the 3 months before their PCI procedure. Among these patients, 1,718 (30%) had LDL-C <70 mg/dl, 1,603 (28%) LDL-C 70 to <100 mg/dl, and 2,333 (42%) LDL-C ≥100 mg/dl.

We also determined the relationship between LDL-C and MACE when we used a shorter 3-month interval for LDL-C assessment after PCI instead of a 6-month interval. The relationship for LDL-C within 3 months after PCI remained similar to our main analysis. Compared with an LDL-C <70 mg/dl, the adjusted sHRs for MACE were 1.18 (95% CI: 1.08 to 1.28) for LDL-C of 70 to <100 mg/dl and 1.79 (95% CI: 1.63 to 1.96) for LDL-C ≥100 mg/dl measured within 3 months after PCI.

TABLE 2 Subgroup Analysis for Major Adverse Cardiovascular Events

	LDL-C Within 6 Months After PCI			
	<70 mg/dl (n = 14,293)	70 to <100 mg/dl (n = 6,880)	≥100 mg/dl (n = 3,758)	p Value for Interaction
Acute coronary syndromes	Reference	1.25 (1.14–1.37)	1.93 (1.74–2.14)	<0.01
Stable coronary artery disease		1.07 (0.95–1.21)	1.39 (1.19–1.61)	
Age >65 yrs	Reference	1.07 (0.96–1.19)	1.66 (1.46–1.89)	0.06
Age ≤65 yrs		1.27 (1.15–1.41)	1.85 (1.65–2.06)	
Statin user*	Reference	1.00 (0.88–1.14)	1.35 (1.09–1.67)	0.89
Nonstatin user		1.05 (0.84–1.30)	1.36 (1.10–1.68)	

Values are adjusted subdistribution hazard ratios (95% confidence interval). *Among patients >65 years of age with prescription medication data.

LDL-C = low-density lipoprotein cholesterol; PCI = percutaneous coronary intervention.

DISCUSSION

In this population-based cohort analysis of patients undergoing initial PCI, we found that only about one-half of all patients had an LDL-C measurement within 6 months of the procedure. Among those tested, 57% had optimal LDL-C <70 mg/dl. Patients with higher LDL-C after PCI had a substantially higher incidence of subsequent cardiovascular events. In fact, patients who had LDL ≥100 mg/dl experienced a higher incidence of cardiovascular death, myocardial infarction, and coronary revascularization. Our findings suggest that improved cholesterol management after PCI, which could include routinely checking LDL-C levels, and increased use of statin therapy, may lead to improved patient outcomes.

CHOLESTEROL SURVEILLANCE AND GOAL ATTAINMENT AFTER PCI. No recent studies had evaluated the level of cholesterol control after an index PCI procedure. Observational studies focusing on CAD patients have shown suboptimal control of LDL-C in clinical practice (7,8,19–21). For instance, in a cross-sectional study of high-risk CAD patients identified from electronic medical records, administrative claims, and national survey databases in the United States, up to 80% of patients had LDL-C levels >70 mg/dl on statin therapy (20). The control of LDL-C in patients with stable CAD and shortly after hospitalization for ACS was no better in a study that evaluated 18 countries in Asia, Europe, and the Middle East. In this cohort, 63% of patients had prior PCI procedures. More than 80% of patients with stable CAD and nearly 70% of patients with recent ACS had LDL-C levels >70 mg/dl, and high-intensity statin therapy was underutilized (7).

The results of our study are consistent with these prior reports (7,20). Control of LDL-C specifically after PCI procedures is suboptimal, with 43% of patients having a level >70 mg/dl. Even more concerning, our study is the first to highlight that many patients do not have any LDL-C measurement after PCI. Furthermore, despite guideline recommendations for high-intensity statin therapy in patients with established CAD (16,22), in our cohort of patients older than 65 years, only 48% were on high-intensity statins and 22% were not on any statin therapy at all. We also found that high-intensity statin use correlated with lower LDL levels, and even with high-intensity statin therapy, 1 in 4 patients still had LDL-C >70 mg/dl. Patients with higher LDL-C were also less likely to be prescribed other evidence-based cardiac medications. We were

not able to evaluate why many patients did not have LDL-C screening after PCI or the reason underlying this pattern of statin and cardiac medication underutilization. A prior study has suggested that in eligible patients who were not prescribed statin therapy, 60% were not offered, whereas only 10% declined therapy (23). However, routinely checking LDL-C after PCI may identify patients who have not reached target LDL-C levels and would benefit from optimizing secondary preventative therapies.

THE ASSOCIATION BETWEEN HIGHER LDL-C AND POORER OUTCOMES. Epidemiological studies have shown a strong relationship between higher LDL-C levels and poorer cardiovascular outcomes (24,25). We were able to extend this finding to a cohort who had recent coronary revascularization with PCI. We found that higher LDL-C measured after PCI was associated with a higher subsequent incidence of adverse cardiac outcomes, and above 70 mg/dl, the association appeared linear. Furthermore, the association with MACE was driven primarily by an increased incidence of myocardial infarction and coronary revascularization, although above 100 mg/dl, the incidence was consistently higher for every component of the outcome when compared to an LDL-C <70 mg/dl, including cardiovascular death. Surveillance of LDL-C after PCI can therefore be used to identify high-risk patients who may benefit from intensification of cholesterol-lowering therapy. This observation is in keeping with the recent ODYSSEY Outcomes (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) trial, where the highest incidence of cardiac events and the largest absolute benefit of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors were seen when baseline LDL-C was above 100 mg/dl (26).

IMPORTANCE OF LDL-C SURVEILLANCE IN ALL PATIENTS AFTER PCI. Recent myocardial infarction identifies high-risk patients with CAD with a tendency toward residual inflammation, plaque progression, and instability. In the international REACH (Reduction in Atherothrombosis for Continued Health) registry, patients with CAD who had recent myocardial infarction had a nearly 2-fold higher risk for future cardiac events when compared with stable CAD patients (27). Furthermore, European guidelines now recommend patients undergo lipid testing within 4 to 6 weeks after ACS to assess therapy response and assess residual risk (22). Our subgroup analysis demonstrated that the risk of MACE for each level of LDL-C was greater in patients who underwent PCI for an ACS in comparison to stable CAD. Yet, higher LDL-C was still associated with a higher risk of MACE among both ACS and stable CAD groups, particularly when LDL-C was above 100 mg/dl. This supports using LDL-C to assess risk after PCI irrespective of the indication for revascularization. This also suggests that recommendations for routine monitoring of LDL-C would be beneficial for all post-PCI patients rather than selected high-risk subgroups, such as those with recent ACS.

Recent clinical trials have demonstrated an incremental benefit of additional lipid-lowering therapy (PCSK9 inhibitors/ezetimibe) on a background of statin therapy (28,29). Also, the linear association between LDL-C and outcomes has been firmly established in statin-treated CAD patients and is similar to the association we observed after PCI (30). The results of our subgroup analysis are in keeping with these findings. We found a consistent relationship between higher LDL-C and poor outcomes in elderly patients treated with and without statins. It was difficult to completely disentangle the relative effect of statin therapy given its impact on lowering LDL-C and its ability to reduce cardiovascular outcomes. However, the results of our subgroup analysis emphasize the importance of both monitoring and achieving optimal LDL-C levels even when prescribed an adequate statin dose.

STUDY LIMITATIONS. First, we used a less contemporary cohort of patients for our study, which may have affected both LDL-C targets and rates of statin use compared to a more modern cohort. However, we feel this is less likely because Canadian practice guidelines in 2009 and 2012 during the study periods still advocated for an aggressive LDL-C target <2 mmol/l (78 mg/dl) and <1.8 mmol/l (70 mg/dl) for high- and very high-risk CAD patients, respectively (31,32). Second, despite our finding that higher LDL-C was associated with a higher incidence of adverse cardiovascular events, our study was not designed to ascertain the optimal target of LDL-C after PCI. Due to a small number of patients with very low LDL-C values, we were not able to evaluate its association with MACE as suggested by recent clinical trials (30,33). Third, we were unable to ascertain baseline lipid-lowering therapy in the entire cohort. However, in our subgroup of elderly patients linked to a provincial outpatient prescription database, statin therapy did not modify the association between LDL-C and MACE. Fourth, we cannot rule out that underutilization of other cardiac medications or cardiac rehabilitation may have accounted for higher event rates when LDL-C was ≥100 mg/dl. However,

over time we found that the differences in cardiac medication use was smaller relative to statins across LDL-C categories. Finally, despite adjustment for multiple clinically relevant predictors of MACE, we cannot rule out residual confounding that may have biased our association between LDL-C and MACE. However, we comprehensively adjusted for known confounders, and the association we observed is still in keeping with prior controlled trials and observational studies, especially for LDL-C >70 mg/dl.

CONCLUSIONS

LDL-C after coronary revascularization with PCI is strongly associated with the subsequent incidence of MACE, and by measuring LDL-C after PCI, patients who have not reached LDL-C targets can be identified for further optimization. These findings support recommendations for routine surveillance of LDL-C after PCI and attaining LDL-C below 70 mg/dl.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: High blood levels of LDL-C are associated with the development and progression of coronary atherosclerotic plaques and occurrence of adverse cardiovascular events during long-term follow-up after PCI.

TRANSLATIONAL OUTLOOK: Further research should be directed toward identifying and optimizing patient, provider, and system-based factors associated with better LDL-C surveillance and goal attainment in the longitudinal care of patients undergoing PCI.

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KEY WORDS acute coronary syndromes, low-density lipoprotein cholesterol, percutaneous coronary intervention, secondary prevention, stable coronary artery disease

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