Received: 12 August 2021 Revised: 7 December 2021 Accepted: 8 December 2021
DOI: 10.1002/pds.5396

Use of negative control outcomes to assess the comparability of patients initiating lipid-lowering therapies

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Funding information
This study was funded by Amgen, Inc.

Abstract

Purpose: Clinical trials have demonstrated efficacy of proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) in reducing risk of cardiovascular disease events, but effectiveness in routine clinical care has not been well-studied. We used negative control outcomes to assess potential confounding in an observational study of PCSK9i versus ezetimibe or high-intensity statin.

Methods: Using commercial claims, we identified U.S. adults initiating PCSK9i, ezetimibe, or high-intensity statin in 2015–2018, with other lipid-lowering therapy (LLT) use in the year prior (LLT cohort) or atherosclerotic cardiovascular disease (ASCVD) in the past 90 days (ASCVD cohort). We compared initiators of PCSK9i to ezetimibe and high-intensity statin by estimating one-year risks of negative control outcomes influenced by frailty or health-seeking behaviors. Inverse probability of treatment and censoring weighted estimators of risk differences (RDs) were used to evaluate residual confounding after controlling for covariates.

Results: PCSK9i initiators had lower one-year risks of negative control outcomes associated with frailty, such as decubitus ulcer in the ASCVD cohort (PCSK9i vs. high-intensity statin RD $= -3.5\%$, 95% confidence interval (CI): -4.6%, -2.5%; PCSK9i vs. ezetimibe RD $= -1.3\%$, 95% CI: -2.1%, -0.6%), with similar but attenuated associations in the LLT cohort. Lower risks of accidents and fractures were also observed for PCSK9i, varying by cohort. Risks were similar for outcomes associated with health-seeking behaviors, although trended higher for PCSK9i in the ASCVD cohort.

Conclusions: Observed associations suggest lower frailty and potentially greater health-seeking behaviors among PCSK9i initiators, particularly those with a recent ASCVD diagnosis, with the potential to bias real-world analyses of treatment effectiveness.

KEYWORDS
cardiovascular disease, cohort study, comparative analyses, ezetimibe, negative control, proprotein convertase subtilisin/kexin type 9 inhibitors, residual confounding, statins

Key Points

- Negative control methods can guide the design and analysis of comparative effectiveness studies of PCSK9i, with applicability to many other therapeutic areas.
- Observed associations suggest lower frailty and possibly higher health-seeking behaviors among patients initiating PCSK9i versus ezetimibe or high-intensity statin, despite controlling for a variety of demographic and clinical variables.
- Comparative effectiveness studies of PCSK9i may be subject to residual bias, possibly due to unmeasured or mismeasured confounders.
- Strategies to minimize this bias in study design and analysis will be employed in future research that seeks to understand the real-world impact of PCSK9i on cardiovascular outcomes.

1 | INTRODUCTION

The clinical benefits of lipid-lowering therapy (LLT) are well-established for decreasing elevated levels of low-density lipoprotein cholesterol (LDL-C) and reducing the risk of atherosclerotic cardiovascular disease (ASCVD).[1] Statin therapy is widely used to attain LDL-C target levels, and the magnitude of lowering action varies by statin intensity.[1,2] Nonstatin LLT can be combined with statins to increase LDL-C lowering and provide an alternative for patients experiencing statin-associated side effects, with ezetimibe most commonly used.[3] Proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) are a novel class of nonstatin LLT indicated for patients at high risk of acute cardiac events, including those with familial hypercholesterolemia or established ASCVD. For patients who do not adequately reduce LDL-C while on LLT, possible treatment options are to intensify statin therapy (i.e., from low- or moderate- to high-intensity) or, for those who cannot tolerate the level of statins needed to achieve LDL-C reductions, to initiate a nonstatin such as ezetimibe or PCSK9i (in addition to or replacing statin use). In clinical trials, adding PCSK9i to a statin (compared to statin monotherapy) reduced the risk of myocardial infarction (MI), ischemic stroke (IS), and other ASCVD events.[4,5] However, little is known about the real-world effectiveness of PCSK9i in improving cardiovascular outcomes outside of clinical trial settings, as compared with initiating ezetimibe or intensifying statin therapy.

Selection of LLT in clinical practice is likely influenced by factors associated with a patient's prognosis, leading to bias when estimating treatment effects. Observational studies have established the potential for confounding arising from risk-based prescribing of statin therapy, and failure to address these imbalances may result in statins appearing ineffective or harmful.[6,7] Similar confounding mechanisms likely operate in PCSK9i prescribing, given that cholesterol treatment guidelines recommend consideration of PCSK9i for patients on maximally tolerated statin therapy and at high risk of ASCVD events.[1] If guidelines translate to practice, patients initiating a PCSK9i will have more severe disease (e.g., higher LDL-C, history of ASCVD) compared to patients intensifying statin therapy or starting ezetimibe.[8,9] Bias in the opposite direction is also possible. Patients starting newer medications, such as a PCSK9i, may have greater access to care and insurance coverage,[10] thereby increasing use of preventive services and reducing risk of poor outcomes. Accounting for these potential imbalances in health status and health-seeking behaviors is necessary to validly compare outcomes among patients initiating different LLT.

Negative control methods are increasingly used to detect uncontrolled confounding between treatment groups in observational studies.[11,12] Negative control outcomes have no plausible mechanism by which they can be caused by the treatment of interest but should share a confounding structure with the treatment-outcome relation. After controlling for measured confounders, any observed association between the treatment and an appropriately selected negative control outcome suggests residual confounding. For example, if the outcome of interest for a comparative effectiveness study of LLT regimens was MI, the ideal negative control outcomes would share a confounding structure with treatment selection (i.e., PCSK9i vs. ezetimibe or high-intensity statin) and MI. Outcomes used in prior negative control studies include decubitus ulcer and accidents (i.e., confounding by disease severity or frailty), and wellness visits, vaccinations, and cancer screenings (i.e., confounding by health-seeking behaviors).[13–16]

This study used negative control outcomes to assess possible bias from unmeasured or mismeasured confounders among patients initiating a PCSK9i, ezetimibe, or high-intensity statin. Results from this study can guide the design and analysis of future comparative effectiveness studies that seek to understand the impact of PCSK9i on risk of ASCVD events, with the ultimate goal of informing optimal LLT regimens and improving cardiovascular outcomes.

2 | METHODS

2.1 | Study population

We used Optum Health commercial insurance data (Clinformatics® Data Mart) from January 1, 2009–June 30, 2019 to identify U.S. adults initiating a PCSK9i, ezetimibe, or high-intensity statin (see statin intensity classifications in Appendix 1). The Optum database captures administrative health claims originating from commercial plans (patients aged <65 years) and employer-sponsored Medicare Supplemental plans (patients aged ≥65 years). Data were available on

inpatient and outpatient diagnoses, procedures, and medications, which were identified using codes from the International Classification of Diseases, Clinical Modification, 9th and 10th Revision (ICD-9-CM, ICD-10-CM), Healthcare Common Procedure Coding System, Current Procedural Terminology, and National Drug Codes (NDC).

Patients were eligible for this study if they initiated a PCSK9i, ezetimibe, or high-intensity statin between July 24, 2015 (FDA approval of the first PCSK9i) and June 30, 2018 (to allow 1 year of follow-up). All available data prior to initiation were used to confirm that patients had not previously received the treatment of interest. Laboratory values such as LDL-C were not available in the data, and to obtain a study population for whom initiation of PCSK9i, ezetimibe, or high-intensity statin would be considered, we used two indicators of inadequately controlled LDL-C and ongoing cardiovascular disease risk. Patients were required to have ≥1 prescription fill of a different LLT in the year before treatment initiation (LLT cohort) or an ASCVD diagnosis in the 90 days before treatment initiation (ASCVD cohort). These criteria were based on discussion with subject matter experts and represented two treatment decision-making points: after a patient has been on prior LLT regimens without sufficient LDL-C reductions (LLT cohort) and after a patient experiences an acute cardiac event (ASCVD cohort). Patients entered the study population at the time of treatment initiation if they were ≥ 18 years of age and had continuous health insurance coverage over the last 365 days.

2.2 | Treatments, outcomes, and follow-up

This study used four treatment group comparisons: (1) PCSK9i versus ezetimibe (LLT cohort); (2) PCSK9i versus high-intensity statin (LLT cohort); (3) PCSK9i versus ezetimibe (ASCVD cohort); and (4) PCSK9i versus high-intensity statin (ASCVD cohort). Treatment use was identified using NDCs and continued until a gap of 45 days occurred beyond the dosing interval for the last-recorded prescription or administration date. Patients could belong to both LLT and ASCVD cohorts or to multiple treatment groups, but they were excluded if a PCSK9i was initiated on the same date as one of the comparators.

An expert panel reviewed possible mechanisms of confounding in the study population and selected 10 negative control outcomes: four associated with frailty (decubitus ulcer, accident, fracture, and cancer, excluding nonmelanoma skin cancer) and six associated with health-seeking behaviors (wellness visit, visual test, influenza vaccine, herpes zoster or pneumococcal vaccine, colon cancer screening, and nonmelanoma skin cancer or Mohs surgery). The majority of negative control outcomes were modeled after those developed in our prior work.[16] An exception was the cancer outcome, which was hypothesized to be associated with frailty given previous findings of high levels of frailty indicators in both older and younger adults diagnosed with cancer.[17,18] For some outcomes, additional exclusion criteria were applied. Analyses of the herpes zoster or pneumococcal vaccine and colon cancer screening outcomes were restricted to patients aged ≥50 years. The fracture outcome was restricted to patients without history of fracture in the 90 days before treatment initiation. Only patients without any history of cancer were included in the prospective analysis.

Study follow-up started on the day following treatment initiation and continued until the earliest of: A given negative control outcome, treatment discontinuation, disenrollment (>30-day gap in insurance enrollment), death, or end of data (June 30, 2019).

2.3 | Covariates

Covariates consisted of demographics (age, sex, geographic region, and insurance plan), medication use (prior LLT use, LDL-C testing, prescribing physician specialty for drug initiated), history of negative control outcomes, and a variety of comorbidities. All negative control outcomes were assessed during baseline and included as covariates (decubitus ulcer, accident, fracture, cancer, wellness visit, visual test, influenza vaccine, herpes zoster or pneumococcal vaccine, colon cancer screening, and nonmelanoma skin cancer or Mohs surgery). Other baseline comorbidities included diagnoses for ASCVD, chronic kidney disease, heart failure, diabetes mellitus, cognitive impairment (diagnoses of dementia, Alzheimer's disease, Pick's disease, memory loss, amnesia, reactive confusion, psychotic disorders, intellectual disabilities, delirium due to drug abuse, and concussion), hypertension, metabolic syndrome, dyslipidemia (including hyperlipidemia), muscle events (rhabdomyolysis/myositis), pancreatitis, chronic obstructive pulmonary disease, hepatic disorders, obesity (including diagnostic codes for gastric restrictive procedures and bariatric surgery), tobacco use (diagnoses of tobacco use disorder or medications for tobacco cessation), and frailty indicators (oxygen use, wheelchair, hospital bed, rehabilitation services, and difficulty walking). Covariates were assessed using all available data leading up to treatment initiation to increase the sensitivity of covariate assessment and improve confounding control.[19]

2.4 | Statistical analysis

Inverse probability of treatment and censoring weighted estimators were used to estimate the one-year cumulative incidence of each negative control outcome. Application of weights addressed confounding by treatment selection and potentially informative censoring.[20,21] A logistic regression model of the treatment choice as a function of all covariates was used to estimate the treatment weights, with pairwise models fit for each contrast. Assuming no model misspecification, application of the weights creates a pseudo-population in which the weighted treatment groups represent patient characteristics in the overall population of patients in a given contrast (targeting populations of PCKS9i and ezetimibe initiators and, separately, PCSK9i vs. high-intensity statin initiators). We verified covariate balance in the weighted treatment groups using the standardized mean difference, with values >0.1 suggesting residual imbalance. A Cox proportional hazards regression model with a Breslow estimator of the baseline hazard function was used to estimate the inverse probability

of censoring weights. We modeled the composite risk of censoring as a function of all covariates from the treatment model; application of censoring weights results in estimates of the effect of initiating and remaining adherent to the treatment, while staying enrolled in insurance throughout follow-up. Death was treated as a competing risk. We compared the weighted cumulative incidence of negative control outcomes for each treatment contrast by estimating one-year risk differences (RDs), with 95% confidence intervals (CIs) estimated using a group-based nonparametric bootstrap procedure. Refer to Appendix 2 for description of the estimating function, bootstrapping, and assumptions.

If the analyses adequately controlled for confounding and measurement error was minimal, we expected RDs for each treatment contrast to be near the null value of 0, with 95% CIs including 0. To explore whether the comparability of treatment groups changed by age or over time, we stratified analyses by age group (<65 years vs ≥65 years) and calendar period (2015–2017 vs. 2018). We also conducted a sensitivity analysis that did not censor for treatment discontinuation to emulate an intention-to-treat approach (e.g., for PCSK9i, all initiators were included regardless of whether the medication was continued after the first fill). This study was a secondary analysis of deidentified data and was approved by the Chesapeake Institutional Review Board. All statistical analyses were performed using R software, version 3.5.2.[22]

3 | RESULTS

Among 54 million patients in the Optum Health database, 3233 PCSK9i, 28 389 ezetimibe, and 157 363 high-intensity statin initiators were included in the LLT cohort, and 3418 PCSK9i, 15 539 ezetimibe, and 148 110 high-intensity statin initiators were included in the ASCVD cohort (Figure 1). Across cohorts, patients initiating high-intensity statins were older and more likely to be male, and patients initiating PCSK9i had greater comorbidities (e.g., heart failure, hypertension, dyslipidemia, muscle events) and received their treatment prescription from a cardiologist (vs. internal medicine provider) (Table 1). For the LLT cohort, one-year history of other therapies varied by treatment initiated (Table 2). PCSK9i initiators had similar use of ezetimibe (47%), high-intensity statins (42%), and moderate-intensity statins (43%); ezetimibe initiators had a history of high-intensity statins (47%) and moderate-intensity statins (56%); and nearly all patients initiating a high-intensity statin previously used a moderate-intensity statin (91%). For the ASCVD cohort, acute events were more likely among patients initiating a high-intensity statin; 30% had a MI (vs. 16% for PCSK9i and ezetimibe), 21% had an IS (vs. 4% PCSK9i, 7% ezetimibe), and 16% had coronary artery bypass grafting and percutaneous coronary intervention (vs. 3% PCSK9i, 4% ezetimibe). Diagnoses for coronary atherosclerosis, angina, or prior MI were common, particularly for PCSK9i (89%)

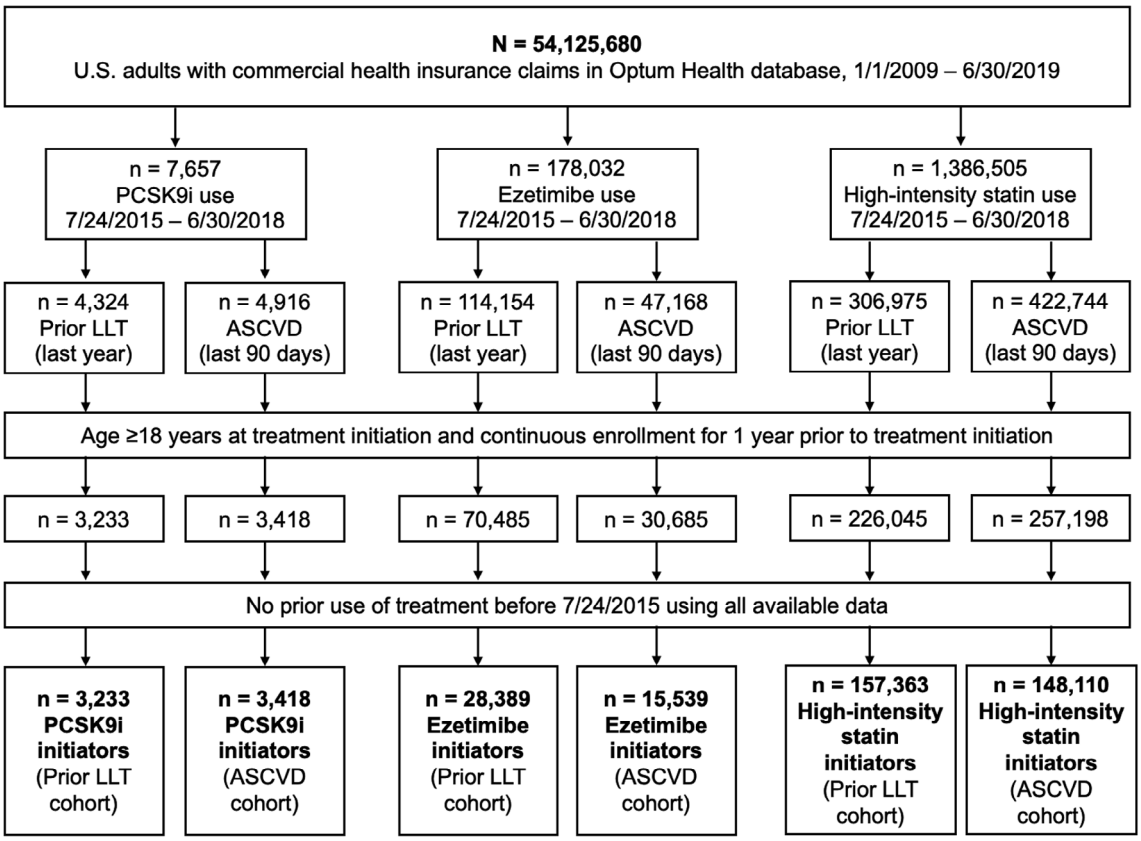

FIGURE 1 Flow chart of inclusion and exclusion criteria to select the study cohorts. ASCVD, atherosclerotic cardiovascular disease; LLT, lipid-lowering therapies; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitors

TABLE 1 Characteristics of patients prior to treatment initiation

	LLT cohort			ASCVD cohort		
% of patients*	PCSK9i $n = 3,233$	Ezetimibe $n = 28,389$	High-intensity statin $n = 157,363$	PCKS9i $n = 3,418$	Ezetimibe $n = 15,539$	High-intensity statin $n = 148,110$
Age group						
18–44	3.5	4.7	4.5	1.8	1.8	2.6
45–54	13.7	13.0	12.5	10.2	8.6	9.1
55–64	28.1	25.2	22.9	25.1	22.3	20.0
65–74	37.4	38.6	37.7	42.0	41.5	37.0
75+	17.3	18.5	22.5	20.8	25.8	31.3
Sex						
Male	53.7	49.8	54.1	54.0	55.7	59.2
Female	46.3	50.2	45.9	46.0	44.3	40.8
Region						
Northeast	10.3	11.4	11.1	10.0	11.9	12.3
Midwest	22.3	18.5	21.2	22.5	20.2	22.5
South	49.7	50.9	45.3	49.3	47.5	42.3
West	17.5	18.9	22.1	17.9	20.1	22.6
Insurance plan						
EPO	5.1	4.0	3.9	4.3	2.9	2.9
HMO	18.1	22.4	27.6	19.3	24.9	28.2
IND	2.0	0.8	0.9	2.1	1.0	1.1
POS	31.4	30.3	25.2	25.5	22.8	20.1
PPO	5.2	6.9	7.4	6.2	8.1	8.4
Other	38.2	35.6	35.1	42.7	40.4	39.4
Prescribing provider						
Cardiology	59.7	26.9	17.4	63.9	44.3	24.5
Internal medicine	36.2	67.9	74.3	31.3	50.5	62.9
Other specialty	2.0	2.6	3.0	2.6	2.6	5.1
Prior LDL-C testing	94.2	93.1	92.1	95.2	94.1	85.1
Any ASCVD diagnosis	90.0	63.1	62.1	100.0	100.0	100.0
Chronic kidney disease	17.2	14.7	17.8	19.4	19.8	20.6
Heart failure	36.8	19.9	20.0	42.8	35.1	31.1
Diabetes	39.9	40.3	47.5	42.0	42.0	40.5
Cognitive impairment	6.1	5.8	8.5	7.5	8.0	12.9
Hypertension	86.2	78.9	81.8	91.1	88.8	84.4
Dyslipidemia	92.3	83.3	80.2	92.9	85.9	66.2
Muscle events	23.0	12.1	8.2	24.6	12.8	8.4
Pancreatitis	1.5	0.9	0.9	1.5	1.0	1.1
COPD	14.8	12.2	14.7	17.1	17.6	19.8
Hepatic disorders	4.4	3.2	3.1	4.5	3.7	3.8
Obesity	38.1	34.4	35.5	39.1	35.6	33.2
Tobacco use	19.7	17.4	20.4	20.1	21.3	26.8
Frailty indicators	60.7	49.5	50.6	64.1	57.3	58.3

Note: *Percentages may not sum to 100 due to missing data (<10% observations missing for any variable).

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; COPD, chronic obstructive pulmonary disease; EPO, exclusive provider organization; HMO, health maintenance organization; IND, indemnity; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapies; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitors; POS, point-of-service; PPO, preferred provider organization.

TABLE 2 Cohort-specific characteristics: One-year history of prior therapies (LLT cohort) and ASCVD diagnoses in past 90 days (ASCVD cohort)

Prior LLT use % of patients[a]	PCSK9i $n = 3233$	Ezetimibe $n = 28\,389$	High-intensity statin $n = 157\,363$
PCSK9i	0.0	0.5	0.0
Ezetimibe	46.6	0.0	3.8
High-intensity statin	41.9	46.8	0.0
Moderate-intensity statin	42.6	55.5	91.1
Low-intensity statin	10.9	13.2	10.5
Recent ASCVD diagnoses % of patients[a]	**PCKS9i $n = 3418$**	**Ezetimibe $n = 15\,539$**	**High-intensity statin $n = 148\,110$**
Aneurysm	3.9	4.2	5.1
Carotid/vertebral/basilar stenosis	15.0	14.7	19.1
Carotid endarterectomy	0.3	0.3	0.6
Cerebrovascular disease	18.9	21.3	33.8
Coronary atherosclerosis/angina/prior MI	88.9	77.7	66.7
CABG/PCI	3.0	3.9	15.5
Carotid/vertebral/basilar stenting	0.1	0.1	0.6
Endovascular stent graft	0.0	0.0	0.1
Ischemic stroke	4.4	6.8	21.4
Myocardial infarction	16.1	16.1	29.6
Peripheral vascular disease	19.7	22.4	22.4
Peripheral artery disease	19.9	22.6	22.9
Transient ischemic attack	3.3	4.3	11.1
Unstable angina	7.8	7.4	16.5

Abbreviations: ASCVD = atherosclerotic cardiovascular disease; CABG = coronary artery bypass graft; LLT = lipid-lowering therapies; PCI = percutaneous coronary intervention; MI = myocardial infarction; PCSK9i = proprotein convertase subtilisin/kexin type 9 inhibitors.
[a]Categories are not mutually exclusive; multiple therapies or multiple diagnoses may have occurred in the time window of interest.

compared to ezetimibe (78%) and high-intensity statin (67%) (Table 2).

The weighted one-year risks of some, but not all, negative control outcomes associated with frailty were lower for patients initiating PCSK9i compared to those starting ezetimibe or high-intensity statin (Table 3, Figure 2). In the ASCVD cohort, there were decreased risks of decubitus ulcer for PCSK9i compared to ezetimibe (RD = −1.3% [95% CI: −2.1%, −0.6%]) and high-intensity statin (−3.5% [−4.6%, −2.5%]), with similar but attenuated associations in the LLT cohort. PCSK9i initiators had lower risks of fracture in the LLT cohort (ezetimibe −0.9% [−1.5%, −0.2%]; high-intensity statin −1.2% [−2.0%, −0.5%]) and lower risks of accident in the ASCVD cohort (ezetimibe −3.1% [−5.0%, −1.1%]; high-intensity statin −5.4% [−8.9%, −1.9%]). There was a slightly higher risk of cancer for PCSK9i compared to ezetimibe in the LLT cohort (1.1% [0.0%, 2.2%]).

There were no clear differences in risks of negative control outcomes associated with health-seeking behaviors, although risks trended higher for PCSK9i in the ASCVD cohort while lower for PCSK9i in the LLT cohort (Table 3, Figure 2B). This divergence in trends was most noticeable for immunizations. PCSK9i initiators in the ASCVD cohort had somewhat higher risks of influenza vaccine compared to ezetimibe (1.9% [−1.1%, 5.0%]) and high-intensity statin (5.6% [0.1%, 11.0%]), but in the LLT cohort, slightly lower risks of herpes zoster or pneumococcal vaccine (ezetimibe −1.8% [−4.1%, 0.5%]; high-intensity statin −2.2% [−4.9%, 0.5%]).

In stratified analyses, there were no systematic changes to effect estimates when restricting to age group or calendar period. In the sensitivity analysis (with no censoring for treatment discontinuation), the percentage of patients censored over 1 year of follow-up decreased dramatically from 50%–60% to 10%–15%. However, we found little change in the extent of residual bias detected by the effect estimates, suggesting that the comparability of treatment groups was not influenced by this analytic decision. Refer to Appendix 3 for model diagnostics and results from subgroup and sensitivity analyses.

4 | DISCUSSION

Using negative control methods with real-world data from a large commercially insured population, we observed some evidence of potential biases when comparing patients initiating PCSK9i to those starting ezetimibe or a high-intensity statin. For most negative control outcomes, there were no clear differences by treatment group; RDs were near-zero with 95% CIs overlapping the null. However, there

TABLE 3 Estimated one-year risks of negative control outcomes by treatment and cohort

	LLT cohort		ASCVD cohort	
Risk (95% CI)	**PCSK9i**	**Ezetimibe**	**PCKS9i**	**Ezetimibe**
Outcomes associated with frailty				
Decubitus ulcer	1.6% (0.9–2.2)	2.3% (2.1–2.5)	2.2% (1.5–2.9)	3.6% (3.2–4.0)
Accident	14.3% (11.6–16.9)	14.8% (14.3–15.4)	14.4% (12.5–16.3)	17.5% (16.6–18.3)
Fracture	1.8% (1.1–2.4)	2.6% (2.4–2.9)	3.3% (2.2–4.3)	3.3% (2.9–3.7)
Cancer excluding nonmelanoma skin cancer	2.5% (1.2–3.7)	1.4% (1.2–1.6)	2.4% (1.1–3.6)	1.8% (1.4–2.1)
Outcomes associated with health-seeking behaviors				
Wellness visit	20.0% (16.7–23.2)	20.0% (19.3–20.7)	23.8% (21.0–26.6)	23.6% (22.6–24.6)
Visual test	6.8% (4.8–8.8)	8.0% (7.5–8.4)	7.9% (6.5–9.3)	8.9% (8.3–9.5)
Influenza vaccine	51.1% (46.3–55.9)	52.9% (51.9–53.9)	57.5% (53.2–61.7)	55.5% (54.1–57.0)
Herpes zoster or pneumococcal vaccine	15.4% (13.1–17.8)	17.2% (16.5–17.9)	19.8% (17.1–22.5)	17.5% (16.6–18.4)
Colon cancer screening	17.9% (15.0–20.8)	18.9% (18.2–19.6)	19.1% (16.7–21.5)	18.4% (17.5–19.3)
Nonmelanoma skin cancer or Mohs surgery	4.3% (3.3–5.4)	4.7% (4.3–5.0%)	5.7% (4.5–7.0)	6.0% (5.5–6.5)
	LLT cohort		**ASCVD cohort**	
Risk (95% CI)	**PCSK9i**	**High-intensity statin**	**PCKS9i**	**High-intensity statin**
Outcomes associated with frailty				
Decubitus ulcer	1.9% (0.9–3.0)	3.9% (3.8–4.0)	2.8% (1.6–4.0)	6.3% (6.2–6.5)
Accident	15.9% (11.2–20.5)	15.3% (15.1–15.6)	13.8% (10.4–17.2)	19.2% (18.9–19.5)
Fracture	1.6% (0.8–2.3)	2.8% (2.7–2.9)	4.0% (1.2–6.9)	3.5% (3.4–3.6)
Cancer excluding nonmelanoma skin cancer	2.9% (1.1–4.7)	1.6% (1.6–1.7)	2.8% (0.9–4.6)	2.1% (2.0–2.2)
Outcomes associated with health-seeking behaviors				
Wellness visit	22.6% (17.6–27.5)	19.3% (19.1–19.6)	22.9% (18.3–27.4)	20.8% (20.5–21.1)
Visual test	6.9% (4.2–9.6)	7.5% (7.3–7.7)	6.0% (4.5–7.6)	7.6% (7.4–7.7)
Influenza vaccine	50.8% (44.6–57.0)	51.1% (50.8–51.5)	54.5% (47.1–61.8)	48.9% (48.5–49.3)
Herpes zoster or pneumococcal vaccine	14.7% (11.8–17.5)	16.8% (16.6–17.1)	19.9% (15.4–24.4)	16.6% (16.3–16.8)
Colon cancer screening	17.5% (13.5–21.5)	18.1% (17.8–18.3)	17.9% (14.0–21.7)	15.5% (15.2–15.7)
Nonmelanoma skin cancer or Mohs surgery	4.2% (2.9–5.4)	4.3% (4.2–4.4)	5.7% (3.2–8.2)	5.0% (4.8–5.1)

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; LLT, lipid-lowering therapies; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitors.

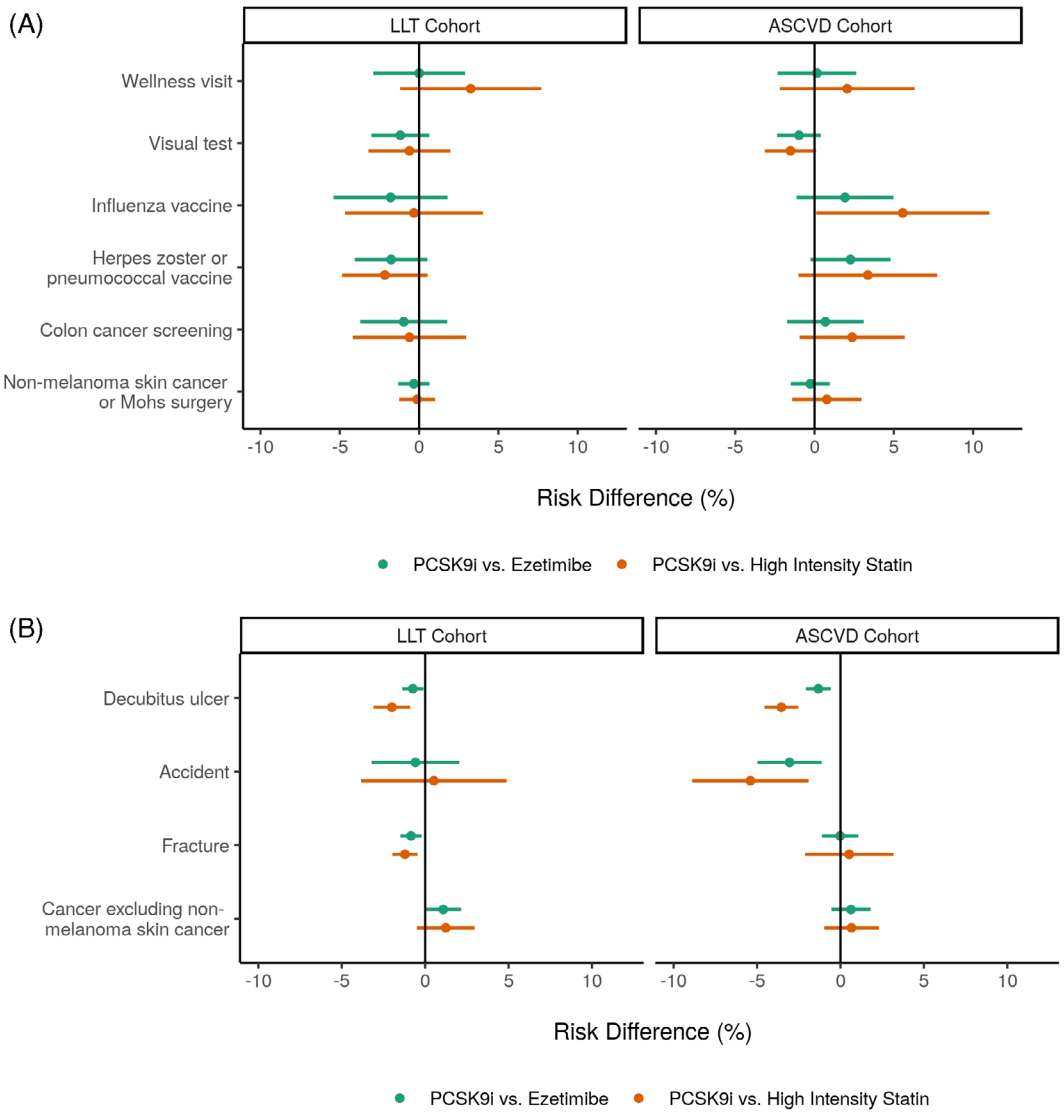

FIGURE 2 (A) Estimated one-year risk differences (95% CI) for negative control outcomes associated with frailty. (B) Estimated one-year risk differences (95% CI) for negative control outcomes associated with health-seeking behaviors. ASCVD, atherosclerotic cardiovascular disease; LLT, lipid-lowering therapies

were a few exceptions, despite no plausible mechanism by which negative control outcomes could be caused by the treatments of interest. Across cohorts, the risk of decubitus ulcer, a strong marker of frailty, was consistently lower for PCSK9i compared to ezetimibe and high-intensity statin. Lower risks of accidents and fractures were also observed for PCSK9i initiators. Risks of negative control outcomes associated with health-seeking behaviors were similar by treatment group, trending higher in the ASCVD cohort for PCSK9i but lower for PCSK9i in the LLT cohort. Although this study used inverse probability weights to control for a variety of demographic and clinical variables, systematic differences between treatment groups appear to persist – possibly due to unmeasured or mismeasured confounders – with the potential to bias comparisons of treatment groups in observational studies.

Imbalances in health status and health-seeking behaviors were hypothesized mechanisms of confounding when LLT modifications are made for patients with inadequately controlled LDL-C and ongoing risk of cardiovascular disease.[9,10] These mechanisms were assessed using negative control outcomes impacted by frailty and health-seeking behaviors. Decreased risks of ulcers, accidents, and fractures for PCSK9i were in the opposite direction than expected if estimates were confounded by poorer health status of PCSK9i initiators. These results suggest higher engagement in health care for PCSK9i initiators (e.g., greater awareness for fall prevention), which is consistent with risks of outcomes associated with health-seeking behaviors trending higher for PCSK9i in the ASCVD cohort (e.g., higher risks of immunizations). However, it is important to note that RD estimates were generally low in magnitude and that risks of most negative control outcomes were similar across treatments.

Taken together, our findings suggest that future comparative studies of PCSK9i may be subject to some residual bias, but this bias could be minimized through greater inclusion of covariates that are

proxies for health-seeking behaviors (e.g., frequency of physician office visits) and improved ascertainment of cardiovascular disease risk factors. For patients who do not achieve sufficient LDL-C reductions on an existing LLT regimen, the effectiveness of PCSK9i in routine clinical care (compared to ezetimibe or high-intensity statin) has not yet been studied, and our results provide important context for the design and analysis of future observational research. In particular, the variety of treatment contrasts and negative control outcomes employed in our study likely capture multiple domains of confounding that are relevant to analyses of treatment effectiveness. Other strengths of this study were the identification of negative control outcomes through engagement of an expert panel and the use of modern causal inference methods that address confounding, censoring, and competing events.

Importantly, however, our findings represent a specific patient population (with employer-based insurance or Medicare supplemental insurance) in the early years of PCSK9i approval (2015–2018) and may not generalize to other populations or more recent years. If prescribing, costs, and authorization rules are different in other populations or time periods, the confounding structure may also be different. Although selected by subject matter experts, the negative control outcomes in our study may not capture all possible mechanisms of confounding, with key differences between treatment groups going undetected. For example, the PCSK9i and ezetimibe groups included patients initiating a nonstatin as an add-on to statin therapy (because statins did not adequately reduce LDL-C) or as a replacement (due to inability to tolerate statins), and confounding mechanisms may vary between these two groups.

We also note a few limitations of our methodological approach. Pairwise inverse probability weights were estimated, leading to slightly different target populations for each treatment contrast. As a result, estimates for ezetimibe and high-intensity statin groups cannot be directly compared. We also note that treating death as a competing risk may invalidate the negative control outcome if treatment affects death (e.g., if PCSK9i decreases risk of death, patients prevented from dying can then experience a negative control outcome—creating an association with treatment). However, this is unlikely to substantially influence results, as the incidence of death is low over 1 year, and PCSK9i has a modest effect on mortality compared with other LLT.[4] Censoring for death is a more problematic alternative, as this creates an estimand that is less clinically relevant and more difficult to interpret (i.e., an estimate of the effect of treatment if patients are prevented from dying).[23] Finally, this study relied on commercial claims data to define covariates, and we may be better able to control confounding with a different data source, such as electronic medical records (e.g., through enabling inclusion of laboratory values, such as LDL-C, in the analysis).

In conclusion, we used negative control outcomes to explore possible bias in comparative effectiveness studies of patients initiating PCSK9i compared to those starting ezetimibe or a high-intensity statin. Observational studies may be biased due to residual confounding by health status and health-seeking behaviors, potentially leading to inappropriate or invalid inferences. However, future research is planned to evaluate to what extent this residual bias changes over time and could be minimized through patient selection (employing more stringent inclusion criteria to balance risk factors and healthcare access) and improved ascertainment of confounders (including time-varying confounding). Results from this study and future work can guide the design of comparative effectiveness studies of PCSK9i, ultimately improving our understanding of the impact of PCSK9i therapies on ASCVD risk and informing how LLT regimens could be optimized to reduce cardiovascular disease.

ACKNOWLEDGMENTS

Portions of this study were presented at the 2021 American College of Cardiology Scientific Session as a poster presentation with interim findings.

CONFLICT OF INTEREST

Kate K. Orroth, Andrew S. Park, Jose H. Flores Arredondo, and Paul Dluzniewski are employees of and own stock in Amgen. Alexander Breskin is an employee of and owns stock in Target RWE. Ann Marie Navar has received funding for research to her institution from BMS, Esperion, Amgen, and Janssen, and honoraria and consulting fees from Amarin, Amgen, Astra Zeneca, BI, CSL, Esperion, Janssen, Lilly, Sanofi, Regeneron, NovoNordisk, Novartis, The Medicines Company, New Amsterdam, Cerner, 89Bio, and Pfizer. Henrik T. Sørensen is an employee at Aarhus University which has received funding from Amgen as an institutional grant. M. Alan Brookhart has served on scientific advisory committees for Amgen, AbbVie, Atara Biosciences, Brigham and Women's Hospital, NIDDK, and Vertex; and he is a consulting chief scientist and owns equity in Target RWE.

DATA AVAILABILITY

Study data are available for purchase from Optum Health (Clinformatics® Data Mart). Readers can request R code from the corresponding author.

ETHICS STATEMENT

This study was approved by the Chesapeake Institutional Review Board.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Levintow SN, Orroth KK, Breskin A, et al. Use of negative control outcomes to assess the comparability of patients initiating lipid-lowering therapies. *Pharmacoepidemiol Drug Saf*. 2022;31(4):383-392. doi:10.1002/pds.5396