Temporal Trends in Statin Prescriptions and Residual Cholesterol Risk in Patients With Stable Coronary Artery Disease Undergoing Percutaneous Coronary Intervention

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Intensive low-density lipoprotein cholesterol (LDL-C) reduction with statins is recommended after elective percutaneous coronary intervention (PCI). We aimed to evaluate adherence to guideline-recommended statin therapy (GRST) and the rate of residual cholesterol risk (RCR) at follow-up after elective PCI. All patients who underwent elective PCI between January 2010 and May 2016 were prospectively included in this single-center study. GRST was defined as high-intensity statin (HIS) therapy for patients ≤75 years old and moderate-intensity statin (MIS) or HIS therapy for patients >75 years. RCR at follow-up was defined as <50% decrease in LDL-C with HIS or <30% with MIS for statin-naïve patients and as LDL-C >70 mg/dL for nonstatin-naïve patients. A total of 2,653 patients were included, with 1,304 (49.2%) discharged with GRST. There was a significant increase in the number of patients discharged with GRST over time from 44.2% in 2010 to 63.0% in 2016 (p <0.001). Conversely, RCR at follow-up was present in 1,120 patients (42.2%) overall and remained stable over time. Risk factors of RCR at follow-up were female gender (odds ratio [OR]: 1.38; 95% confidence interval [CI] 1.13 to 1.70), previous myocardial infarction (OR: 1.37; 95% CI 1.12 to 1.64), smoking (OR: 1.30; 95% CI 1.01 to 1.67), higher LDL-C level at baseline (OR: 1.22; 95% CI 1.18 to 1.25). The presence of RCR was associated with an increased adjusted risk of death within 1 year of the second LDL-C measurement (adjHR: 2.78; 95% CI 1.15 to 6.67). In conclusion, although the rate of GRST at discharge has improved significantly over time in patients who underwent elective PCI, the prevalence of RCR at follow-up has not changed appreciably suggesting that further implementation of guidelines as well as novel or more intensive pharmacotherapy may be warranted. **(Am J Cardiol 2019;123:1788−1795)**

Intensive low-density lipoprotein cholesterol (LDL-C) reduction is a cornerstone of secondary prevention among patients with established coronary artery disease (CAD).[1,2] In randomized controlled trials, high-intensity statins (HIS) have induced greater reduction of cardiovascular risk and LDL-C levels than low- or moderate-intensity statins.[3,4] The 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults recommended the use of HIS for secondary prevention of CAD among patients ≤75 years and moderate- to high-intensity statins in older patients.[1] Monitoring of LDL-C levels was also recommended to assess adherence and therapeutic response.[1,5,6] The 2013 ACC/AHA guidelines described an anticipated therapeutic response as ≥50% decrease in LDL-C with HIS and a 30% to 50% decrease with moderate-intensity statins (MIS) from an untreated baseline. These recommendations were upheld in the recent 2018 update of these guidelines.[5] The European Society of Cardiology/European Society of Atherosclerosis (ESC/ESA) guidelines for the management of dyslipidemia promoted a treatment goal of LDL-C <70 mg/dL in very high-risk patients.[2] However, observational registries worldwide have reported that such LDL-C targets were achieved in a majority of patients[7,8] who could therefore be considered as presenting a persistent residual cholesterol risk (RCR) despite lipid lowering therapy. Since the publication of the 2013 AHA/ACA guidelines, the use of HIS

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has increased among patients hospitalized for myocardial infarction (MI) in the United States,[9,10] which may have resulted in a lower prevalence of RCR as more patients reached their respective LDL-C reduction targets. Despite the increase in the prescription and usage of HIS, the reduction of RCR in real-world patients who underwent percutaneous coronary intervention (PCI) for stable CAD has not been specifically studied. We aimed to describe the temporal trends of real-world adherence to guideline recommendations of statin prescriptions and the incidence of RCR after PCI for stable CAD in a US population.

METHODS

All consecutive patients who underwent PCI with balloon angioplasty or stent implantation for stable CAD at The Mount Sinai Hospital in New York from January 2010 to May 2016 and who had ≥2 LDL-C measurements taken at least 4 weeks apart were retrospectively included.[1] Exclusion criteria included the absence of an LDL-C measurement at baseline, the absence or unknown dosage of statin prescription at discharge and less than 4 weeks between the 2 LDL-C measurements. First LDL-C measurement was performed during the index hospitalization. Baseline and procedural characteristics, as well as the lipid-lowering drug prescribed at hospital discharge were obtained through a review of medical records contained in our PCI registry, which was reviewed and approved by our institutional review board. The present study was supported by a research grant from Regeneron Pharmaceuticals, Inc.; however, the authors independently performed and are solely responsible for the design and conduct of this study, all study analyses, as well as the drafting and editing of the paper and its final contents.

Guideline-recommended statin therapy (GRST) was defined as the prescription of a HIS in patients ≤75 years or a moderate- or high-intensity statin in patients >75 years.[5] Among statin-naïve patients, RCR was defined as a <50% decrease in LDL-C from baseline when a HIS was prescribed and as a <30% decrease in LDL-C when a non-HIS was prescribed according to the guidelines.[1] In patients who were not naïve to statin therapy, RCR was defined as LDL-C > 70 mg/dL at follow-up.[2] Intensity of statin therapy was defined according to ACC/AHA guideline definitions.[1,5,9] HIS included atorvastatin 40 to 80 mg, rosuvastatin 20 to 40 mg, and simvastatin 80 mg. MIS included atorvastatin 10 to 20 mg, rosuvastatin 5 to 10 mg, simvastatin 20 to 40 mg, pravastatin 40 to 80 mg, lovastatin 40 mg, fluvastatin 40 mg b.i.d or fluvastatin XL 80 mg, and pitavastatin 2 to 4 mg. Finally, low-intensity statins included simvastatin 10 mg, pravastatin 10 to 20 mg, lovastatin 20 mg, fluvastatin 20 to 40 mg, and pitavastatin 1 mg.

End points of interest were all-cause death, MI (according to the third universal definition),[11] target vessel revascularization (TVR), the composite of all-cause death or MI and the composite of death, MI or TVR within 1 year following the second LDL-C measurement. Complete 1-year follow-up was performed by trained research coordinators and includes a telephone follow-up at 30 days and 1 year and a review of medical records and clinical visits obtained events through clinical visits.

Descriptive statistics are reported as mean ± standard deviation, median and interquartile range, or number and percentage when appropriate. The chi-square test was used to compare differences between categorical variables. The independent-samples *t* test was used to compare continuous variables with normal distribution and the Mann-Whitney U test was used to compare continuous variables without a normal distribution. Event rates were compared using the log-rank test and time-to-event curves were constructed using the Kaplan-Meier method. Independent correlates of RCR were assessed with a multivariable logistic regression model. The association between RCR and clinical events were determined with a multivariable Cox regression model with the following covariates: age, female gender, Caucasian race, diabetes mellitus, smoking status, history of MI, history of anemia, body mass index value, serum creatinine at baseline, LDL-C level at baseline SYNTAX score of the index procedure, overall stent length, and guidelines recommended statins therapy at discharge. SAS version 9.4 (SAS institute Inc., Cary, NC) was used for all analyses. A p value <0.05 was considered significant unless otherwise specified.

RESULTS

Of the 8,618 patients who underwent PCI for stable CAD at our center during the specified time period, a total of 2,653 (30.8%) had serial LDL-C measurements ≥4 weeks apart and were therefore included in the study (Figure 1). Overall, 2,288 patients (86.2%) were treated with statins at baseline and 1,304 patients (49.2%) were discharged with GRST, with a significant increase over time from 44.2% in 2010 to 63.0% in 2016 (Figure 2). Median time between LDL-C measurements was 8.8 (5.0 to 50.6) weeks for patients without RCR at follow-up and 12.2 (5.0 to 71.7) weeks for patients with RCR at follow-up (p <0.001). Overall, RCR was present at follow-up in 1,120 patients (42.2%), without significant changes during the 7-year study period. The proportion of patients discharged on GRST increased significantly after the publication of the 2013 ACC/AHA cholesterol guidelines.

Baseline and procedural characteristics of patients according to the presence or absence of RCR at follow-up are detailed in Table 1. There was no difference regarding GRST at discharge between patients with and without RCR at follow-up. After adjustment, independent risk factors for the persistence of RCR at follow-up were female gender, previous MI, active smoking, and LDL-C level (per 10-unit increase) at admission (Table 2).

Rates of all-cause death, MI, and TVR were numerically higher in patients presenting with RCR at follow-up in univariate models (Table 3 and Figure 3). After adjustment for baseline characteristics and discharge medications, the presence of RCR at follow-up was independently associated with all-cause death, MI, or TVR. One-year outcomes in patients with or without LDL-C ≤ 70 mg/dL at follow-up are detailed in Supplemental Table 1. Finally, 1-year outcomes according to the presence of GRST at discharge are detailed in Table 4. Although GRST was associated

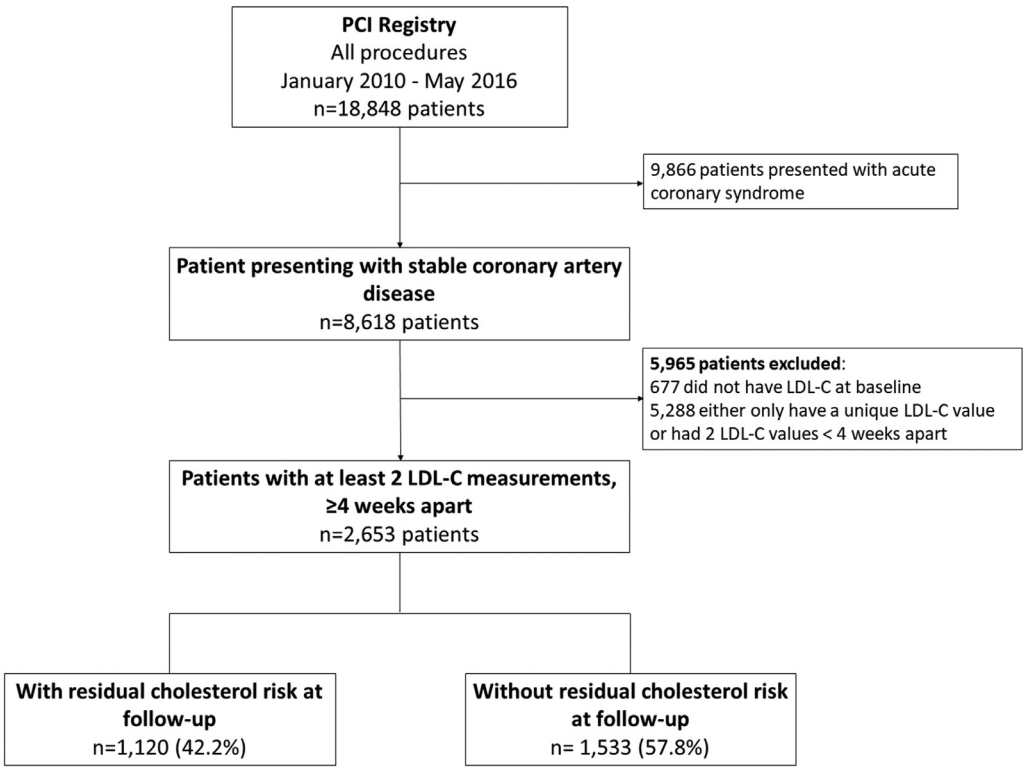

Figure 1. Flow chart of the study.
PCI = percutaneous coronary intervention.

with adverse outcomes in univariate analysis, this was no longer the case after multiple adjustments on baseline and procedural covariates.

DISCUSSION

The main results of our study are as follows: (1) despite a significant increase in guideline-recommended statins prescription after PCI for stable CAD over time, the proportion of patients presenting with RCR at follow-up remained stable; (2) risk factors for RCR at follow-up were female gender, previous MI, active smoking, and higher LDL-C level at baseline; (3) the presence of RCR at follow-up was associated with all-cause death and the composite of all-cause death or MI within 1 year from the second LDL-C measurement.

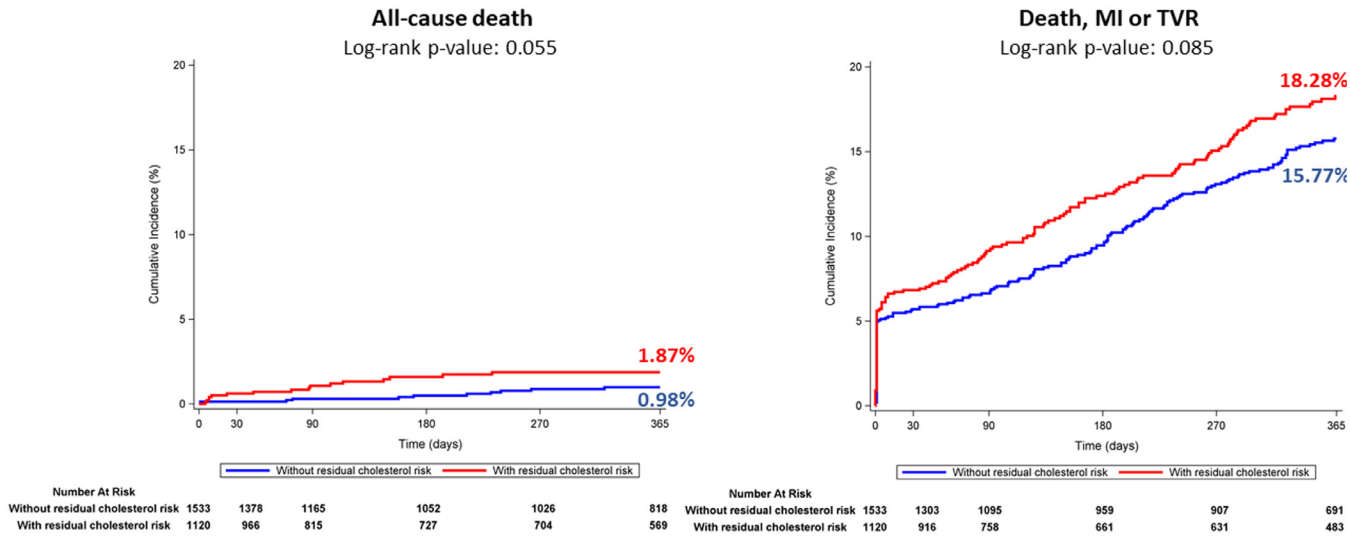

Figure 2. Temporal trend in guideline-recommended statin prescriptions at discharge and residual cholesterol risk at follow-up.
PCI = percutaneous coronary intervention.

Table 1
Baseline characteristics according to the presence of residual cholesterol risk at follow-up

		Residual cholesterol risk at follow-up		
	Overall population n = 2,653	Yes (n = 1,120)	No (n = 1,533)	p Value
Variables				
Age (years)	65.1 ± 10.8	64.3 ± 11	65.7 ± 10.7	0.001
Race/ethnicity				0.029
Asian	569 (21.4%)	223 (19.9%)	346 (22.6%)	
Black	217 (8.2%)	110 (9.8%)	107 (7%)	
White	1,055 (39.8%)	429 (38.3%)	626 (40.8%)	
Hispanic	533 (20.1%)	237 (21.2%)	296 (19.3%)	
Other	279 (10.5%)	121 (10.8%)	158 (10.3%)	
Women	633 (23.9%)	318 (28.4%)	315 (20.5%)	<0.001
Body mass index (kg/m^2)	28.9 ± 5.9	29.1 ± 6.2	28.8 ± 5.5	0.22
Hypertension	2,540 (95.7%)	1,064 (95%)	1,476 (96.3%)	0.11
Diabetes mellitus	1,395 (52.6%)	588 (50.9%)	837 (54.6%)	0.015
Chronic kidney disease	741 (28.9%)	299 (27.6%)	442 (29.8%)	0.23
Anemia	1,081 (41.4%)	430 (39%)	651 (43.1%)	0.039
Current smoker	341 (12.9%)	175 (15.6%)	166 (10.8%)	<0.001
Previous myocardial infarction	666 (25.1%)	307 (27.4%)	359 (23.4%)	0.02
Peripheral artery disease	239 (9%)	111 (9.9%)	128 (8.3%)	0.16
Clinical presentation				
Asymptomatic	267 (10.1%)	111 (9.9%)	156 (10.2%)	0.82
Stable angina pectoris	2,386 (89.9%)	1,009 (90.1%)	1,377 (89.8%)	0.82
Medications at admission				
Aspirin	2,359 (88.9%)	985 (87.9%)	1,374 (89.6%)	0.17
Statin	2,288 (86.2%)	906 (80.9%)	1,382 (90.2%)	<0.001
Medications at discharge				
Aspirin	2,595 (97.8%)	1,092 (97.5%)	1,503 (98%)	0.34
High-intensity statin	968 (36.5%)	435 (38.8%)	533 (34.8%)	0.03
Moderate-intensity statin	1,473 (55.5%)	585 (52.2%)	888 (57.9%)	0.004
Low-intensity statin	212 (8%)	100 (8.9%)	112 (7.3%)	0.13
Guideline-recommend statin therapy	1,304 (49.2%)	560 (50%)	744 (48.5%)	0.45
Co-prescription of Ezetimibe/Niacin	37 (1.4%)	10 (0.9%)	27 (1.8%)	0.06
Beta blockers	2,243 (84.5%)	948 (84.6%)	1,295 (84.5%)	0.91
Dual antiplatelet therapy	2,585 (97.4%)	1,086 (97%)	1,499 (97.8%)	0.19
Laboratory values at baseline				
Hemoglobin (g/dL)	13 ± 1.6	13 ± 1.7	13 ± 1.6	0.97
Serum Creatinine (mg/dL)	1.3 ± 1.3	1.3 ± 1.4	1.3 ± 1.3	0.88
Total cholesterol (mg/dL)	137.3 ± 35.9	148.9 ± 33.7	128.8 ± 35	<0.001
LDL-C (mg/dL)	70 (53.8-91)	81 (66.6-100)	61 (48 - 79)	<0.001
HDL-C (mg/dL)	40.8 ± 11.9	41.2 ± 11.8	40.6 ± 12	0.18
Triglycerides (mg/dL)	107.6 ± 58.9	111.6 ± 58.7	104.7 ± 58.9	0.003
C-reactive protein (mg/dL)	5.5 ± 39.9	5.8 ± 43	5.2 ± 37.5	0.7
Laboratory values at follow-up				
LDL-C (mg/dl)	68.6 ± 28.2	86.3 ± 27.4	50.5 ± 14	<0.001
Procedural characteristics				
Treated vessel				
Left anterior descending artery	1,148 (43.3%)	497 (44.4%)	651 (42.5%)	0.33
Left circumflex artery	917 (34.6%)	388 (34.6%)	529 (34.5%)	0.94
Right coronary artery	789 (29.7%)	318 (28.4%)	471 (30.7%)	0.19
Left main artery	110 (4.1%)	46 (4.1%)	64 (4.2%)	0.93
Syntax score	12.9 ± 10.5	12.5 ± 10.2	13.2 ± 10.7	0.097
Bare-metal stent	257 (9.7%)	109 (9.7%)	148 (9.7%)	0.007
Stent length (mm)	35.5 ± 20.7	35.1 ± 20.7	35.7 ± 20.8	0.42

HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

The rate of GRST remained overall limited even in the latest period of a study, despite the significant increase observed following the implementation of 2013 ACC/AHA guidelines on the treatment of blood cholesterol. In a previous study, we reported stable angina as index event to be a risk factor of not being discharge with high-intensity statins following PCI, in patients below 75 years of age.[10] Indeed, in this elective setting, reluctance to change chronic lipid-lowering medication by the patients or clinical inertia by the physician may result in undertreatment in term of statin's intensity, despite recent guidelines. Notwithstanding, the rates of GRST in this study remained higher that

Table 2
Risk factors of the presence of residual cholesterol risk at follow-up

Variables	Odds ratio	95% confidence interval	p Value
Age (per 1-year increase)	0.99	0.99 - 1.00	0.17
Female sex	1.38	1.13 - 1.70	0.002
Caucasian	1.00	0.83 - 1.19	0.97
Prior myocardial infarction	1.37	1.12 - 1.64	0.002
Active smoking at admission	1.30	1.01 - 1.67	0.045
LDL-C level at baseline (per 10-unit increase)	1.22	1.18 - 1.25	<0.001
Insulin-treated diabetes mellitus	0.80	0.61 - 1.03	0.083
Noninsulin treated diabetes mellitus	0.88	0.74 - 1.06	0.20
Serum creatinine level at baseline (per one-unit increase)	1.05	1.05 (0.99 - 1.12)	0.13
C-reactive protein level at baseline (per 1-unit increase)	1.12	0.94 - 1.33	0.18
Guidelines-recommended statin treatment	1.11	1.19 - 1.32	<0.001

LDL-C = low-density lipoprotein cholesterol.

Table 3
One-year clinical outcomes according to the presence of residual cholesterol risk at follow-up

	Residual cholesterol risk at follow-up				
	Yes (n = 1,120)	No (n = 1,533)	p Value*	Adjusted HR (95% CI)	p Value†
All-cause death	16 (1.87%)	11 (0.98%)	0.055	2.78 (1.15-6.67)	0.024
Myocardial infarction	85 (9.19%)	99 (7.64%)	0.18	1.25 (0.92-1.72)	0.16
Target vessel revascularization	82 (10.73%)	108 (10.05%)	0.52	1.08 (0.78-1.47)	0.67
Death or myocardial infarction	95 (10.31%)	105 (8.15%)	0.073	1.35 (1.00-1.82)	0.053
Death, myocardial infarction or target vessel revascularization	158 (18.28%)	188 (15.77%)	0.085	1.28 (1.01-1.62)	0.039

CI = confidence interval; HR = hazard ratio.
Results are expressed as Kaplan-Meier estimates (n).
* log-rank p value.
† Wald p value; Covariates included in the model: age, female gender, Caucasian race, diabetes mellitus, smoking status, history of MI, history of anemia, body mass index value, serum creatinine at baseline, LDL-C level at baseline SYNTAX score of the index procedure, overall stent length, and prescription of guideline-recommended treatment at discharge.

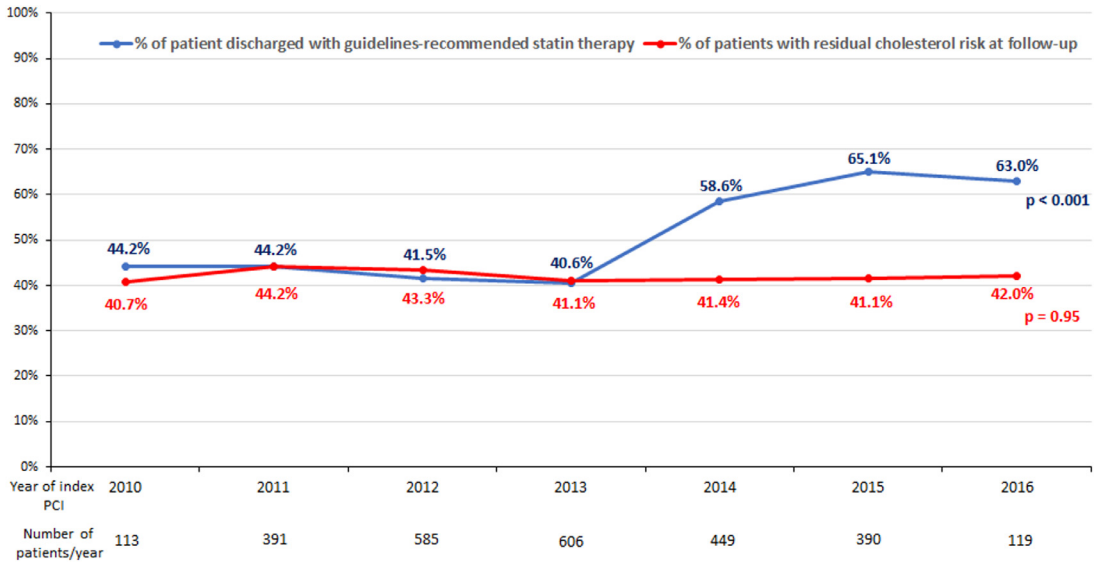

Figure 3. Kaplan-Meier curves depicting the cumulative incidence of all-cause death and the composite of death, MI, or TVR.
MI = myocardial infarction; TVR = target vessel revascularization.

Table 4
One-year clinical outcomes according to the prescription of guideline recommended statins therapy at discharge

	Guideline-recommended statins therapy at discharge				
	Yes (n = 1,304)	No (n = 1,349)	p Value*	Adjusted HR (95% CI)	p Value†
All-cause death	19 (1.93%)	8 (0.80%)	0.019	2.17 (0.54-8.68)	0.27
Myocardial infarction	115 (10.65%)	69 (6.06%)	<0.001	1.51 (0.91-2.52)	0.11
Target vessel revascularization	89 (10.13%)	101 (10.52%)	0.86	0.82 (0.43-1.57)	0.55
Death or myocardial infarction	125 (11.58%)	75 (6.66%)	<0.001	1.62 (0.99-2.64)	0.054
Death, myocardial infarction or target vessel revascularization	190 (18.75%)	156 (14.98%)	0.005	1.32 (0.88-1.96)	0.18

CI = confidence interval; HR = hazard ratio.
Results are expressed as Kaplan-Meier estimates (n).
* log-rank p value.
† Wald p value; Covariates included in the model: age, female gender, Caucasian race, diabetes mellitus, smoking status, history of MI, history of anemia, body mass index value, serum creatinine at baseline, LDL-C level at baseline SYNTAX score of the index procedure, overall stent length, and the presence of residual cholesterol risk at follow-up.

previously reported in other US patients population with clinical atherosclerotic cardiovascular disease.[12]

In the present study, the overall proportion of patients presenting with a RCR was lower than previously reported in registries worldwide,[7,8,13] albeit consistent with results from randomized controlled trials.[4] In a meta-analysis including 38,153 patients, Boekholdt et al reported achievement of an LDL-C target <70 mg/dL in 59.6% of trial participants assigned to high-dose statin therapy.[4] However, in the present study, despite a significant increase in HIS prescriptions following the 2013 ACC/AHA guidelines, the incidence of RCR remained stable over time. One potential reason for this unexpected finding may be a lack of statin adherence. Indeed, high rates of statin nonadherence, up to 63.6%, have been reported in real-world registries in the United States.[14,15] High rates of discontinuation or mediocre adherence have also been described in other industrialized countries worldwide.[16] Statin-related side effects such as muscular pain are a major cause of nonadherence or discontinuation.[17] Non-Caucasian ethnicity or race have also been associated with poorer adherence, although this was not the case in our study, where the population was highly diversed.[9,18]

It is unlikely that lack of statin adherence would be the sole explanation of our results. Indeed, in the present study, 80.9% of the patients with RCR at follow-up were already on statin medication at admission and LDL-C levels at baseline and follow-up were consistent with what was observed in the control group of the FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) and the Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab (ODYSSEY OUTCOMES) randomized trials.[19,20] Thus, there might also be a limit to the extent of LDL-C reduction with statins despites the use of a guideline-recommended dose. In fact, large interindividual variations in response to statin therapy have been described, and a ceiling effect may be observed with some patients.[4,20] Furthermore, greater progression of atherosclerosis has been observed in patients who fail to achieve a proper response to statin therapy.[21] Therefore, it is paramount to diagnose insufficient LDL-C response to statin therapy, despite proper adherence, as these patients could benefit from the use of ezetimibe and/or more potent lipid-lowering drugs such as proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors.[5] Further LDL-C reduction with these agents, on top of optimized lipid-lowering therapy, has resulted in improved outcomes.[19,22,23] Identifying risk factors of RCR at follow-up may help defining subgroups of patients who could benefit from more intensive surveillance and pharmacotherapy. Gender has been commonly described as a correlate of LDL-C response, although the nature of its impact has been debated.[21,24,25] In this study, female gender was an independent risk factor for RCR at follow-up, as previously reported.[26] Further studies dedicated to understanding the impact of gender on statin treatment adherence and LDL-C response may be warranted. The other risk factors of RCR at follow-up in the present study—active smoking, previous MI, and higher LDL-C level at baseline—are consistent with previous reports.[27,28]

In the present study, the presence of RCR at follow-up was associated with the occurrence of adverse outcomes, particularly all-cause death. The association between lower level of LDL-C and reduced risk of major adverse cardiovascular events, including death, has been consistently reported by randomized trials.[3,4] The quite strong association of RCR at follow-up with all-cause death, however, should be cautiously interpreted in the light of existing limitations, first of which may be the presence of unmeasured cofounders related to the observational nature of the study. Consistently, the prescription of GRST at discharge was associated with adverse outcomes in univariate analysis, which was likely explained by the presence of more severe co-morbidities in these patients, as the association was no longer significant after multivariate adjustment on baseline and procedural characteristics. This result is consistent with previous findings emphasizing the correlation between the risk profile of the patients and the prescription of high-intensity statins.[10]

We acknowledge other limitations. This is a single-center study and the present results may not be generalizable to other centers, although this limitation is mitigated by the relatively large sample size of patients. LDL-C measurements were not performed in a standardized fashion but left at the

prescribing physician's discretion, leading to suboptimal assessment of LDL-C level, whereas treatment adherence was not evaluated; thus, our results may not be extrapolated to patients with whom serial LDL-C measurements are not performed and we cannot exclude a selection bias. Our population underwent elective PCI for stable CAD, limiting our ability to extrapolate our findings to those patients presenting with an acute coronary syndrome. Overall, these results should only be considered as hypothesis-generating. Finally, RCR may only be one of several modifiable mechanisms contributing to the overall residual cardiovascular risk, whereas other important aspect, such as chronic inflammation, was not evaluated in the present trial.[29]

In conclusion, although the rate of guideline-recommended statin treatment has significantly improved over time in patients who underwent PCI for stable CAD, the incidence of RCR at follow-up has not changed appreciably and remains a risk factor of adverse events. Further implementation of guidelines, the promotion of statin treatment adherence and the use of more potent lipid-lowering therapies may be targets of interest in the effort to improve LDL-C reduction following elective PCI for stable CAD.

Disclosures

Drs. Guedeney, Claessen, Camaj, Blum, Chandiramani, Goel, Elsayed, Baber, Kovacic, Aquino, Sorrentino, Kini have no conflicts of interest to declare.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.03.005.

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