ORIGINAL RESEARCH

Projected Real-World Effectiveness of Using Aggressive Low-Density Lipoprotein Cholesterol Targets Among Elderly Statin Users Following Acute Coronary Syndromes in Canada

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***Background*—**The extent to which outcome benefits may be achieved through the implementation of aggressive low-density lipoprotein (LDL) cholesterol targets in real world settings remains unknown, especially among elderly statin users following acute coronary syndromes.

***Methods and Results*—**A population-based cohort study consisting of 19 544 post-acute coronary syndrome statin-users aged ≥66 years between January 1, 2017 and March 31, 2014 was used to project the number of adverse outcome events (acute myocardial infarction or death from any cause) that could be prevented if all post-acute coronary syndrome elderly statin users were treated to 1 of 2 LDL cholesterol target levels (≤50 and ≤70 mg/dL). The number of preventable adverse outcomes was estimated by using model-based expected event probabilities as derived from Cox Proportional hazards models. In total, 61.6% and 25.5% of the elderly patients met LDL cholesterol targets of ≤70 and ≤50 mg/dL, respectively, based on current management. No more than 2.3 adverse events per 1000 elderly statin users (95% confidence interval: −0.7 to 5.4, P=0.62) could be prevented over 8.1 years if all patients were to be treated from current LDL cholesterol levels to either of the 2 LDL cholesterol targets of 70 or 50 mg/dL.

***Conclusions*—**The number of acute myocardial infarctions or death that could be prevented through the implementation of LDL cholesterol targets with statins is negligible among an elderly post-acute coronary syndrome population. Such findings may have implications for the applicability of newer agents, such as proprotein convertase subtilisin/kexin type-9- inhibitors. **(*J Am Heart Assoc*. 2018;7:e007535. DOI: 10.1161/JAHA.117.007535.)**

Key Words: aging • cardiology • cardiovascular disease • epidemiology • geriatrics • health services research • pharmacology • secondary prevention • statins

Available evidence from clinical trials has demonstrated that aggressive low-density lipoprotein (LDL) cholesterol lowering using statins following acute coronary syndromes (ACS) is associated with improved cardiovascular outcomes.[1–5] More recently, evolocumab, a proprotein convertase subtilisin/kexin type-9 (PCSK-9) inhibitor with potent LDL cholesterol lowering properties, has also been shown to improve composite cardiovascular outcomes among high-risk populations, although mortality rates alone were similar between the 2 groups.[6] While such studies support the clinical efficacy associated with aggressive LDL cholesterol lowering strategies, the population-based effect of implementing such strategies on outcomes remains unclear.

Ambiguity in the clinical effectiveness of aggressive LDL cholesterol lowering strategies relates to several factors. First, real-world populations are older and have greater

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Accompanying Table S1 and Figures S1, S2 are available at http://jaha.ahajournals.org/content/7/10/e007535/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- To our knowledge, this is the first study to use real-world data to estimate the number of adverse events prevented by using aggressive low-density lipoprotein cholesterol targets among elderly statin-users following acute coronary syndrome hospitalizations.

What Are the Clinical Implications?

- While aggressive low-density lipoprotein cholesterol lowering using statins or proprotein convertase subtilisin/kexin type-9 inhibitors have been shown to improve clinical outcomes among younger clinical trial populations, the projected number of acute myocardial infarctions or deaths prevented by using aggressive low-density lipoprotein cholesterol targets among elderly statin-users following acute coronary syndromes in the real-world settings is marginal.

comorbidities than those enrolled in clinical trials.[7–10] Because of differences in life expectancy and comorbidity burden, elderly patients may have fewer modifiable risks and attenuated outcome benefits, than those seen from clinical trial populations. Second, the potential incremental clinical effectiveness of an aggressive LDL cholesterol lowering strategy will depend upon the levels with which LDL cholesterol can be controlled through usual-care in the real-world. For example, if LDL cholesterol levels were already well controlled, the incremental outcome benefits that might be expected from higher doses of statins, and/or other therapies such as PCSK-9 inhibitors may be marginal. The importance of exploring the clinical effectiveness of aggressive LDL cholesterol lowering strategies in high-risk elderly populations using contemporary management becomes even more important when considering the costs associated with PCSK-9 inhibitors.

To the best of our knowledge, no study has estimated the number of adverse events that could be prevented if all elderly statin users were treated to aggressive LDL cholesterol targets following an ACS. Accordingly, the objective of this study was to estimate the projected number of adverse outcome events which could be prevented if all post-ACS elderly statin users were treated from current LDL cholesterol levels as observed in real-world settings to 1 of 2 LDL cholesterol target levels (≤50 and ≤70 mg/dL). Canada serves as an ideal setting in which to explore the clinical effectiveness of aggressive LDL cholesterol targets among elderly statin users, given that medications are covered free of charge for patients aged ≥65 years, thereby mitigating the potential confounding effects of affordability.

Methods

Data Sources

The data set from this study is held securely in coded form at the Institute for Clinical Evaluative Sciences (ICES). While data sharing agreements prohibit ICES from making the data set publicly available, access may be granted to those who meet pre-specified criteria for confidential access, available at https://www.ices.on.ca/DAS. The full data set creation plan and underlying analytic code are available from the authors upon request, understanding that the programs may rely upon coding templates or macros that are unique to ICES.

The study population was derived from the Cardiovascular Health in Ambulatory Care Research Team (CANHEART) cohort (www.canheart.ca), which comprised the linkage of multiple individual-level databases using encoded personal identifiers.[11] Databases that were linked include the Canadian Institute for Health Information (CIHI) Discharge Abstract Database and the Ontario Diabetes Database, to identify hospitalizations for ACS and comorbidities; Same Day Surgery, and National Ambulatory Care Reporting System to identify same day surgical and emergency room visits respectively; Registered Persons Database for death information; the Ontario Drug Benefit prescription database, which was used to determine outpatient prescription drug use for patients aged ≥65 years; the Gamma-Dynacare Medical Laboratory database, which captures 25% to 30% of all outpatient laboratory testing in Ontario was used to determine cholesterol levels; and the Registrar General of Ontario Vital Statistics Database, which was used to determine cause of death of all Ontarians. These data sets were linked using unique encoded identifiers and analyzed at ICES. This study was approved by the institutional review board at Sunnybrook Health Sciences Centre, Toronto, Canada. The requirement for informed consent was waived.

Study Sample

The study population was comprised of Ontario residents aged ≥66 years with (1) a valid health card number; (2) who were hospitalized for ACS (codes for myocardial infarction *International Classification of Diseases, Tenth Revision (ICD-10):* I21, I22, *ICD-9*: 410; unstable angina *ICD-10*: I20, *ICD-9*: 411, 413) between January 1, 2007 and March 31, 2014; (3) who had one or more outpatient LDL cholesterol measurements in Ontario between 30 and 365 days of their ACS hospitalization, and (4) who received at least one statin prescription within 6 months of their ACS hospitalization. The first LDL cholesterol measurement was excluded if such measurements were taken within the first 30 days of an ACS. We imposed a 30-day ACS survival period to ensure accuracy in LDL cholesterol levels, which may be artificially low within

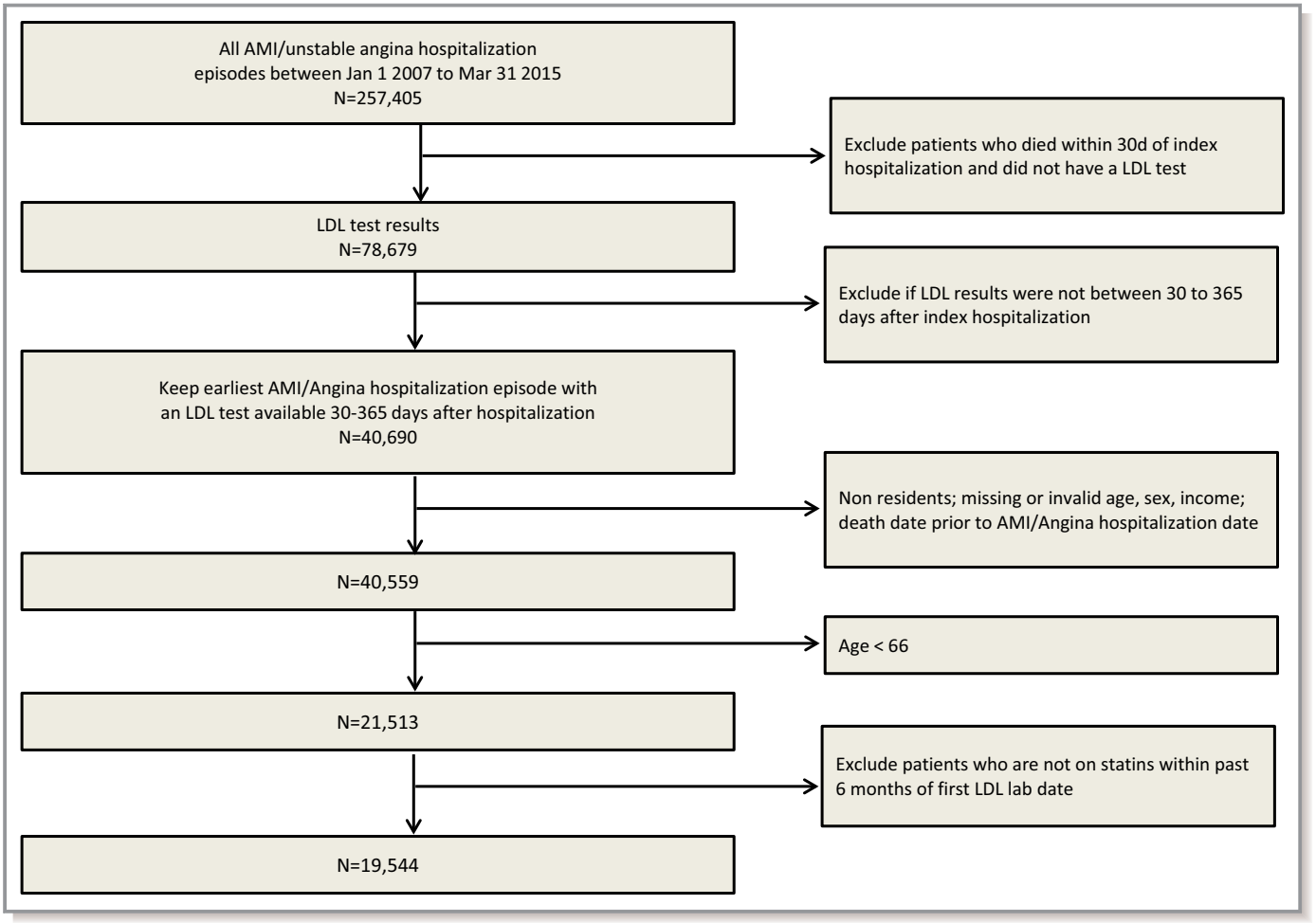

Figure 1. Study participant selection. Study participation selection and exclusion criteria. AMI indicates acute myocardial infarction; LDL, low-density lipoprotein cholesterol.

the first 30 days following ACS.[12,13] Patients who had not received any statin prescriptions were excluded from the study given that our objective was not to evaluate the efficacy of statins versus non-statins, but rather, to explore the potential outcome yield of adopting aggressive LDL cholesterol targets among elderly patients already on statins (Figure 1).

LDL Cholesterol and Statin-Intensity

The LDL cholesterol measurement of interest was the first such measurement performed in the outpatient setting between 30 and 365 days following ACS hospitalization. Nineteen statin preparations and dosages were classified in accordance to the 2013 ACC/AHA guidelines into low-intensity, medium-intensity, or high-intensity which took into account the specific statin drug and pill-strength of each prescription.[14]

We explored 2 pre-specified LDL cholesterol targets: (1) An LDL cholesterol target of ≤70 mg/dL as recommended by the European Society of Cardiology/Canadian Cardiovascular Society guidelines for post-ACS populations,[15,16] and (2) an LDL cholesterol target of ≤50 mg/dL, which approximates the mean LDL cholesterol levels associated with aggressive LDL lower strategies in recent clinical trials.[1,3,4]

Outcomes

Our primary outcomes were the number of adverse events (the first occurrence of acute myocardial infarction or death from any cause) prevented if all elderly statin users were treated from their current LDL cholesterol levels as observed in real-world settings to LDL cholesterol targets of ≤70 or ≤50 mg/dL. The primary outcomes incorporated model-based expected event probabilities of adverse events using Cox Proportional hazards models.

Patients were followed from the date of their first LDL cholesterol measurement following their ACS hospitalization until a primary outcome event, or until the end of follow up (March 31, 2015) (Figure S1).

Statistical Analysis

The baseline characteristics of the cohort were reported by LDL quintiles. Baseline characteristics were compared across the LDL strata using one-way analysis of variance for continuous variables, and chi-squared test for categorical variables.

We determined expected probabilities of an adverse outcome according to LDL cholesterol levels for elderly statin users in Ontario using Cox proportional hazard models after adjusting for age, sex, socioeconomic status (neighborhood income quintile), clinical risk factors, invasive cardiac procedure use, comorbidity, and statin intensity as determined at study baseline for each of our 2 LDL target levels across statin intensity groups. To examine whether the hazards associated with LDL cholesterol measurements varied according to age, all statistical models also used an age-LDL cholesterol interaction within each of the age stratum (66–74 years old versus 75 years and beyond) given uncertainty in the efficacy of statin therapy among patients aged ≥75 years as compared with younger populations.[17,18] Based on the fitted Cox model, the predicted probability of an adverse event within a specified duration of follow-up could be determined for any patient covariate pattern.

For each subject, we computed 2 probabilities based on the fitted Cox model. First, the patient's model-based probability of an event over a duration of 8.1 years (which corresponded to the maximum duration of study follow-up) conditional on his/her existing LDL and his/her measured baseline covariates. Second, the patient's model-based probability of an event over a time-duration of 8.1 years under the assumptions that his/her LDL cholesterol was lowered to the desired target threshold, and that other baseline covariates remaining unchanged. For subjects who were currently at or below the LDL threshold, we assumed that these 2 probabilities were equal to one another (ie, that their LDL would not change). We then computed the difference in these 2 probabilities. The average of this difference in probabilities across the sample of patients is the population-average reduction in the probability of an event. This average probability was multiplied by the size of the initial cohort to estimate the reduction in the number of events if LDL was lowered to the target level. These analyses assumed that a treatment-to-target approach was feasible even among patients already receiving high-intensity statins, given that adherence rates to statins (irrespective of intensity) remain suboptimal.[19] Confidence intervals were determined using bootstrapping. When examining the number of acute myocardial infarctions (AMIs) prevented, the Fine-Gray sub-distribution hazard model,[20] was used to account for the competing risk of non-AMI mortality.

Several sensitivity analyses were undertaken in which we varied the outcomes to include broader composite outcomes (ie, stroke or all-cause hospitalization) as well as narrower non-composite outcomes (all-cause mortality alone or AMI alone), sex, and comorbidity (Charlson comorbidity index of >2 versus ≤2). Another sensitivity analyses adjusted for adherence to statins using prescription refill data and the proportion of days covered (PDC) of ≥80% versus <80%.

Two-tailed *P* values <0.05 were considered significant. Analyses were performed with the use of SAS software, version 9.3 (SAS Institute Inc, Cary, NC) R Statistical Software (rms package) was used for the creation of hazard-LDL plots.[21]

Results

Baseline Characteristics

Our cohort consisted of 19 544 patients. The mean age of the cohort was 76.3±7.0 years; 39.7% of patients were female. In total, 61.6% and 25.5% of the elderly population met LDL cholesterol targets of ≤70 and ≤50 mg/dL, respectively at baseline. In general, increasing age, male sex, higher intensity statins, diabetes mellitus, hypertension, and a higher Charlson comorbidity index were associated with lower baseline LDL cholesterol (Table 1). Patients on higher intensity statins at baseline were younger, more likely to be male, had diabetes mellitus, hypertension, and a higher Charlson comorbidity index than those on lower intensity statins.

Fluctuations in LDL Cholesterol and Statin Intensities Over Time

In total, 72% of the cohort had ≥2 LDL cholesterol measurements over a maximum duration of follow-up of 8.1 years (median duration of follow-up of 2.8 years). The majority of patients (14 075/19 544, 72%) did not change dose intensities of statins throughout the follow-up period. Among those with ≥2 measurements, LDL cholesterol on average did not change significantly between an individual's first and last available measurement (mean difference of 0.37 mg/dL, 95% confidence interval: −0.80±0.07, *P*=0.10). Each patient received a median of 16 statin prescriptions (interquartile range: 7–30) throughout the follow-up period. In total, ≥80% of patients were on medium- or high-intensity statins, irrespective of age throughout the study period. The fluctuations in LDL cholesterol and statin intensities were similar among patients ≥75 years as amongst those ages 66 to 74 years (Figure S2 and Table S1).

Projected Number of Adverse Outcome Events According to LDL Targets

After adjustment for all baseline factors including statin intensities, the relationship between LDL cholesterol and

Table 1. Baseline Characteristics According to LDL Cholesterol Categories Among Post ACS Patients Aged ≥66 Years on Statins in Ontario

	LDL <50	LDL 50 to 69	LDL 70 to 99	LDL ≥100	
	n=4984	n=7047	n=5599	n=1914	*P* Value
Age					
Mean±SD	76.56±7.07	76.37±6.99	76.03±6.88	75.88±7.03	<0.001
66 to 74 y	2153 (43.2%)	3120 (44.3%)	2553 (45.6%)	911 (47.6%)	0.004
≥75 y	2831 (56.8%)	3927 (55.7%)	3046 (54.4%)	1003 (52.4%)	
Sex					
F	1663 (33.4%)	2628 (37.3%)	2453 (43.8%)	1009 (52.7%)	<0.001
M	3321 (66.6%)	4419 (62.7%)	3146 (56.2%)	905 (47.3%)	
Income quintile at index date					
1	975 (19.6%)	1320 (18.7%)	1130 (20.2%)	413 (21.6%)	0.099
2	1074 (21.5%)	1574 (22.3%)	1149 (20.5%)	419 (21.9%)	
3	1043 (20.9%)	1405 (19.9%)	1153 (20.6%)	381 (19.9%)	
4	949 (19.0%)	1400 (19.9%)	1112 (19.9%)	373 (19.5%)	
5	943 (18.9%)	1348 (19.1%)	1055 (18.8%)	328 (17.1%)	
LDL cholesterol					
Mean±SD	39.18±8.13	59.08±5.59	80.99±8.28	123.89±25.59	<0.001
HDL cholesterol					
Mean±SD	44.99±14.42	47.98±13.92	49.87±14.13	51.43±14.60	<0.001
Triglyceride cholesterol					
Mean±SD	115.26±61.61	113.52±51.79	126.72±55.83	149.83±64.37	<0.001
Non-HDL cholesterol					
Mean±SD	62.28±13.91	81.84±11.96	106.40±14.53	153.89±30.16	<0.001
Total cholesterol					
Mean±SD	107.28±17.65	129.83±15.92	156.26±17.56	205.32±32.14	<0.001
Low-intensity statin	47 (0.9%)	125 (1.8%)	225 (4.0%)	161 (8.4%)	<0.001
Medium-intensity statin	1533 (30.8%)	2757 (39.1%)	2710 (48.4%)	981 (51.3%)	
High-intensity statin	3404 (68.3%)	4165 (59.1%)	2664 (47.6%)	772 (40.3%)	
Diabetes mellitus	2794 (56.1%)	3273 (46.4%)	2333 (41.7%)	777 (40.6%)	<0.001
Hypertension	4527 (90.8%)	6283 (89.2%)	4940 (88.2%)	1693 (88.5%)	<0.001
Stroke or TIA	317 (6.4%)	358 (5.1%)	296 (5.3%)	125 (6.5%)	0.004
Congestive heart failure	1940 (38.9%)	2464 (35.0%)	1890 (33.8%)	667 (34.8%)	<0.001
Atrial fibrillation	1219 (24.5%)	1548 (22.0%)	1193 (21.3%)	412 (21.5%)	<0.001
Peripheral vascular disease	228 (4.6%)	334 (4.7%)	277 (4.9%)	96 (5.0%)	0.786
Chronic obstructive lung disease	1533 (30.8%)	1969 (27.9%)	1648 (29.4%)	574 (30.0%)	0.008
Charlson index					
Mean±SD	2.74±1.96	2.36±1.89	2.22±1.89	2.25±1.96	<0.001
Primary cancer	302 (6.1%)	388 (5.5%)	292 (5.2%)	83 (4.3%)	0.031
Metastatic cancer	45 (0.9%)	63 (0.9%)	51 (0.9%)	27 (1.4%)	0.191
Peptic ulcer disease	127 (2.5%)	152 (2.2%)	111 (2.0%)	42 (2.2%)	0.254
Mild liver disease	32 (0.6%)	34 (0.5%)	25 (0.4%)	11 (0.6%)	0.51
Moderate or severe liver disease	10 (0.2%)	8 (0.1%)	9 (0.2%)	6 (0.3%)	0.264

Continued

Table 1. Continued

	LDL <50	LDL 50 to 69	LDL 70 to 99	LDL ≥100	
	n=4984	n=7047	n=5599	n=1914	*P* Value
Connective tissue/rheumatic disease	57 (1.1%)	71 (1.0%)	64 (1.1%)	27 (1.4%)	0.509
Dementia	251 (5.0%)	256 (3.6%)	182 (3.3%)	58 (3.0%)	<0.001
Hemiplegia or paraplegia	60 (1.2%)	80 (1.1%)	53 (0.9%)	22 (1.1%)	0.609
Coronary angiography 1 y	3657 (73.4%)	5259 (74.6%)	4020 (71.8%)	1316 (68.8%)	<0.001
Percutaneous coronary intervention	2202 (44.2%)	2944 (41.8%)	2194 (39.2%)	660 (34.5%)	<0.001
Coronary artery bypass surgery	811 (16.3%)	1243 (17.6%)	1021 (18.2%)	342 (17.9%)	0.056
Number of days from AMI/angina to LDL measurement					
Median (IQR)	115 (63–204)	114 (62–204)	122 (67–209)	129 (74–210)	<0.001
Number of days from statin to LDL test					
Median (IQR)	18 (5–43)	22 (6–50)	25 (7–55)	40 (11–80)	<0.001

ACS indicates acute coronary syndrome; AMI, acute myocardial infarction; HDL, high density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; TIA, transient ischemic attack.

outcomes varied by age (age-LDL cholesterol interaction, $P<0.001$). While in both age groups, the adjusted probabilities of the occurrence of our primary composite outcome within 8.1 years decreased from LDL cholesterol levels of 100 mg/dL down to 70 mg/dL, the incremental adjusted probabilities of AMI or death were not significantly lower at LDL cholesterol levels under 70 mg/dL as compared with those estimated using current LDL cholesterol levels as observed in the real-world (Figure 2).

After adjusting for all baseline clinical factors, no more than 2.3 adverse events per 1000 post-ACS patients (95% confidence interval: −0.7 to 5.4, $P=0.62$) would have been prevented over 8.1 years if all patients' LDL cholesterol levels were to have been reduced from current levels to LDL cholesterol targets of ≤70 or ≤50 mg/dL. There were no significant differences in the numbers of adverse events prevented between patients aged ≥75 years versus those 66 to 74 years of age, or when reducing LDL cholesterol levels down from current levels to a target of ≤70 mg/dL versus a target of ≤50 mg/dL ($P>0.6$) (Table 2).

Sensitivity Analyses

A sensitivity analysis when including stroke in our composite outcomes did not meaningfully alter our results. Additional sensitivity analyses examined non-composite outcomes of all-cause mortality alone and AMI alone. While the projected impact of aggressive LDL cholesterol targets varied by outcomes, the absolute numbers of projected adverse events prevented were uniformly low with overlapping confidence intervals irrespective of age, sex, comorbidity, target levels, and outcomes assessed (Tables 3 and 4). Finally, a sensitivity analysis in which we adjusted for prescription refill adherence data (proportion of days covered) did not meaningfully change our results.

Discussion

Our study explored the projected number of incremental adverse outcomes that could have been prevented if all post-ACS elderly statin users were treated to aggressively low LDL cholesterol target levels. We projected no significant reductions in the numbers of adverse events prevented over a duration of 8.1 years if all elderly statin users post-ACS had been treated from their current LDL cholesterol levels to LDL cholesterol targets of ≤70 or ≤50 mg/dL.

Our study builds on the growing body of evidence examining the incremental clinical effectiveness of aggressive LDL cholesterol lowering in the management of cardiovascular disease. Our findings were consistent with those of a recent observational study examining statin adherers among a population with pre-existing ischemic heart disease in Israel, in which LDL cholesterol levels of ≤70 mg/dL were not associated with any differences in the risk of adverse cardiovascular events than LDL cholesterol levels of between 70 and 100 mg/dL.[22] To the best of our knowledge, our study is the first to project the population effectiveness of using LDL cholesterol targets among an exclusively elderly population of statin users. Moreover, our study focused on lower LDL cholesterol targets than previous observational studies (≤50 mg/dL), and did so among a post-ACS population, where the debate over the implementation of aggressively low LDL cholesterol targets remains greatest.[1,3,4,23,24] Finally, our study took place within the Canadian healthcare setting, which covers the costs of medications for patients aged ≥65 years, thereby mitigating the potential effects of medication affordability on outcomes.

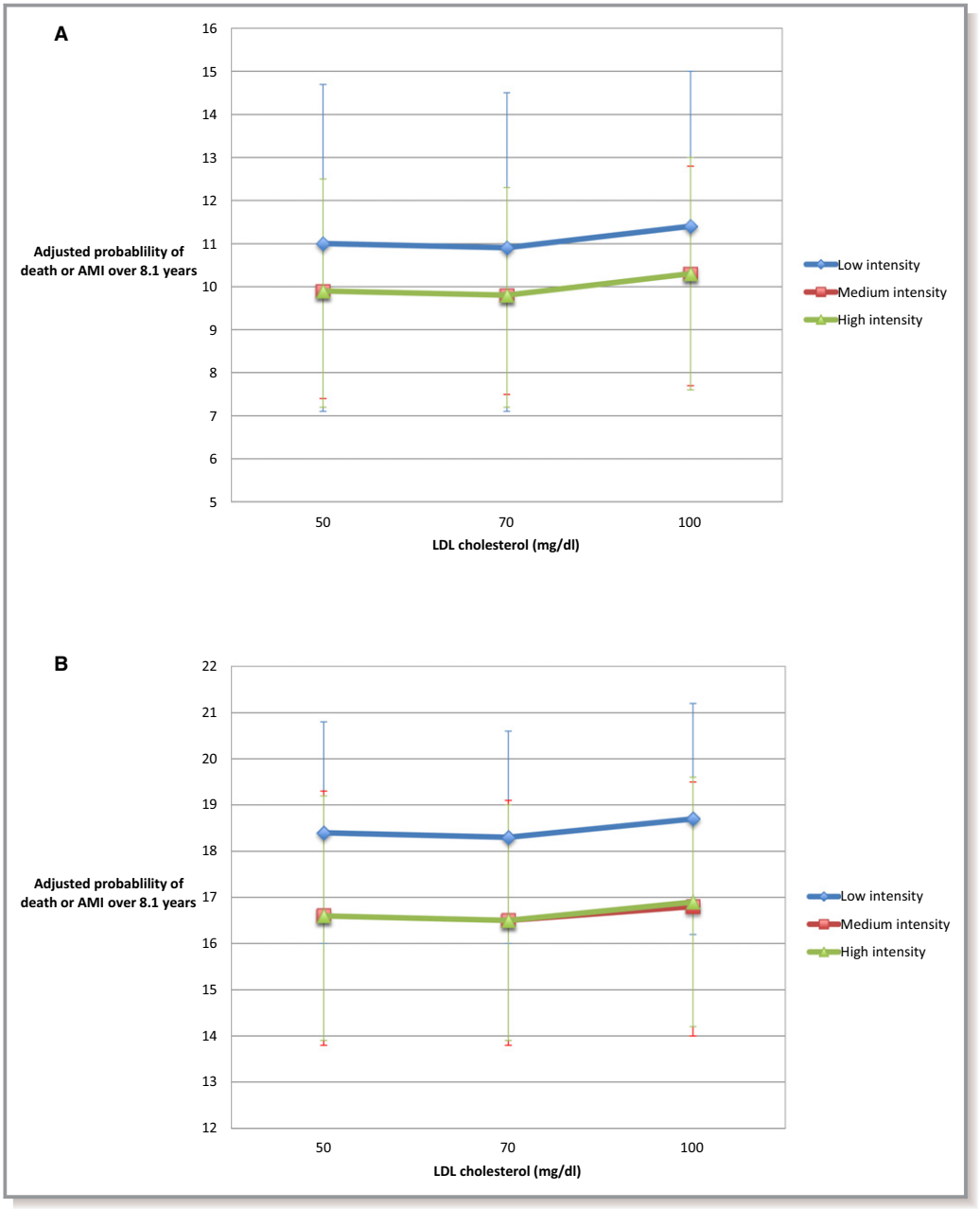

Figure 2. The relationship between LDL cholesterol and the adjusted probability of death or acute myocardial infarction according to statin dose intensity. A, Among patients ages 66 to 74 years old. B, Among patients ages ≥75 years. AMI indicates acute myocardial infarction; LDL, low-density lipoprotein cholesterol.

Clinical trials, such as IMPROVE-IT (The Improved Reduction of Outcomes: Vytorin Efficacy International Trial), demonstrated that patients randomized to a combination of simvastatin and ezetemibe achieved a modest 6.4% relative improvement in composite cardiovascular outcomes of death from cardiovascular disease, a major coronary event, or nonfatal stroke, compared with those randomized to simvastatin alone although mortality rates did not differ between the 2 groups. Such outcome improvements were thought to be attributable to variations in LDL cholesterol levels between the 2 groups (ie, average LDL cholesterol of 53.7 mg/dL versus 69.5 mg/dL)[1]—LDL cholesterol levels similar to the targets examined in our study.

PCSK-9 inhibitors have emerged as a potent LDL cholesterol lowering therapy, which may serve as an adjunctive (or alternate) therapy to statins among high-risk populations. The recently published FOURIER (Further Cardiovascular OUTcomes Research with PCSK9 Inhibitors in Subjects with Elevated risk) trial, a phase 3 double-blind randomized placebo controlled trial, enrolled 27 500 high-risk patients

Table 2. The Estimated Number of Deaths or AMI Events Prevented Had All Post-ACS Elderly Statin Users in Ontario, Canada Been Treated From Current LDL Cholesterol Levels to One of Two LDL Cholesterol Targets (ie, the LDL Cholesterol Levels ≤50 mg/dL and LDL Cholesterol Levels ≤70 mg/dL)

Age Groups	LDL Target Levels, mg/dL	Number of Patients Currently in Ontario Whose LDL Cholesterol Exceeding the Corresponding LDL Target Level	Number of Adverse Outcomes Prevented (+/− 95% Confidence Interval) Per 1000 Patients Treated to Achieve the Corresponding LDL Target Level*	Number of Adverse Outcomes Prevented in the Sample (+/− 95% CI)	*P* Value
All patients	≤70	7513	2.3 (−0.7 to 5.4)	45 (−14 to 106)	0.62
	≤50	14 560	0.7 (−7.7 to 8.9)	13 (−150 to 173)	
66 to 74 y	≤70	3464	3.6 (−1.4 to 8.9)	31 (−12 to 77)	0.83
	≤50	6584	2.5 (−9.8 to 14.9)	22 (−86 to 130)	
≥75 y	≤70	4049	1.3 (−2.3 to 4.9)	14 (−25 to 53)	0.63
	≤50	7979	−0.8 (−11.2 to 9.3)	−9 (−121 to 100)	

ACS indicates acute coronary syndrome; AMI, acute myocardial infarction; CI, confidence interval; LDL, low-density lipoprotein cholesterol.
*Average outcome rates were derived using Cox proportional hazards models adjusted for age, sex, socioeconomic status, clinical risk factors, invasive cardiac procedures, comorbid diseases, statin intensity, and an age-LDL cholesterol interaction. For each subject, we computed 2 probabilities based on the fitted Cox model. First, the patient's model-based probability of an event over 8.1 years (which corresponds to the maximum duration of study follow-up) conditional on his/her existing LDL and their measured baseline covariates. Second, the patient's model-based probability of an event over 8.1 years, under the assumption that his/her LDL cholesterol was lowered to the desired target threshold (and that other baseline covariates remaining unchanged). For subjects who were currently at or below the LDL threshold, we assumed that these 2 probabilities were equal to one another (ie, that their LDL would not change). We then computed the difference in these 2 probabilities. The average of this difference in probabilities across the sample of patients is the population-average reduction in the probability of an event. This average probability was multiplied by the size of the initial cohort to estimate the reduction in the number of events if LDL was lowered to the target level. Negative numbers imply more rather than fewer adverse events prevented as a result of the projected treatment strategy.

on optimal statin therapy whose LDL cholesterol levels were 70 mg/dL or greater (or a non HDL cholesterol of 100 mg/dL or greater).[6] The study demonstrated a 15% relative risk reduction of the composite cardiovascular end point among patients randomized to evolocumab as compared with placebo. Improvement of evolocumabs in outcomes was attributed to the 59% reduction in mean LDL cholesterol as compared with placebo (mean LDL cholesterols: 30.2 mg/dL versus 92 mg/dL in evolocumab versus placebo, respectively). Outcome benefits associated with evolocumab were driven predominantly by a reduction in non-fatal rather than fatal vascular events (ie, myocardial infarction, stroke, coronary revascularization), and were considered modest in magnitude relative to the large decreases in LDL levels achieved.

The debate regarding the relationship between LDL cholesterol and outcomes continues to evolve. A recent consensus document summarizing the results of >200 studies led the authors to unequivocally conclude that the relationship between LDL cholesterol and adverse outcomes was "dose-dependent" and linear.[25] However, most studies that have supported a "lower is better" linear relationship between LDL cholesterol and outcomes have been conducted in younger populations. Indeed, elderly populations have been significantly under-represented in statin and PCSK-9 inhibitor outcome trials.[5,26–35] Our study suggests that the linear "dose-dependent" relationship between LDL cholesterol and outcomes may not apply to elderly populations on statins following ACS hospitalizations, and the effectiveness of using aggressive LDL cholesterol targets among such elderly subpopulations may be unwarranted. In this regard, our findings support the 2013 American College of Cardiology/American Heart Association, United States Preventative Task Force, and the Department of Veterans Affairs and Department of Defense practice guidelines which do not advocate for cholesterol targets among secondary prevention in the ≥75-year population.[14,36,37]

Our findings have important implications. First, the negligible outcome benefits, combined with the potential side-effects and higher costs may make the adoption of aggressive LDL cholesterol targets using statins among an elderly post-ACS population unattractive from a clinical and cost-effectiveness standpoint.[38] Moreover, our results may question the merits of serial LDL cholesterol monitoring among statin-adherent elderly populations. Not only did our study demonstrate that LDL cholesterol levels fluctuated little among those with ≥2 measurements over the follow-up period, but the marginal incremental outcome benefits expected may not justify serial LDL cholesterol monitoring among elderly patients already on statins unless serial monitoring is used among patients suspected of being non-adherent or intolerable to statins. Our results may also have implications for PCSK-9 inhibitor research, especially given their costs and their uncertain benefits in elderly populations. In summary, our findings underscore the need for greater clinical effectiveness data for aggressive LDL cholesterol lowering strategies among elderly populations—a population who comprise the majority demographic of the cardiovascular

Table 3. The Estimated Number of Adverse Outcomes (ie, AMI or Death) Prevented Had All Post-ACS Elderly Statin Users in Ontario, Canada Been Treated From Current LDL Cholesterol Levels to One of Two LDL Cholesterol Targets (ie, the LDL Cholesterol Levels ≤50 mg/dL and LDL Cholesterol Levels ≤70 mg/dL) According to Specific Outcomes

Outcome	Age Groups	LDL Target Levels, mg/dL	Number Of Patients Currently in Ontario Whose LDL Cholesterol Exceeding the Corresponding LDL Target Level	Number of Adverse Events Avoided (+/− 95% Confidence Interval) Per 1000 Patients Treated to Achieve the Corresponding LDL Target Level*	Number of Events Prevented in the Sample (+/− 95% CI)	*P* Value
AMI	All patients	≤70	7513	5.3 (3.1–7.8)	104 (60–152)	<0.001
		≤50	14 560	12.8 (7.5–18.2)	249 (146–356)	
	65 to 74 y	≤70	3464	2.4 (−1.2 to 6.3)	21 (−11 to 55)	0.28
		≤50	6584	5.8 (−1.7 to 13.7)	51 (−15 to −120)	
	75+ y	≤70	4049	6.3 (3.6–9.2)	68 (39–100)	<0.001
		≤50	7976	15.1 (8.7–21.6)	164 (94–234)	
All-cause mortality	All patients	≤70	7513	−1.4 (−4.3 to 1.7)	−27 (−84 to 33)	0.01
		≤50	14 560	−9.8 (−17.8 to −1.6)	−192 (−348 to −30)	
	65 to 74 y	≤70	3464	1.6 (−2.9 to 6.3)	14 (−25 to 55)	0.35
		≤50	6584	−3.1 (−15.1 to 8.8)	−27 (−132 to 77)	
	≥75 y	≤70	4049	−3.8 (−7.5 to 0.0)	−41 (−81 to 0)	0.009
		≤50	7976	−15.2 (−25.3 to −4.6)	−164 (−274 to −50)	
All-cause readmission or death	All patients	≤70	7513	2.5 (−0.3 to 5.5)	49 (−7 to 108)	0.74
		≤50	14 560	1.4 (−6.6 to 9.4)	28 (−128 to 184)	
	65 to 74 y	≤70	3464	3.4 (−1.3 to 8.3)	30 (−11 to 72)	0.48
		≤50	6584	−0.4 (−13.4 to 12.6)	−3 (−117 to 110)	
	≥75 y	≤70	4049	1.8 (−1.7 to 5.4)	19 (−19 to 58)	0.79
		≤50	7976	2.9 (−6.9 to 12.6)	31 (−74 to 136)	

ACS indicates acute coronary syndrome; AMI, acute myocardial infarction; CI, confidence interval; LDL, low-density lipoprotein cholesterol.
*Average outcome rates were derived using Cox proportional hazards models adjusted for age, sex, socioeconomic status, clinical risk factors, invasive cardiac procedures, comorbid diseases, statin intensity, and an age-LDL cholesterol interaction. For each subject, we computed 2 probabilities based on the fitted Cox model. First, the patient's model-based probability of an event over 8.1 years (which corresponds to the maximum duration of study follow-up) conditional on his/her existing LDL and their measured baseline covariates. Second, the patient's model-based probability of an event over 8.1 years, under the assumption that his/her LDL cholesterol was lowered to the desired target threshold (and that other baseline covariates remaining unchanged). For subjects who were currently at or below the LDL threshold, we assumed that these 2 probabilities were equal to one another (ie, that their LDL would not change). We then computed the difference in these 2 probabilities. The average of this difference in probabilities across the sample of patients is the population-average reduction in the probability of an event. This average probability was multiplied by the size of the initial cohort to estimate the reduction in the number of events if LDL was lowered to the target level. Negative numbers imply more rather than fewer adverse events prevented as a result of the projected treatment strategy.

disease population, yet for whom clinical efficacy of aggressive LDL cholesterol lowering remains less clear than that of younger populations.

Our study has several important limitations. First, our study relies on observational data and makes the assumption that the number of cardiovascular events prevented among patients on statins whose LDL cholesterols exceeded a pre-specified target would reflect the outcomes associated with LDL cholesterol levels at or below the pre-specified LDL target of interest. We do not know whether lowering of LDL cholesterol to aggressive target levels would have been feasible or would have translated into outcomes that mirrored those individuals whose LDL cholesterol levels were already at or below the targets of interest. Moreover, residual confounding may have existed, as we had no information on other lifestyle behaviors or anthropometric measures beyond cholesterol levels themselves. As has been seen in other studies such as SPRINT (Systolic Blood Pressure Intervention Trial) for blood pressure control, the clinical benefits of aggressive risk-factor modification may not always be apparent originally using observational study designs.[39] Furthermore, our median follow-up time was only 2.8 years. That said, insufficient clinical trial and/or intervention data existed that could inform the efficacy of a treatment-to-target approach in real-world elderly populations beyond the use of observational data.

Second, our study was not designed to determine why some patients' baseline LDL cholesterol levels were lower than others despite the fact that all patients were on statins. In our study, patients with lower LDL cholesterol levels were

Table 4. The Estimated Number of Adverse Outcomes (AMI or Deaths) Prevented Had All Post-ACS Elderly Statin Users in Ontario, Canada Been Treated From Current LDL Cholesterol Levels to One of Two LDL Cholesterol Targets (ie, the LDL Cholesterol Levels ≤50 mg/dL and LDL Cholesterol Levels ≤70 mg/dL) According to Sex and Charlson Index

Outcome	LDL Target Levels, mg/dL	Number of Patients Currently in Ontario Whose LDL Cholesterol Exceeding the Corresponding LDL Target Level	Number of Adverse Events Avoided (+/− 95% Confidence Interval) Per 1000 Patients Treated to Achieve the Corresponding LDL Target Level*	Number of Events Prevented in the Sample (+/− 95% CI)	*P* Value
Female	≤70	3462	2.8 (−1 to 6.8)	22 (−8 to 53)	0.49
	≤50	6090	0.9 (−8.3 to 10.4)	7 (−64 to 80)	
Males	≤70	4051	2 (−0.4 to 4.6)	24 (−5 to 54)	0.52
	≤50	8470	0.4 (−6.9 to 8)	5 (−81 to 95)	
Charlson ≤2	≤70	4690	2.3 (−0.7 to 5.4)	26 (−8 to 61)	0.51
	≤50	8845	0.6 (−7.5 to 8.9)	6 (−84 to101)	
Charlson >2	≤70	2823	2.4 (−0.5 to 5.5)	20 (−4 to 45)	0.49
	≤50	5715	0.6 (−7.1 to −8.8)	5 (−59 to 72)	

ACS indicates acute coronary syndromes; AMI, acute myocardial infarction; CI, confidence interval; LDL, low-density lipoprotein cholesterol.

*Average outcome rates were derived using Cox proportional hazards models adjusted for age, socioeconomic status, clinical risk factors, invasive cardiac procedures, comorbid diseases, statin intensity, and an age-LDL cholesterol interaction. For each subject, we computed 2 probabilities based on the fitted Cox model. First, the patient's model-based probability of an event over 8.1 years (which corresponds to the maximum duration of study follow-up) conditional on his/her existing LDL and their measured baseline covariates; second, the patient's model-based probability of an event over 8.1 years, under the assumption that his/her LDL cholesterol was lowered to the desired target threshold (and that other baseline covariates remaining unchanged). For subjects who were currently at or below the LDL threshold, we assumed that these 2 probabilities were equal to one another (ie, that their LDL would not change). We then computed the difference in these 2 probabilities. The average of this difference in probabilities across the sample of patients is the population-average reduction in the probability of an event. This average probability was multiplied by the size of the initial cohort to estimate the reduction in the number of events if LDL was lowered to the target level. Negative numbers imply more rather than fewer adverse events prevented as a result of the projected treatment strategy.

more likely to be older and of male sex, were more likely to have diabetes mellitus, hypertension, and comorbidity, and were more likely to be receiving higher intensity statins than those who had higher LDL cholesterol levels at baseline. Accordingly, we hypothesize that variations in LDL cholesterols are multifactorial, and likely attributable to differences in treatment aggressiveness (statin intensity and doses), variations in statin adherence, biological responsiveness to therapy, genetic predisposition, and/or frailty. That being said, sensitivity analyses demonstrated that the absolute number of preventable adverse events from aggressive LDL cholesterol targets were similarly low among younger (65–74 years old) versus older (≥75 years old) patients, males versus females, and those with higher versus lower Charlson comorbidity scores. Moreover, adjusting for prescription refill data did not significantly alter our results.

Third, we assumed that every patient whose LDL cholesterol exceeded our pre-specified targets could have actually achieved lower LDL cholesterol levels regardless of whether or not they were already on maximum intensities of statins. Given that any potential incremental benefits from aggressive LDL cholesterol lowering would have only applied to those who were not receiving maximum intensities of high-intensity statins, our results, if anything, provide a best-case scenario regarding the projected incremental benefit among this elderly population.

Fourth, LDL cholesterol levels were well controlled with the majority of patients receiving medium- or high-intensity statins. The optimal penetrance of statin therapy in this population is not unique to Ontario,[40] and likely reflects on a multitude of factors including increasing evidence, better education, evolving clinical guidelines, as well as provincial and national quality control best-practice initiatives that have been undertaken to optimize secondary prevention management throughout the past decade. It is possible that the incremental yield of aggressive LDL cholesterol targets might have been greater had LDL cholesterol levels been less tightly controlled than that of the elderly Ontario statin population.

Finally, our study was restricted to the Ontario population. While the population size of Ontario is the largest of any other province and comprises 40% of the Canadian population, it is possible that results may not be generalizable to other jurisdictions, particularly those whose LDL cholesterol levels were generally less well-controlled and/or where statins were less well-penetrated. Nonetheless, these limitations must be counterbalanced against the strengths of this natural history population-based study, in which detailed serial cholesterol measurements and statin prescriptions were available.

In conclusion, the number of acute myocardial infarctions or death that could be prevented through the implementation of LDL cholesterol targets with statins is negligible among an elderly post-ACS population. Such findings may have

implications for the applicability of newer agents, such as PCSK-9 inhibitors.

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SUPPLEMENTAL MATERIAL

Table S1. The relationship between an individual's statin intensity and the statin intensity at the end of study follow-up, among all patients, and among age-specific subgroups of less 75 years of age, and 75+ years).

Age Group: <75 yr

Statin Intensity at the baseline vs. at the end of the study					
Statin Intensity at baseline	**Statin Intensity at the end of the study**				
Frequency Row Pct	**Off**	**Low**	**Medium**	**High**	**Total**
Low	38 20.54	77 41.62	60 32.43	10 5.41	**185**
Medium	446 14.27	58 1.86	2151 68.81	471 15.07	**3126**
High	626 11.54	31 0.57	593 10.93	4176 76.96	**5426**
Total	**1110**	**166**	**2804**	**4657**	**8737**

The median number (Interquartile range) of statin prescriptions filled during follow-up among patients age 75 years and older was 15 (7-19).

Age Group: 75+ yr

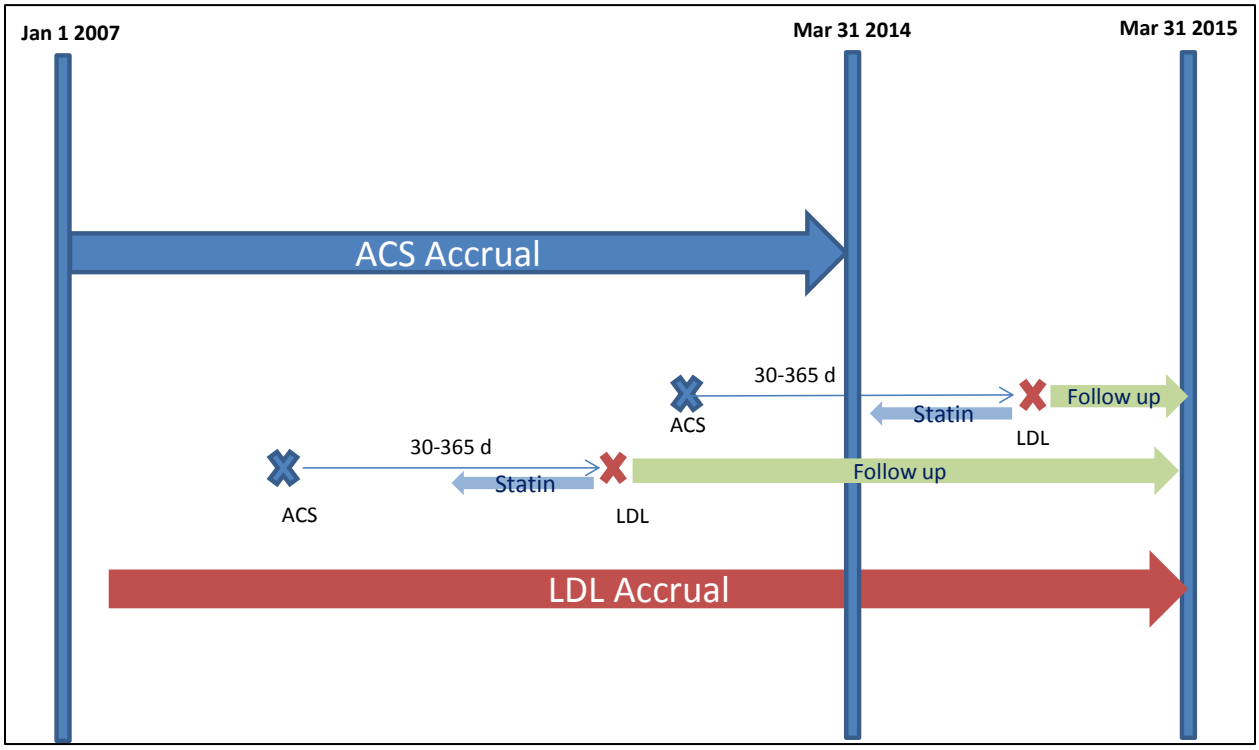
Statin Intensity at the baseline vs. at the end of the study					
Statin Intensity at baseline	**Statin Intensity at the end of the study**				
Frequency Row Pct	**Off**	**Low**	**Medium**	**High**	**Total**
Low	84 22.52	198 53.08	73 19.57	18 4.83	**373**
Medium	908 18.7	52 1.07	3500 72.09	395 8.14	**4855**
High	910 16.31	38 0.68	658 11.79	3973 71.21	**5579**
Total	**1902**	**288**	**4231**	**4386**	**10807**

The median number (Interquartile range) of statin prescriptions filled during follow-up among patients age 75 years and older was 16 (7-39).

All patients:

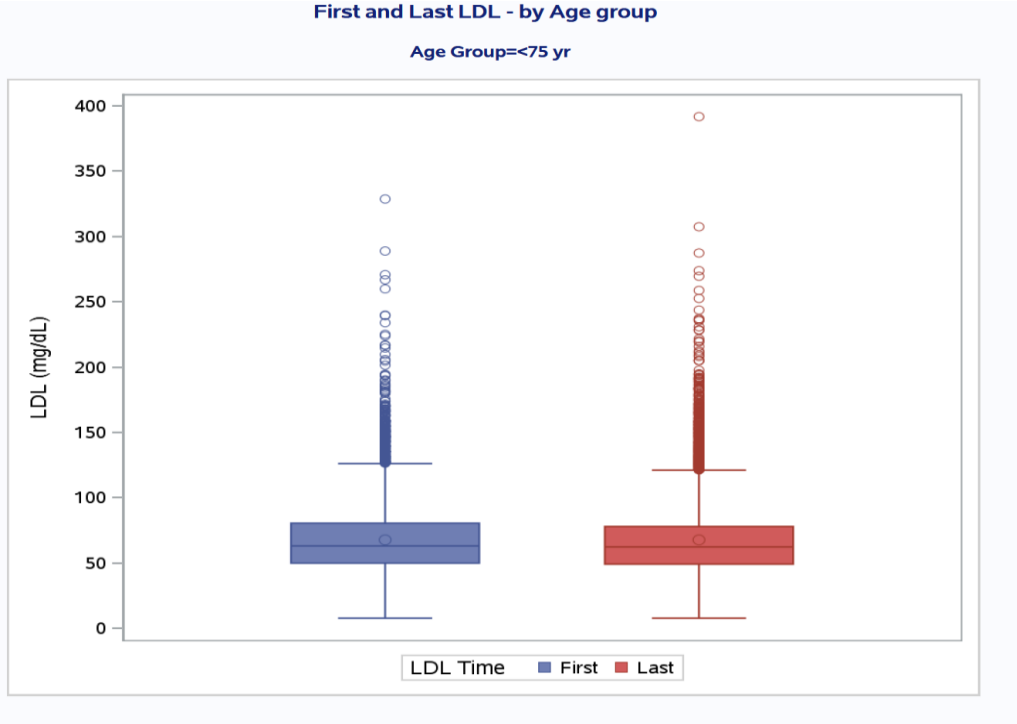
Statin Intensity at the baseline vs. at the end of the study					
Statin Intensity at baseline	**Statin Intensity at the end of the study**				
Frequency **Row Pct**	**Off**	**Low**	**Medium**	**High**	**Total**
Low	122 21.86	275 49.28	133 23.84	28 5.02	**558**
Medium	1354 16.97	110 1.38	5651 70.81	866 10.85	**7981**
High	1536 13.96	69 0.63	1251 11.37	8149 74.05	**11005**
Total	**3012**	**454**	**7035**	**9043**	**19544**

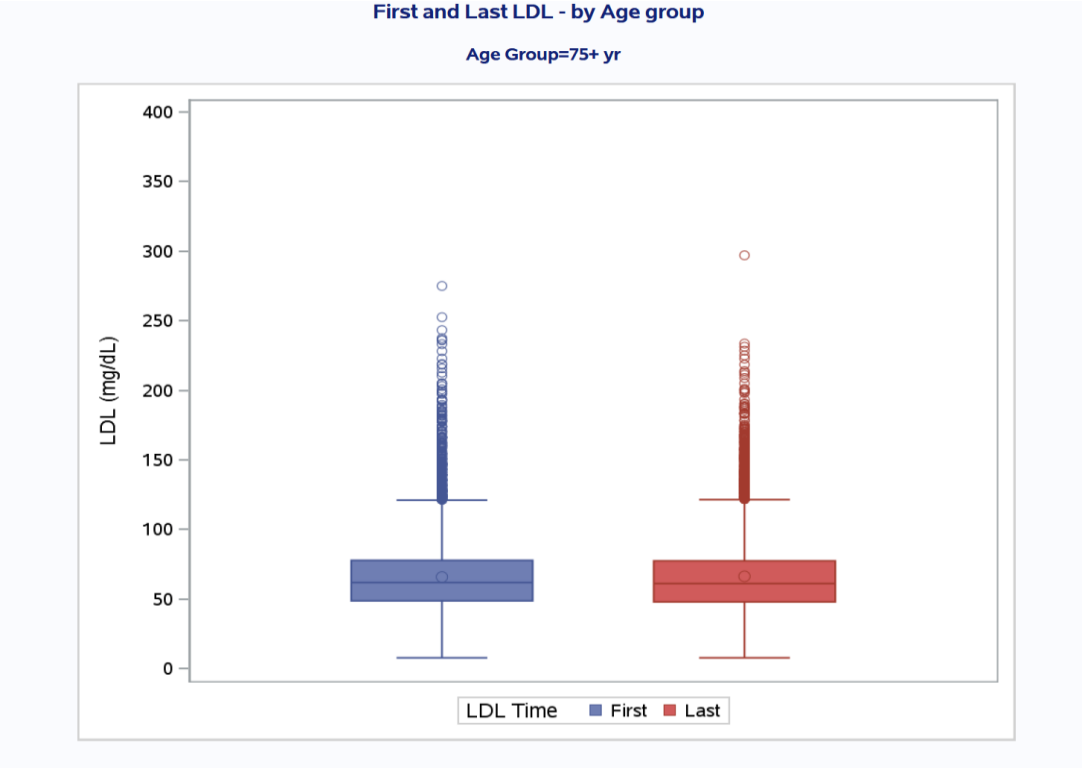
Figure S1. The schematic diagram of the study design.



ACS=Acute Coronary Syndromes
LDL=Low-density Lipoprotein Cholesterol

Figure S2. The distribution of LDL cholesterol during the first and last measurements among patients less than 75 years old, and those 75 years of age and older.





LDL=Low-Density Lipoprotein Cholesterol