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ORIGINAL RESEARCH

Effect of statin use for the primary prevention of cardiovascular disease among older adults: a cautionary tale concerning target trials emulation

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Abstract

Objectives: Evidence concerning the effect of statins in primary prevention of cardiovascular disease (CVD) among older adults is lacking. Using Quebec population-wide administrative data, we emulated a hypothetical randomized trial including older adults >65 years on April 1, 2013, with no CVD history and no statin use in the previous year.

Study Design and Setting: We included individuals who initiated statins and classified them as exposed if they were using statin at least 3 months after initiation and nonexposed otherwise. We followed them until March 31, 2018. The primary outcome was the composite endpoint of coronary events (myocardial infarction, coronary bypass, and percutaneous coronary intervention), stroke, and all-cause mortality. The intention-to-treat (ITT) effect was estimated with adjusted Cox models and per-protocol effect with inverse probability of censoring weighting.

Results: A total of 65,096 individuals were included (mean age = 71.0 ± 5.5, female = 55.0%) and 93.7% were exposed. Whereas we observed a reduction in the composite outcome (ITT−hazard ratio (HR) = 0.75; 95% CI: 0.68−0.83) and mortality (ITT-HR = 0.69; 95% CI: 0.61−0.77) among exposed, coronary events increased (ITT-HR = 1.46; 95% CI: 1.09−1.94). All multibias E-values were low indicating that the results were not robust to unmeasured confounding, selection, and misclassification biases simultaneously.

Conclusion: We cannot conclude on the effectiveness of statins in primary prevention of CVD among older adults. We caution that an in-depth reflection on sources of biases and careful interpretation of results are always required in observational studies.

Keywords: Statin use; Primary prevention; Older adults; Cardiovascular disease; All-cause mortality; Quebec; Hypothetical randomized trial

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Plain language summary

We conducted a study to determine the effect of statins in older adults on cardiovascular disease (CVD) using administrative data from Quebec. People aged over 65 years on April 1, 2013, with no CVD history and no statin use in the previous year were followed until March 31, 2018. We examined an outcome comprised of coronary events, stroke, and all-cause mortality. The effect was estimated with different statistical methods. Some of our results appear implausible, and we cannot draw any conclusion about the benefit of statins in this population.

What is new?

Key findings

- In this target trial that included 65,096 individuals, the hazard ratios of the composite outcome and mortality were reduced in persistent users of statins, while those for coronary events increased.

What this adds to what was known?

- The results do not allow for drawing conclusions regarding the benefits of statins, as residual biases appear to have persisted despite the emulation of a targeted trial.

What is the implication and what should change now?

- It is important to investigate the potential impact of biases, even if the results are in the expected direction.
- Emulating a hypothetical trial is a relevant tool for minimizing bias, but it does not entirely rule out residual bias.

1. Introduction

CVD is among the leading causes of disability-adjusted life years worldwide [1] and has major global public health impacts [2]. Several randomized clinical trials (RCTs) have shown that the use of statins is beneficial in reducing the risk of CVD in primary prevention [3−8].

Evidence of the efficacy of statins in primary prevention among older adults (≥65 years) is lacking [9]. Clinical trials generally include a highly selected, younger, healthier population with better follow-up and compliance than the target population [10]. They are also less likely to include individuals aged 75 years and over who represent a substantial proportion of real-world statin users [11]. Observational studies are crucial because they facilitate an assessment under realistic settings with a longer follow-up and therefore are more generalizable than RCTs. A recent systematic review including 10 observational studies with follow-up between 4.7 and 24 years, indicated that statin therapy is associated with a 14%, 20%, and 15% risk reduction in all-cause mortality, CVD mortality, and stroke, respectively, in people over 65 years of age without CVD, and this reduction remained in people over 75 years of age [12]. Some of the studies included in this systematic review considered nonusers of statins as a reference group [13−16], which may lead to indication bias, and were subject to confounding [15,17−20], selection [18] and misclassification [16,21] biases. Moreover, few studies have performed subgroup analyses according to characteristics more frequent in older adults such as polypharmacy or multimorbidity, which may help identify heterogeneity between groups of individuals.

The target trial methodology is a causal inference approach that harmonizes the objectives and analytical methods of randomized trials and observational studies [22]. Target trials limit the potential for bias in the analysis of observational data [22,23]. In this study, we emulated a hypothetical randomized trial (target trial) using administrative data from Quebec, Canada, to assess the effectiveness of statins to prevent a first CVD event or death among new users aged >65 years. We first describe all the steps taken to minimize the biases and showcase that the results obtained are regardless not very credible. We then propose an in-depth reflection on the sources of residual bias.

2. Methods

2.1. Hypothetical target trial specification

Table 1 summarizes the key components of the hypothetical randomized trial that we aimed to emulate (ie, the target trial) and the procedures used to emulate it, which were determined before the analysis [22]. Each component is described in Supplement Material A.

2.2. Target trial emulation

The target trial was emulated using observational data from the Quebec Integrated Chronic Disease Surveillance System (QICDSS), which comprises five health administrative databases: 1) the health insurance registry, 2) the pharmaceutical services database, 3) the physician claims database, 4) the hospitalization database, and 5) the death registry. The health insurance registry includes data on sociodemographic characteristics, eligibility and admissibility

Table 1. Specification and emulation of a target trial of statin use and all-cause mortality and CVD

Component	Target trial specification	Target trial emulation
Eligibility criteria	• Older adults aged >65 y • No prior statin treatment in their lifetime • No history of CVDs (myocardial infarction, heart failure, other ischemic heart disease and cerebrovascular disease) in their lifetime • No long-term care residence in the past year • Not transferred to long-term care residence before statin initiation	Same, except that we included people with continuous medical insurance coverage in their lifetime and excluded people with history of CVD from 1996, who had used statins in the year before April 1, 2013, and who experienced the outcomes within 30 d of the index date.
Treatment strategies	• Initiation and persistence of statin usage • Noninitiation of statin usage	• Consistently use statins during the first 3 mo following initiation (statin persistence) • Statins discontinuation during the 3 mo following initiation (statin nonpersistence)
Treatment assignment	Individuals are randomly assigned to a treatment strategy and are aware of their treatment strategy.	We considered that older adults are randomly assigned within levels of baseline covariates (Table 2)
Outcomes	• Composite endpoint: coronary event, stroke, and all-cause mortality • Coronary event • All-cause mortality	Same
Follow-up	Starts after assignment to a strategy and end at diagnosis of coronary event, stroke, death, or March 31, 2018, whichever comes first.	Same
Causal contrasts	Intention-to-treat and per-protocol effects	Observational analog of the intention-to-treat and per-protocol effects
Analysis plan	For each outcome: • Intention-to-treat analysis: compare the hazard ratio under each treatment strategy • Per-protocol analysis: same as the intention-to-treat analysis except that older adults who deviate from the protocol are censored. The analysis uses inverse probability of censoring weights to adjust for both baseline and postbaseline covariates. • Subgroup analysis	For each outcome: • Intention-to-treat-analysis: contrast those persistent vs nonpersistent with adjustment for baseline covariates • Per-protocol analysis with adjustment for baseline covariates and for censoring (due to changes in statins use and other reasons) by inverse probability of censoring weights with both baseline and postbaseline covariates. • Same

CVD, cardiovascular disease.

to the public health and the drug insurance plans. The pharmaceutical services database provides information on medication claims, including the name of the medication, the quantity dispensed and the length of supply. Data on health services and hospitalizations are provided by the physician claims and hospitalization databases, and notably include diagnostic codes. Dates of death are recorded in the death registry and the health insurance registry. The entire population is included in medical databases, and 90% of people ≥65 are covered by public drug insurance (excluding people in long-term care and those with private insurance).

Statin treatment included atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin, and the combination niacin/lovastatin; the associated common denomination and Anatomical/Therapeutic/Chemical codes are provided in Supplement Table 1.

Cardiovascular events were identified using validated definitions from the *Institut national de santé publique du Québec* based on the International Classification of Diseases ninth and 10th version [24–26]. These definitions are also used by the Public Health Agency of Canada. Individuals were considered having a stroke if the diagnosis of stroke or transient ischemic attack was mentioned at least twice within a 1-year period in the fee-for service physician database or once in the hospitalization database [27,28]. This definition has a sensitivity of 68% and a specificity of 99% [26,27]. Coronary event was defined as follows: i) at least 2 diagnoses of myocardial infarction or unstable angina within a 1-year period in the physician service database, ii) 1 diagnosis (primary or secondary) of myocardial infarction or unstable angina in the hospitalization database, or iii) the presence of a coronary artery bypass graft or percutaneous coronary intervention codes in the hospitalization database. This definition has a sensitivity of 77% and a specificity of 98% [26]. Diagnostic codes are listed in Supplement Table 2.

Baseline covariates included age, sex (male/female), residence area (urban [≥10,000 inhabitants]/rural), health services variables (number of visits in the previous year

to a generalist, to a specialist, to an emergency room and number of hospitalizations in the previous year), prevalent diabetes (yes/no) [29], hypertension (yes/no) [30−33], chronic kidney disease (yes/no) [34], comorbidity score constituted of Charlson and Elixhauser scores which includes 32 diseases [34], number of different medications claimed in the previous year, material and social deprivation index [35], and current use of aspirin/antiplatelet agents (yes/no), oral anticoagulants (yes/no), blood pressure therapy (yes/no), and other lipid-lowering drugs (yes/no). Other covariates (eg, smoking, cholesterol, family history of CVD) were not available.

2.2.1. Eligibility criteria

Participants who met the eligibility criteria of the target trial were included in the emulated trial, except that we excluded people with a history of CVD since 1996, the date of inception of the databases, instead of life-time history. We excluded those who had experienced the outcomes within 30 days of the index date, ie, during the correspondent trial run-in period. Including those who would have experienced the outcomes within 30 days of index date may not only induce protopathic bias, which occurs when treatment is prescribed for an early manifestation of a disease that has not yet been detected, but also increases the bias due to unmeasured factors (see hypothesized directed acyclic graph, Supplement Figure 1). A flow chart of the selected individuals is presented in Figure 1.

2.2.2. Treatment strategies and assignment

We included all individuals who a had a first claim of a statin between April 1, 2013, and March 31, 2018. Individuals who consistently filled their medications at the pharmacy, ensuring an adequate supply of medication to cover at least 80% of the first 3 months, were considered as having persistent statin use and formed the exposed group. Individuals who discontinued statins during the first 3 months following their initiation were considered as nonpersistent and formed the control group. In addition to ensuring that included individuals were those for whom statin initiation was considered by their physician, this choice of control group ensures that all included individuals had an indication for treatment, as opposed to a nonuser control group. However, the reasons for prescribing statins are not all known and available in administrative data (eg, family history, cholesterol level).

Individuals were classified to the treatment with which their data were compatible, and we attempted to emulate randomization by adjusting for the covariates.

2.2.3. Outcomes and follow-up

The outcomes and the follow-up were similar to those described in the target trial. There was no loss of follow-up.

2.2.4. Causal contrasts and analysis plan

The causal contrasts were the observational analogs of intention-to-treat (ITT) and per-protocol effects.

The follow-up was divided into 3-month periods. Standard differences were calculated to assess the balance of covariates between the 2 groups of treatment, with <0.1 being an indicator of good balance. For the ITT analysis, Cox models were used and adjusted for baseline covariates. Data on deaths were right censored for the analysis of coronary event outcome. The proportionality assumption of the hazards was visually assessed based on Schoenfeld's partial residuals. To control for potential selection bias caused by censoring in the per-protocol analysis, each individual was assigned a time-varying, stabilized inverse

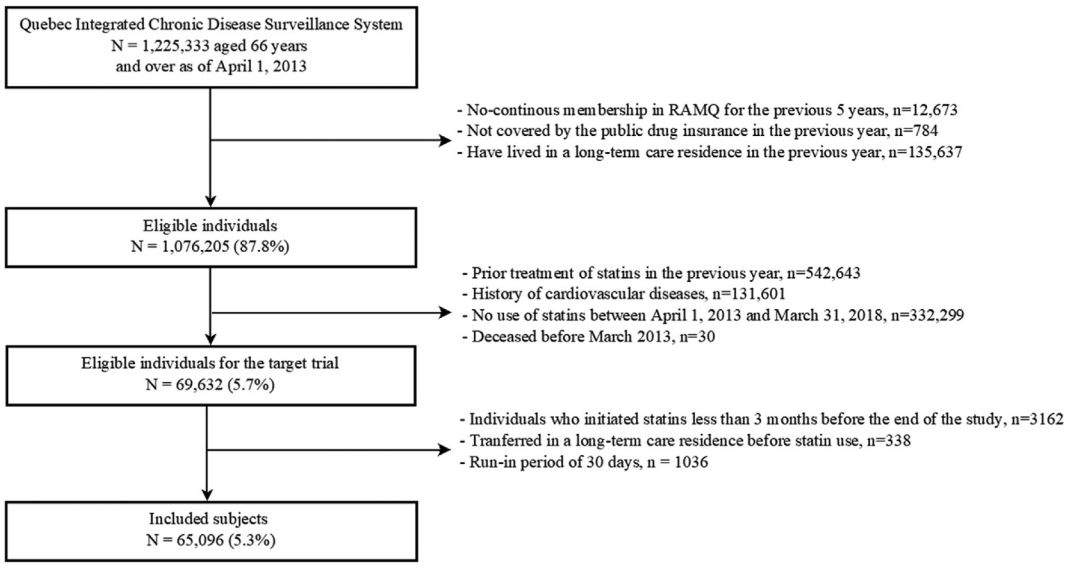

Fig. 1. Flow chart of included individuals from the Quebec Integrated Chronic Disease Surveillance System, 2013 to 2018, Quebec, Canada.

probability weight in each period. Weights were conditioned on baseline covariates (sex, age, deprivation indices) and time-varying confounders (hypertension, chronic kidney disease, diabetes, comorbidity score, number of medications, use of aspirin, use of anticoagulants, use of lipid-lowering drugs other than statins, blood pressure treatment, number of healthcare visits in the previous year (to a general practitioner, a specialist, and an emergency) and number of days of hospitalization). To avoid extreme weights, truncation at the 99th percentile was applied [36,37]. Then, a weighted pooled logistic regression model [38], an approximation to the Cox model, was performed for each outcome.

Four sensitivity analyses were performed. The two first analyses consisted of: i) using a run-in period of 180 days instead of 30 days and ii) not considering a run-in period (ie, including all individuals) and aimed to assess the effect of protopathic bias on our estimates. In a third analysis, we varied the definition of persistent users, from 3 months of persistent use to 6 months. In a fourth analysis, we allowed for a longer wash-out period to better identify incident statin users by considering individuals older than 67 years and excluding those who had received statins in the past 2 years.

We also conducted quantitative bias analyses. Silent events (ie, missing CVD diagnoses) are common in patients with CVD [39,40], ranging between 1.3% and 27% according to a systematic review [41]. Thus, we performed simulations to estimate the extent to which information bias due to missing CVD diagnoses may affect our results. Based on the assumption that persistent users may have more health-seeking behaviors, and are therefore more likely to be diagnosed with CVD and offered percutaneous interventions, we considered 1 scenario in which the misclassification bias was nondifferential and two scenarios in which the misclassification bias was differential, with different levels of imbalance between the two groups. The simulated scenarios can be summarized as follows: 1) 20% of all events are silent in both exposure groups, 2) 20% of all events are silent in the nonpersistent group and 15% in the persistent group, and 3) 20% of all event are silent in the nonpersistent group and 10% in the persistent group. Silent coronary events were randomly generated in each exposure group by replacing some censoring indicators by an event indicator, and five replications were generated for each scenario.

Finally, we calculated the multibias E-value to assess the sensitivity of the results to unmeasured confounders, selection, and misclassification biases simultaneously [42,43]. This measure estimates the minimum value required for the sensitivity parameters of each bias to be consistent with a true null effect. A large E-value means that considerable bias would be required to explain the effect estimate while a small E-value (ie, close to 1) would require only a little bias.

All analyses were performed on R.4.1.0 software (© 2021 The R Foundation for Statistical Computing, Austria). This article follows the Strengthening the Reporting of Observational studies in Epidemiology guideline (Table 2).

2.3. Ethics

The use of the QICDSS is authorized for surveillance purposes by the *Commission d'accès à l'information du Québec*, the *Régie de l'assurance maladie du Québec* and the *ministère de la Santé et des Services sociaux*.

3. Results

Table 3 shows the baseline characteristics of the 65,096 included subjects, among which 60,971 persisted on statins treatment over 3 months and 4125 did not. All covariates were well balanced between persistent and nonpersistent users, apart from hypertension, blood pressure treatment and the number of medications in the year of statin initiation. Unadjusted Kaplan−Meier curves, without exclusions for the run-in-period, are presented in Supplement Figure 2.

3.1. Intention-to-treat analysis

Table 4 presents the adjusted associations between statin persistence and each of the three outcomes. We found a 25% reduction in the hazard of the composite outcome among persistent users compared to nonpersistent users (hazard ratio [HR] = 0.75, 95% CI = 0.68−0.83). A 31% reduction in the hazard of all-cause mortality was observed among persistent users compared to nonpersistent users (HR = 0.69, 95% CI = 0.61−0.77). Persistent users had a higher hazard of coronary event compared to nonpersistent users (HR = 1.46, 95% CI = 1.09−1.94). The proportionality assumption was met in most of the range of the data, with deviations at the extremes where few data points were present (not shown). We performed Fine & Gray models for the coronary event outcome, and the results were similar to those of the Cox models (not shown). The results of the subgroups analyses were mostly similar (Supplement Material B).

3.2. Per-protocol analysis

After truncation, the means of censoring weights varied from 1.0 to 2.1 (Supplement Figure 3). Results for the per-protocol analysis were consistent with the ITT analysis (Table 1, Supplement Tables 3−6).

3.3. Assessment of quantitative bias

Varying the prevalence of silent events in both groups, the HR for the composite outcome and coronary event were less than 1 and the 95% CIs indicated that the data were compatible with associations ranging from moderately to highly preventive (Supplement Figure 3). The reduction was greater for the extreme scenario (Supplement Figure 3, Scenario 3). E-values for confounding bias were

Table 2. STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) Statement—Checklist of items that should be included in reports of cohort studies

Items	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2
Objectives	3	State specific objectives, including any prespecified hypotheses	2
Methods			
Study design	4	Present key elements of study design early in the paper	2
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	2
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4
		(b) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than 1 group	2–4
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	-
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	4–5
		(b) Describe any methods used to examine subgroups and interactions	3
		(c) Explain how missing data were addressed	-
		(d) If applicable, explain how loss to follow-up was addressed	4
		(e) Describe any sensitivity analyses	5
Results			
Participants	13	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed	4
		(b) Give reasons for nonparticipation at each stage	NA
		(c) Consider use of a flow diagram	4
Descriptive data	14	(a) Give characteristics of study participants (eg, demographic, clinical, social) and information on exposures and potential confounders	5
		(b) Indicate number of participants with missing data for each variable of interest	-
		(c) Summarize follow-up time (eg, average and total amount)	-
Outcome data	15	Report numbers of outcome events or summary measures over time	7

around two, suggesting that the results were robust to unmeasured confounding with a maximum odds ratio with either exposure or outcome of two (Supplement Table 11). All multibias E-values were low indicating that the results were not robust to unmeasured confounding, selection, and misclassification biases simultaneously (Supplement Table 11).

4. Discussion

In this paper, we observed a reduction in the hazard of the composite outcome and of mortality, and an increase in the hazard of coronary events among persistent users compared to nonpersistent users. Our results for all-cause mortality were in the same direction as other observational studies that found statin use was associated with a lower risk [14–16,44] but the reduction we observed was considerably larger. The results for coronary events were contrary to the literature [14–16,18,44,45]. Despite our efforts to control and minimize all biases, our results are not biologically plausible, indicating the presence of residual bias.

To better understand our results and assess their robustness, we performed several sensitivity analyses. Although for some sensitivity analyses, the risk of the composite outcome and all-cause mortality was lower in persistent

Table 3. Characteristics of included individuals in the target emulation trial, Quebec Integrated Chronic Disease Surveillance System, 2013 to 2018, $n = 65{,}096$, Quebec, Canada

Variables	Statin persistence		Standardized mean differences[a]
	Yes, $n = 60{,}971$ (93.7%)	No, $n = 4125$ (6.3%)	
Sex, *n* (%)			
Female	33,517 (55.0)	2474 (60.0)	−0.08
Male	27,454 (45.0)	1651 (40.0)	
Age, mean (SD)[b]	71.0 (5.5)	70.9 (5.8)	0.02
Residence area[c], *n* (%)			
Urban	46,179 (75.8)	3207 (77.8)	−0.04
Rural	14,747 (24.2)	916 (22.2)	
Material deprivation quintile[c], *n* (%)			
Quintile 1 (most privileged)	10,169 (17.7)	717 (18.6)	−0.02
Quintile 2	10,941 (19.0)	726 (18.8)	0.00
Quintile 3	11,416 (19.8)	781 (20.2)	−0.01
Quintile 4	12,516 (21.7)	800 (20.7)	0.02
Quintile 5 (most deprived)	12,518 (21.7)	839 (21.7)	0.00
Social deprivation quintile[c], *n* (%)			
Quintile 1 (most privileged)	10,717 (18.6)	679 (17.6)	0.02
Quintile 2	11,547 (20.1)	751 (19.4)	0.01
Quintile 3	12,315 (21.4)	811 (21.0)	0.01
Quintile 4	11,731 (20.4)	784 (20.3)	0.00
Quintile 5 (most deprived)	11,250 (19.5)	838 (21.7)	−0.04
Hypertension, *n* (%)	30,955 (50.8)	1637 (39.7)	0.18
Chronic kidney disease, *n* (%)	3698 (6.1)	230 (5.6)	0.02
Diabetes, *n* (%)	8209 (13.5)	601 (14.6)	−0.03
Use of aspirin, *n* (%)	25,573 (41.9)	1245 (30.2)	0.20
Use of anticoagulants, *n* (%)	5323 (8.7)	377 (9.1)	−0.01
Use of lipid-lowering drugs other than statins, *n* (%)	3243 (5.3)	3243 (5.3)	0.00
Blood pressure treatment, *n* (%)	43,928 (72.0)	2362 (57.3)	0.26
Comorbidity score in the year of statin initiation[b], mean (SD)	1.9 (2.8)	1.7 (3.0)	0.07
Number of medications in the year of statin initiation[b], mean (SD)	9.0 (5.4)	8.0 (5.4)	0.19
Number of visits to a general practitioner in the year of statin initiation[b], mean (SD)	1.1 (1.4)	1.1 (1.6)	0.00
Number of visits to a specialist in the year of statin initiation[b], mean (SD)	2.7 (5.7)	2.8 (6.8)	−0.02
Number of visits to an emergency, in the year of statin initiation[b], mean (SD)	0.3 (0.8)	0.3 (0.8)	0.00
$\geq$1 visit for an emergency, in the year of statin initiation, *n* (%)	10,114 (16.6)	699 (16.9)	−0.01
Number of days of hospitalization in the year of statin initiation[b], mean (SD)	0.1 (0.3)	0.1 (0.3)	0.00
$\geq$1 d of hospitalization in the year of statin initiation, *n* (%)	3146 (5.2)	211 (5.1)	0.00
Composite outcome, *n* (%)	5396 (8.9)	392 (9.5)	−0.02
Coronary events, *n* (%)	1654 (2.7)	49 (1.2)	0.08
Stroke, *n* (%)	313 (0.5)	11 (0.3)	0.02
All-cause mortality, *n* (%)	3685 (6.0)	346 (8.4)	−0.08

[a] A difference <0.1 is often deemed negligeable.
[b] SD: Standard deviation.
[c] Sum of counts for residence area, material and social deprivation quintiles does not equal the total number of subjects due to missing values.

Table 4. Adjusted hazard ratios for the association between the use of statins and the outcomes (composite outcome, all-cause mortality, and coronary event) with 30-d run-in period, Quebec Integrated Chronic Disease Surveillance System, 2013–2018, $n = 65{,}096$, Quebec, Canada

Analysis/Outcomes	Composite outcome	All-cause mortality	Coronary event
Intention-to-treat	0.75 (0.68–0.83)	0.69 (0.61–0.77)	1.46 (1.09–1.94)
Per protocol	0.77 (0.73–0.82)	0.73 (0.68–0.79)	1.46 (1.35–1.59)

The composite outcome includes coronary event, stroke, and all-cause mortality.

Analyses were adjusted for sex, age, residence area, deprivation indices, hypertension, chronic kidney disease, diabetes, comorbidity score, number of medications, use of aspirin, use of anticoagulants, use of lipid-lowering drugs other than statins, blood pressure treatment, number of health visits (to a general practitioner, a specialist, and an emergency), and number of days of hospitalization.

users, the harmful HR for coronary events remained. Therefore, we performed a quantitative bias analysis to evaluate the potential strength needed to modify our results. In the following paragraphs, we discuss each potential bias and how it relates to this study. See also Supplement Material C for a discussion of the challenges we encountered in emulating our target trial.

Although the definitions of cardiovascular events we have used have been validated, they are not perfect. First, for stroke and coronary events, there were slight differences between the definition used in the QICDSS and those validated [27,28]. Second, the QICDSS definition of coronary events, that we used, includes not only acute coronary events but also coronary bypass and percutaneous interventions. Because the application of percutaneous interventions is subject to physician subjectivity and may be offered less frequently to nonpersistent users, it may induce differential information bias. However, from a public health perspective, these interventions were relevant to consider because they are important for health resource planning.

Another factor that may play a role in misclassification bias is the presence of silent events. Studies have shown that silent myocardial infarction is common in patients referred for coronary event [39,40] and the prevalence varies between studies, reaching up to 37% in diabetic patients [41]. We showed how the presence of silent events may have impacted our results for the composite outcome and coronary events, with a more pronounced effect for coronary events.

Lifestyle and clinical factors were not available. Therefore, we were unable to adjust for some cardiovascular risk factors such as physical activity, obesity, smoking, family history of CVD, cholesterol level, which may induce residual confounding bias. However, we believe that this bias was minimized by using nonpersistent users as the control group. Indeed, because both treatment groups initiated statins, we know that they met the indication criteria for initiating, whether these criteria were measured or not. In addition, we performed several sensitivity analyses to control for this bias. The sensitivity analysis that included individuals that had the events within 30 days (ie, no run-in) suggests that early events are a proxy for unmeasured factors. These may include risk factors for death that are more common in nonpersistent users, and risk factors for coronary events that are more common in persistent users.

Another limitation is related to the fact that nonpersistent individuals may not be the ideal comparison group, as they have different characteristics than persistent users. Nevertheless, they are the best control group that we can consider in this study. Finally, due to the nature of the data, the definitions of statins and other medication were based on filled prescriptions and not on actual usage. As further limitations, we acknowledge the fact that the protocol for this study was not registered and that the access to the data is restricted.

The sensitivity analyses revealed that not all biases affect the results in the same way, and that target trials, like other observational studies, may have limitations. We observed that the sensitivity analysis with a run-in-period of 180 days yielded more plausible results for some outcomes such as all-cause mortality, suggesting that this adjustment for protopathic bias reduced residual confounding bias. Indeed, the Kaplan–Meier curves without a run-in-period show that most events occur in the early period of follow-up among exposed subjects, consistent with the presence of a protopathic bias. However, misclassification bias seems to also play an important role on the results obtained for coronary events. Although we considered the possibility of incorporating negative control analyses into the paper, this could not be done as we found no outcomes or exposures for which statins had no effect and which share the same confounding factors. Through this paper, we would like to encourage researchers to always investigate the potential impact of biases, even if the results are in the expected direction. Specifically, researchers should i) perform sensitivity analyses to evaluate the robustness of the results, ii) assess the impact of multiple biases on the results using quantitative bias analyses, and iii) discuss the limitations of the data. As we have shown, emulating a hypothetical trial is a crucial tool for minimizing biases, but it does not entirely preclude residual bias.

CRediT authorship contribution statement

Miceline Mésidor: Writing – original draft, Visualization, Validation, Software, Methodology, Formal analysis. **Caroline Sirois:** Writing – review & editing, Visualization, Supervision, Software, Project administration, Methodology, Funding acquisition, Conceptualization. **Jason**

Robert Guertin: Writing − review & editing, Visualization, Funding acquisition, Conceptualization. **Mireille E. Schnitzer:** Writing − review & editing, Visualization, Funding acquisition, Conceptualization. **Bernard Candas:** Writing − review & editing, Visualization, Funding acquisition, Conceptualization. **Claudia Blais:** Writing − review & editing, Visualization, Conceptualization. **Benoit Cossette:** Writing − review & editing, Visualization, Funding acquisition, Conceptualization. **Paul Poirier:** Writing − review & editing, Visualization, Funding acquisition, Conceptualization. **James M. Brophy:** Writing − review & editing, Visualization, Funding acquisition, Conceptualization. **Lisa Lix:** Writing − review & editing, Visualization, Funding acquisition, Conceptualization. **Mina Tadrous:** Writing − review & editing, Visualization, Funding acquisition, Conceptualization. **Awa Diop:** Writing − review & editing, Visualization. **Denis Hamel:** Writing − review & editing, Data curation. **Denis Talbot:** Writing − review & editing, Visualization, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization.

Data availability

The authors do not have permission to share data.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests.

Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jclinepi.2024.111284.

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