ORIGINAL RESEARCH

Eligibility, Clinical Outcomes, and Budget Impact of PCSK9 Inhibitor Adoption: The CANHEART PCSK9 Study

Dennis T. Ko, MD, MSc; Anam M. Khan, MPH; Gynter Kotrri, BHSc; Peter C. Austin, PhD; Harindra C. Wijeysundera, MD, PhD; Maria Koh, MSc; Anna Chu, MHSc; Cynthia A. Jackevicius, PharmD, MSc; Patrick R. Lawler, MD, MPH; Jack V. Tu, MD, PhD

***Background*—**The FOURIER (Further Cardiovascular Outcomes Research With PCSK9i [Proprotein Convertase Subtilisin-Kexin Type 9 Inhibitors] in Subjects With Elevated Risk) trial found a reduction in cardiovascular events in patients with atherosclerotic cardiovascular disease (ASCVD). Our objective was to estimate the eligibility, clinical outcomes, and budget impact of adopting PCSK9i in a large healthcare system.

***Methods and Results*—**Ontario, Canada, residents alive in 2011, aged 40 to 85 years, were eligible for inclusion. PCSK9i eligibility was determined on the basis of FOURIER trial definition. Hazard ratios observed in the FOURIER trial were applied to assess the number of events that could be avoided. Budget impact was calculated as the difference between projected costs of treatment adoption and events avoided if PCSK9i were used. Of the 2.4 million included individuals, 5.3% had a history of ASCVD. We estimated that 2.7% of the general population and 51.9% of the patients with ASCVD would be eligible for PCSK9i. Adoption of PCSK9i in all eligible patients with ASCVD was projected to reduce primary events rates by 1.8% after 3 years. Despite cost reduction of $44 million in events, PCSK9i adoption would have a net budget impact of $1.5 billion over 3 years. Potential benefits of PCSK9i varied widely across subgroups, with the largest absolute risk reduction estimated to be 4.3% at 3 years in peripheral artery disease. In this subgroup of 5601 patients, the budget impact of treatment adoption was $116 million.

***Conclusions*—**We estimated that ≈1 in 2 patients with ASCVD would be eligible for PCSK9i. The budget impact of adopting PCSK9i for all patients with ASCVD is substantial. Selective adoption to high-risk patients will lessen the overall budgetary impact of PCSK9i treatment. **(*J Am Heart Assoc*. 2018;7:e010007. DOI: 10.1161/JAHA.118.010007)**

Key Words: atherosclerosis • low-density lipoprotein cholesterol • outcome • proprotein convertase subtilisin-kexin type 9

Lowering low-density lipoprotein (LDL) cholesterol levels with statins has been a mainstay therapy for patients with established atherosclerotic cardiovascular disease (ASCVD).[1] Despite treatment, patients continue to be at significantly increased risk for adverse cardiac events in the long term.[2] The ability of PCSK9i (proprotein convertase subtilisin-kexin type 9 inhibitors) to substantially reduce LDL cholesterol has ushered in a new era of managing patients with ASCVD.[3,4] In the FOURIER (Further Cardiovascular Outcomes Research With PCSK9i in Subjects With Elevated Risk) trial, 27 564 patients with ASCVD, who were already receiving statin therapy with LDL cholesterol levels of ≥70 mg/dL, were randomized to receive evolocumab or placebo.[4] Over a median follow-up of 2.2 years, the study found a significant 15% relative hazard reduction and a 1.4% absolute risk reduction in major cardiovascular events associated with evolocumab.[4]

Given the high costs of PCSK9i, however, healthcare systems are grappling with its potential impact in clinical practice.[5] Several major gaps in knowledge currently exist. First, it is uncertain how many patients in the general population

From the Institute for Clinical Evaluative Sciences, Toronto, Ontario, Canada (D.T.K., A.M.K., G.K., P.C.A., H.C.W., M.K., A.C., C.A.J., P.R.L., J.V.T.); Schulich Heart Centre, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada (D.T.K., H.C.W., J.V.T.); University of Toronto, Ontario, Canada (D.T.K., G.K., P.C.A., H.C.W., C.A.J., J.V.T.); University Health Network, Toronto, Ontario, Canada (C.A.J., P.R.L.); and Western University of Health Sciences, Pomona, CA (C.A.J.).

Correspondence to: Dennis T. Ko, MD, MSc, Institute for Clinical Evaluative Sciences, G106-2075 Bayview Ave, Toronto, Ontario, Canada M4N 3M5. E-mail: dennis.ko@ices.on.ca

Received June 11, 2018; accepted September 6, 2018.

Clinical Perspective

What Is New?

- Using actual population-based data to estimate the impact of proprotein convertase subtilisin-kexin type 9 inhibitors in Ontario, Canada, we found that ≈1 in 2 patients with prior cardiovascular disease could be eligible for therapy.
- The potential budget impact to adopt proprotein convertase subtilisin-kexin type 9 inhibitors is large if the medication was used in the entire population.

What Are the Clinical Implications?

- Our findings suggest that adopting proprotein convertase subtilisin-kexin type 9 inhibitors for patients at the highest risk of future adverse events would lessen the potential budget impact of therapy adoption.

may be eligible for treatment. Second, because patients enrolled in randomized controlled trials typically differ from those managed in routine clinical practice, it is possible that the baseline cardiovascular event rates of patients with ASCVD may differ substantially from those observed in clinical trials.[6,7] Third, eligibility and event rates associated with PCSK9i have largely been derived from a selected sample or from simulation models, and none has access to real-world data from the entire healthcare system.[8–10] Real-world data are important because they can provide accurate projections on the baseline rate of the general population, which would allow estimation of the avoidable number of events and the subsequent budget impact associated with widespread therapy adoption. Accordingly, our first objective was to estimate the proportion of individuals who would be eligible for PCSK9i. Second, we examined real-world event rates in patients with ASCVD eligible for therapy using population-based longitudinal data. Finally, to assess affordability, we estimated the budget impact to Ontario, Canada, if PCSK9i were fully adopted among eligible patients.

Methods

System Context

The Canadian health insurance system provides universal coverage for all medically necessary ambulatory and laboratory testing for all its citizens. National practice guidelines currently recommend screening with full fasting lipid profile every 1 to 3 years for men who are aged >40 years and women who are postmenopausal or aged >50 years.[11] Lipid testing is also recommended for individuals with cardiovascular risk factors, renal insufficiency, or evidence of atherosclerosis at any age.[11] The Ontario Drug Benefit program is a government-funded drug benefit program that covers outpatient drug costs, including statins and ezetimibe, for all Ontario residents aged ≥65 years.[12]

Data Sources

The CANHEART (Cardiovascular Health in Ambulatory Care Research Team) study cohort was created by merging 17 different longitudinal individual-level data sources.[13,14] These data sets were linked using unique encoded identifiers and analyzed at the Institute for Clinical Evaluative Sciences to protect patient confidentiality. Additional detail on the construction of this big-data cohort is detailed elsewhere (http://www.canheart.ca).[13,14] Specific data sources essential to this current study included the following: (1) the Ontario Registered Persons Database, which is a registry of all Ontario residents with health insurance coverage; (2) the Canadian Institute for Health Information Discharge Abstract Database, the Ontario Diabetes Database, the Ontario Hypertension Database, and the Ontario Cancer Registry, which were used to identify cardiac risk factors and medical conditions; (3) the Drug Benefit database, used to determine outpatient prescription drug use for patients aged ≥65 years; (4) the Ontario Laboratory Information System, which captures >90% of all outpatient laboratory testing in Ontario and currently contains >2 billion laboratory tests results, and was used to determine cholesterol levels; (5) the Registrar General of Ontario Vital Statistics Database, which was used to determine cause of death of all patients; and (6) the Canadian Community Health Survey, an ongoing Canada-wide population-based survey that collected information on self-reported health status, health determinants, and healthcare use. The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Study Sample

Ontario residents who were alive on January 1, 2011, were aged 40 to 85 years, had a complete lipid panel in the previous year, and had a valid Ontario Health Insurance Plan number were eligible for inclusion in the study cohort. The inception year 2011 was chosen to allow for at least 3 years of follow-up on every individual. We excluded individuals who had lived in Ontario for <5 years before the inception date because they may represent temporary residents of the province. We also excluded individuals who were residents of long-term care facilities.

Determination of PCSK9i Eligibility

To construct a cohort of patients who may be eligible for PCSK9i, we first identified patients with ASCVD by

determining the presence of prior hospitalization of myocardial infarction, nonhemorrhagic stroke, or peripheral artery disease (PAD) in the past 20 years using the Canadian Institute for Health Information Discharge Abstract Database. The *International Classification of Diseases, Ninth* and *Tenth Revisions* (*ICD-9* and *ICD-10*, respectively), codes used to define these conditions are shown elsewhere.[13] Patients receiving statin therapy who had LDL cholesterol levels ≥70 mg/dL, non–high-density lipoprotein cholesterol levels ≥100 mg/dL, and triglycerides <400 mg/dL were considered as eligible for PCSK9i. Because of the lack of medication information for patients aged <65 years, we initially assumed statins were prescribed in all subjects in this age group. Cholesterol measurements were considered if they were performed in the outpatient setting within 1 year before the cohort inception. For patients who had multiple measurements, the cholesterol level closest to January 1, 2011, was chosen to determine the cholesterol eligibility criteria. Patients diagnosed as having metastatic cancer within 5 years and those with end-stage renal disease who were receiving hemodialysis were considered ineligible for PCSK9i. Although the FOURIER trial had more extensive exclusion criteria, we chose a more simplistic approach because many exclusions in the trial were not absolute contraindications to treatment and were relatively uncommon.[4,15]

Cholesterol Measurement and Statin Intensity

LDL cholesterol levels were calculated by the Friedewald equation.[16] High-density lipoprotein cholesterol levels were determined by homogeneous assay. Nineteen statin dosages were classified in accordance to the practice guidelines into low, medium, or high intensity, which took into account the specific statin prescription.[17] Determination of medication use and its intensity was made in the 100 days before the cohort inception and using information from the last filled prescription.

Definition of Primary and Secondary Outcomes

We used the FOURIER trial outcome definitions and defined the primary outcome as a composite of cardiovascular death, myocardial infarction, unstable angina, stroke, or coronary revascularization.[4] The secondary outcome was defined as the composite of cardiovascular death, myocardial infarction, or stroke.[4]

Statistical Analysis

First, we determined the number of individuals in Ontario who would be eligible for PCSK9i. Second, we obtained their event rates at different time points, with complete follow-up available for all patients through December 31, 2013. The Kaplan-Meier method was used to estimate the survival probability and survival function of the study cohort. To generate a survival function as it would have been observed for patients treated with PCSK9i, we applied the hazard ratios observed in the FOURIER trial to our estimated survival function using the following formula: $S(t|\mathbf{X}) = S_0(t)^{e^{\beta}}$, where $S_0(t)$ denotes the estimated survival function in our study population under control (no PCSK9 exposure) at a given time, and β denotes the logarithm of the estimated hazard ratio of treatment from the FOURIER trial (e^{β} denotes the estimated hazard ratio from the FOURIER trial). The difference between the observed empirical survival function under no treatment and the expected survival function under PCSK9i use was used to estimate the number of events that could be avoided by treatment. Number needed to treat over 3 years was estimated by the inverse of the absolute rate reduction of PCSK9i.

We were able to determine the cost of illness by directly following the encounter of each patient with ASCVD eligible for PCSK9i because Ontario has a single-payer system and the availability of linked population-based data captures all direct costs related to health status.[18–20] A bottom-up approach was used that identified costs for hospitalizations, emergency department visits, same-day surgeries, outpatient visits, complex continuing care services, home care services, and long-term care; costs were determined using resource intensity weights and case-mix method.[18–20] To determine the budget impact of PCSK9i, we estimated the mean costs for PCSK9i-eligible patients with and without clinical outcomes during the follow-up period to calculate the mean cost saved by each avoided clinical event. Then, we determined the total number of events that could be avoided on the basis of the differences in the survival functions, as previously described, and multiplied it by the mean cost averted to determine the total cost offset. Third, we subtracted cost averted from reduction of clinical events from the cost of PCSK9i to allow us to estimate the budget impact of adopting PCSK9i in Ontario. We took a perspective of the health system in Ontario and, therefore, included all health-related direct costs. The analyses were reported in Canadian dollars. The annual PCSK9i costs were assumed to be the Canadian wholesale price of Can $8000 (Can $1 ≈ US $0.78).

We repeated these analyses in prespecified subgroups (sex, diabetes mellitus status, ASCVD types [myocardial infarction, nonhemorrhagic stroke, and PAD], and LDL cholesterol levels). We also altered the adoption rate of PCK9i from full adoption to 60% adoption as a sensitivity analysis. Similar to the primary analyses, hazard ratios from the FOURIER trial were used to generate r estimated survival function in the subgroups. To assess the change in the

PCSK9-eligible population and its 95% confidence interval, assuming lower use of statins in patients aged <65 years, we applied the bootstrapping techniques to 1000 random samples without replacement. Two-tailed $P<0.05$ was considered significant. Analyses were performed with the use of SAS software, version 9.3 (SAS Institute Inc, Cary, NC). The use of data in this project was authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a Research Ethics Board, and the informed consent requirement was waived.

Results

Determination of PCSK9i Eligibility

A total of 2.4 million individuals, aged 40 to 85 years, had a complete lipid panel in the year before January 1, 2011. Figure 1 shows the steps used to determine patients who would be eligible for PCSK9i. We first identified 130 033 patients (5.3% of all individuals) with a history of myocardial infarction, nonhemorrhagic stroke, or PAD. We then excluded 2106 patients who had a history of metastatic cancer in the past 5 years or were receiving hemodialysis and 13 064 patients aged >65 years who were not receiving statin therapy. The most common reason for exclusion was not meeting the lipid criteria, in which 47 359 patients (36.4% of those with ASCVD) had a fasting LDL cholesterol level of ≤70 mg/dL, a non–high-density lipoprotein cholesterol level of ≤100 mg/dL, or a triglycerides level of ≥400 mg/dL. After applying the inclusion and exclusion criteria, a total of 67 504 patients, representing 2.7% of the population of similar age with cholesterol testing, would be eligible for PCSK9i. For patients who had a history of ASCVD, we estimated that 51.9% would be eligible for PCSK9i.

Baseline Characteristics of Patients Eligible for PCSK9i and Enrolled in the FOURIER Trial

The mean age of our study cohort was 66.1 years, 30.5% were women, 40.6% had diabetes mellitus, 79.7% had a history of myocardial infarction, 14% had nonhemorrhagic stroke, and 11.7% had PAD (Table 1). Among the 34 144 eligible patients aged >65 years and eligible for the Ontario Drug Benefit Plan, 42.9% were prescribed high-intensity statins, 52.5% were prescribed medium-intensity statins, and 10.3% were prescribed ezetimibe. The median LDL cholesterol level was 85 mg/dL, and the median total cholesterol level was 159 mg/dL.

In comparison to patients enrolled in the FOURIER trial, our study cohort was older (66.1 versus 62.2 years), had a higher proportion of women (30.5% versus 24.6%), and had more ezetimibe prescriptions (10.2% versus 5.2%). Conversely, patients enrolled in the FOURIER trial had slightly higher cholesterol levels (LDL, 92 mg/dL; total cholesterol, 167 mg/dL) and were more likely to be taking high-intensity statins (69.3%).

Clinical Outcomes of Patients Eligible for PCSK9i and Enrolled in the FOURIER Trial

Clinical outcomes in our cohort compared with the outcomes observed in the treatment and the placebo arms of the FOURIER trial are shown in Table 2. Rates of primary outcome were 4.7% after the first year, 9.1% after the second year, and 13.2% after the third year in PCSK9i-eligible patents. Secondary outcome event rates were 2.8%, 5.6%, and 8.5% after 1, 2, and 3 years, respectively. Event rates of our cohort were lower than the placebo group of the FOURIER trial but higher than the treatment arm. For example, at 3 years, primary event rates were 12.6% in the treatment arm of the FOURIER trial, 14.6% in the placebo arm, and 13.2% in our cohort (Table 2).

Figures 2 and 3 show the cumulative incidence of the primary and secondary outcomes observed in the PCSK9i-eligible patients and the projected event rates by applying the hazard ratios observed in the FOURIER trial associated with evolocumab. The absolute risk reduction increased over time. Notably, the risk reduction was 0.7% in the first year, increased to 1.3% in the second year, and 1.8% in the third year (Figure 2). A similar trend was also observed for the secondary outcome, in that the absolute risk reduction increased over time from 0.6% after the first year to 1.1% after the second year, and 1.6% after the third year (Figure 3).

The magnitude of the absolute risk reduction calculated using the hazard projection method for primary and secondary events was slightly smaller in our study when compared with the FOURIER trial. For the primary outcome, the FOURIER trial observed a reduction of 1.6% after 2 years (versus 1.3% in our study) and 2% (versus 1.8%) after 3 years.

Budget Impact Associated With PCSK9i Adoption to All Eligible Patients

Table 3 shows the calculation of the budget impact of fully adopting PCSK9i to all eligible patients in Ontario for 3 years. The mean cost for patients who experienced a primary outcome was $57 329 as opposed to $22 330 for those who did not have an event. At 3 years, we estimated PCSK9i would avoid 1255 primary events and save $43.9 million from event reduction. Balanced against this reduction is the cost of the medication itself in all eligible patients, resulting in an estimated budget impact of $1.5 billion over 3 years in Ontario (Table 3).

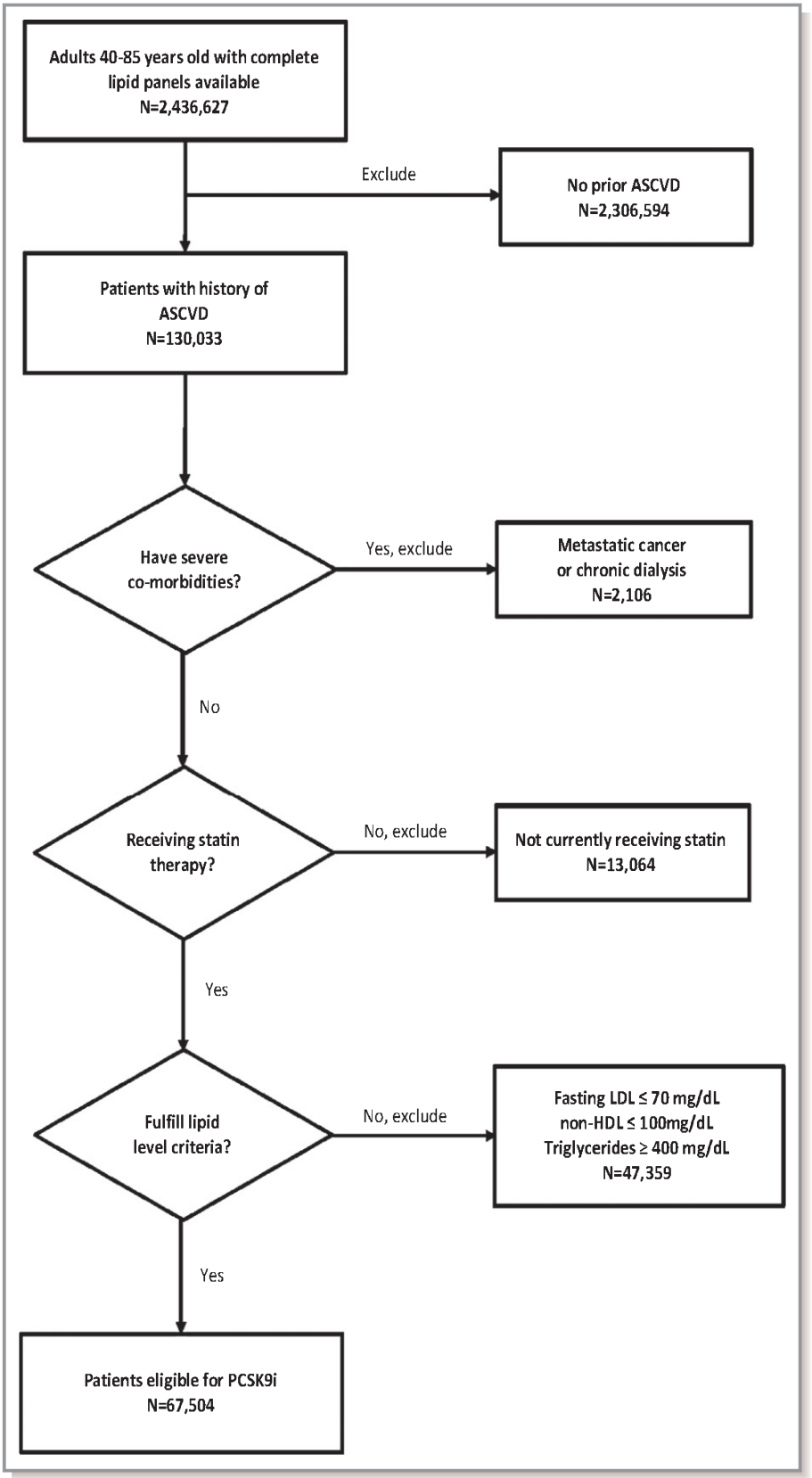

Figure 1. Determination of PCSK9i (proprotein convertase subtilisin-kexin type 9 inhibitor) eligibility in study cohort. ASCVD indicates atherosclerotic cardiovascular disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 1. Comparison of Baseline Characteristics of PCSK9i-Eligible Patients in Ontario, Canada, With Patients Enrolled in the FOURIER Trial

Characteristics	PCSK9i-Eligible Patients (N=67 504)	Patients Enrolled in the FOURIER Trial (N=27 564)
Patient demographics		
Age, mean±SD, y	66.1±10.4	62.5±9
Women, n (%)	20 618 (30.5)	6769 (24.6)
Type of atherosclerosis, n (%)		
Myocardial infarction	53 802 (79.7)	22 351 (81.1)
Nonhemorrhagic stroke	9453 (14.0)	5337 (19.4)
Peripheral artery disease	7927 (11.7)	3642 (13.2)
Cardiovascular risk factors, n (%)		
Hypertension	53 918 (79.9)	22 084 (80.1)
Diabetes mellitus	27 407 (40.6)	10 081 (36.6)
Current smoker*	468 (26.3)	7777 (28.2)
Statin use, n (%)†		
High intensity	14 645 (42.9)	19 103 (69.3)
Medium intensity	17 922 (52.5)	8392 (30.5)
Low intensity	1577 (4.6)	69 (0.25)
Ezetimibe use†	3511 (10.3)	1440 (5.2)
Lipid measures, median (IQR), mg/dL		
LDL cholesterol	85 (75–102)	92 (80–109)
Total cholesterol	159 (144–181)	167 (151–188)
HDL cholesterol	44 (37–53)	44 (37–53)
Triglycerides	125 (90–179)	133 (100–181)
Non-HDL cholesterol	112 (100–133)	NA

FOURIER indicates Further Cardiovascular Outcomes Research With PCSK9i in Subjects With Elevated Risk; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; NA, not available; PCSK9i, proprotein convertase subtilisin-kexin type 9 inhibitors.

*Smoking information was available on 1777 individuals who had completed the Canadian Community Health Survey.

†Medication information was available among 34 144 individuals who were eligible for the Ontario Drug Benefit Program.

Clinical Outcomes and Budget Impact in Subgroups of Patients With ASCVD

Table 4 summarizes the number of eligible patients by prespecified subgroups, their observed and projected treatment event rates, absolute risk reduction, number needed to treat, and the potential budget impact at 3 years. Patients with ASCVD with diabetes mellitus (n=27 407) had an event rate of 16.9% for the primary outcome, the absolute risk reduction was estimated at 2.7% at 3 years with PCSK9i, the number needed to treat was 38, and the budget impact was estimated at $597 million. Patients who had PAD (n=5601) had the highest absolute risk reduction of the primary event rate with PCSK9i: 4.3% at 3 years and a number needed to treat of 23. The budget impact of adopting PCSK9i to this cohort was estimated to cost $116 million.

Table 2. Outcomes of PCSK9i-Eligible Patients and Patients in the FOURIER Trial

Outcomes	PCSK9i-Eligible Patients (n=67 504)	FOURIER Placebo Patients (n=13 780)	FOURIER Treated Patients (n=13 784)
Primary outcomes, %			
1 y	4.7	6	5.3
2 y	9.1	10.7	9.1
3 y	13.2	14.6	12.6
Secondary outcomes, %			
1 y	2.8	3.7	3.1
2 y	5.6	6.8	5.5
3 y	8.5	9.9	7.9

Outcomes were assessed on the basis of the Kaplan-Meier survival method. Primary outcome was defined as the composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, and coronary revascularization. Secondary outcome was defined as the composite of cardiovascular death, myocardial infarction, and stroke. FOURIER indicates Further Cardiovascular Outcomes Research With PCSK9i in Subjects With Elevated Risk; PCSK9i, proprotein convertase subtilisin-kexin type 9 inhibitors.

The impact of PCSK9i on patients with different baseline LDL cholesterol is also shown in Table 4. The absolute event rate associated with PCSK9i was higher in patients with the lowest quartile of cholesterol levels, at 2.5% compared with the highest quartile at 1.5%, because the hazard ratio observed with PCSK9i was slightly lower among patients with very-low LDL cholesterol levels. However, the overall budget impact was similar across different LDL cholesterol levels.

Clinical Outcomes and Budget Impact With Varying Adoption Rate of PCSK9i

Table 5 summarizes the potential clinical and budget impact if PCSK9i adoption rates were altered. For example, if PCSK9i were adopted in 60% of the eligible patients, we estimated that we would observe 752 avoidable events and the budget impact would be $905 864 994 at 3 years.

Discussion

The availability of a "big-data" contemporary cardiovascular cohort afforded a unique opportunity to generate new insights on the implications of adopting PCSK9i in a large healthcare system. First, we estimated that 2.7% of all adults and ≈1 in 2 patients with ASCVD would be eligible for PCSK9i on the basis of clinical trial criteria. Second, we estimated a large budget impact of adopting PCSK9i for all

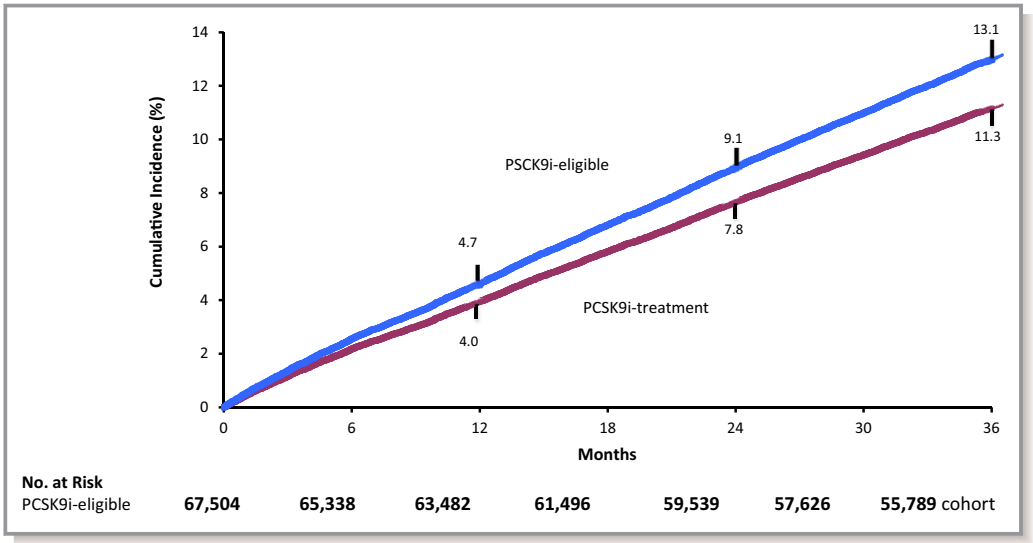

Figure 2. Cumulative incidence of primary outcome events in PCSK9i (proprotein convertase subtilisin-kexin type 9 inhibitor)–eligible patients and treated patients. The *y* axis shows cumulative incidence of primary outcome event rate rates, and the *x* axis shows time in months. Blue line depicts event rates for PCSK9-eligible patients, and red line depicts event rates for PCSK9-eligible and treated patients.

patients with ASCVD. This was because of the relatively low rates of clinical events in routine clinical practice and the large number of patients meeting eligibility criteria. In contrast, the projected absolute risk reduction associated with PCSK9i for restricted subgroups of patients with diabetes mellitus, stroke, and PAD was substantially higher. Compounded with the smaller number of patients in these subgroups, the budget impact was substantially lower. Accordingly, selective adoption to high-risk patients will lessen the budgetary impact of PCSK9i treatment, but because we did not perform a formal cost-effectiveness analysis, we were unable to weigh these added costs against the corresponding reductions in ASCVD events.

Our findings are in contrast to those of Kazi and colleagues, who used the National Health and Nutrition Examination Survey to estimate the eligibility of PCSK9i in the United States.[8] They found that ≈6.4% of the adult population (8.8 million individuals) would be eligible for PCSK9i and

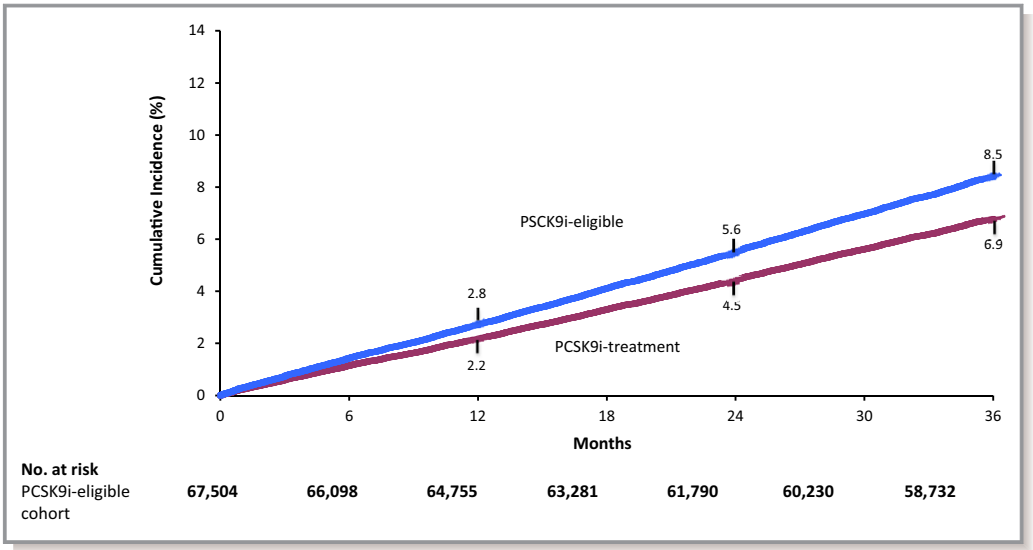

Figure 3. Cumulative incidence of secondary outcome events in PCSK9i (proprotein convertase subtilisin-kexin type 9 inhibitor)–eligible patients and treated patients. The *y* axis shows cumulative incidence of secondary outcome event rate rates, and the *x* axis shows time in months. Blue line depicts event rates for PCSK9-eligible patients, and red line depicts event rates for PCSK9-eligible and treated patients.

Table 3. Budget Impact Associated With PCSK9i Adoption to All Eligible in Ontario, Canada, at 3 Years

Characteristics	Costs, $
Mean cost for patients with primary outcome	57 329
Mean cost for patients without primary outcome	22 330
Cost offset	
Costs for PCSK9i	1 553 647 600
Costs averted from clinical event reduction	43 909 697
Budget impact to adopt therapy in all eligible patients for 3 y	1 509 737 903

Costs for PCSK9i per year were assumed to be the Canadian wholesale price at Can $8000. PCSK9i indicates proprotein convertase subtilisin-kexin type 9 inhibitors.

estimated a budget impact of $125 billion per year for full adoption.[8] In contrast, we estimated that only 2.7% of the adult population would be eligible for PCSK9, which would alter the budget impact of PCSK9 adoption in the United States drastically. We do not believe this discrepancy is attributable to a difference in ASCVD characteristics and treatment between the United States and Canada, because we have previously demonstrated similarity of patients with coronary artery disease in the 2 countries.[21,22] Instead, it is possible that the discordance of eligibility estimates could be related to higher prevalence of baseline ASCVD in the simulation model given a reducing trend of cardiovascular disease. It is also possibly related to the difference in method used to define ASCVD. In our study, we defined ASCVD on the basis of the FOURIER trial, which included prior hospitalizations of myocardial infarction, nonhemorrhagic stroke, and PAD, whereas Kazi et al used a broader definition of ASCVD, which also encompassed angina and cardiac arrest.[8]

Other recent studies assessing the proportion of patients with ASCVD who could be eligible for PCSK9i have also varied significantly.[10,23] Although our study demonstrated that ≈1 in 2 patients with ASCVD could be eligible, Cannon et al estimated, through a simulated cohort modeled from US medical and pharmacy claims, that 75% of patients with ASCVD would have an LDL cholesterol level ≥70 mg/dL and may subsequently be eligible for PCSK9i.[10] In contrast, Virani et al estimated that only 25% of patients with ASCVD in the Veterans Affairs population would be eligible for evolocumab.[23] Despite these differences, a consistent observation across all studies is that a substantial proportion of patients who are currently eligible for PCSK9i could further lower their LDL cholesterol levels by more aggressive treatment with conventional therapy before initiation of PCSK9i therapy.[8,10,23] In our cohort, we observed that

Table 4. Observed Event Rates and Projected Risk Reduction in All PCSK9i-Eligible Patients and Subgroups Over 3 Years

Variable	No. of Patients	Event Rates			Absolute Risk Reduction	No. Needed to Treat	Avoidable Events	Budget Impact, $
		PCSK9i Eligible	PCSK9 Treatment	Hazard Ratio				
Primary outcomes								
All patients	67 504	13.1	11.3	0.85	1.9	54	1254	1 509 737 903
Sex								
Men	46 886	13.6	11.8	0.86	1.8	56	837	1 051 382 515
Women	20 618	12.2	10.0	0.81	2.2	46	452	352 361 058
Diabetes mellitus status								
Yes	27 407	16.9	14.3	0.83	2.7	38	729	593 718 538
No	40 097	10.6	9.3	0.87	1.3	76	527	914 672 880
ASCVD type								
Myocardial infarction	50 566	12.9	11.4	0.88	1.5	69	735	1 148 134 735
Nonhemorrhagic stroke	7816	10.1	7.2	0.70	2.9	34	228	171 443 092
Peripheral artery disease	5601	13.6	9.3	0.67	4.3	23	239	115 618 664
LDL cholesterol levels, mg/dL								
<75	16 481	13.1	10.6	0.8	2.5	41	407	364 019 720
75–84	17 057	12.2	10.1	0.82	2.1	48	355	379 563 341
>84–102	17 154	12.8	11.5	0.89	1.3	75	228	387 007 650
>102	16 812	14.6	13.1	0.89	1.5	67	251	379 249 638

Hazard ratios used to estimate treatment effect were obtained from the FOURIER (Further Cardiovascular Outcomes Research With PCSK9i in Subjects With Elevated Risk) trial. ASCVD indicates atherosclerotic cardiovascular disease; LDL, low-density lipoprotein; PCSK9i, proprotein convertase subtilisin-kexin type 9 inhibitors.

Table 5. Observed Event Rates and Projected Risk Reduction in All PCSK9i-Eligible Patients According to Different Adoption Rates at 3 Years

Variable	No. of Patients Treated With PCSK9i	Avoidable Events	Reduction of Events Relative to the Entire Population, %	Budget Impact, $
Primary outcomes				
Adoption rate of PCSK9i				
Full adoption (100%)	67 504	1254	1.9	1 509 774 990
90%	60 754	1128	1.7	1 358 797 491
80%	54 003	1003	1.5	1 207 819 992
70%	47 253	878	1.3	1 056 842 493
60%	40 502	752	1.1	905 864 994

Hazard ratiosused to estimate treatment effect were obtained from the FOURIER (Further Cardiovascular Outcomes Research With PCSK9i in Subjects With Elevated Risk) trial. PCSK9i indicates proprotein convertase subtilisin-kexin type 9 inhibitors.

≈20% of PCSK9i-eligible patients with ASCVD aged >65 years were not prescribed statins, and only 43% of those prescribed statins were receiving a high-intensity dose. Although Virani et al assumed that eligibility of PCSK9i could change 20% to 60% on the basis of increasing aggressiveness of existing lipid-lowering therapy,[23] it is difficult to know whether this is actually feasible because of the lower tolerability and compliance of statin therapy in the real world. It is also possible that many patients are already receiving maximally tolerated dosages. We were unable to perform a modeling analysis to estimate the budget impact of varying statin aggressiveness because our study was based on actual clinical outcomes observed in our cohort.

It is traditionally known that patients enrolled in randomized controlled trials have lower risk profiles than patients cared for in clinical practice because of the frequent exclusion of women, elderly patients, and those with comorbidities from clinical trials.[6,24,25] If this were the case for PCSK9i, then the published cost-effectiveness estimates that were reliant on the clinical trial event rates would be substantially different than anticipated. In examining real-world event rates in our PCSK9-eligible cohort, although patients in our cohort were older, we found that adverse cardiovascular outcomes in our population were actually in line with the placebo group in the FOURIER trial, suggesting patients enrolled in the trial were highly representative of those in clinical practice.

We conducted a budget impact analysis using real-world data to assess the affordability of PCSK9i for patients with ASCVD. This is of particular importance because PCSK9 costs in Canada are substantially lower than in the United States (Can $8000 versus US $14 000 per year). Despite this, we estimated that it would cost >$500 million per year to adopt this therapy in Ontario, which has a population of 13.6 million people. To place this expenditure into context, Ontario spent $12.4 billion on all prescribed medications in 2015.[26] The uptake of PCSK9i among all eligible patients with ASCVD would increase the total medication budget by 4.1% alone in Ontario. This estimate was almost identical with the budget impact of PCSK9i adoption in the United States of 4%.[8,9] Although we did not perform an analysis to examine the optimal price of PCSK9i for cost effectiveness in Ontario, a study performed in the Canadian setting found that PCSK9i price needs to decrease to $1200 to satisfy the $50 000 cost per year of life saved ratio.[27]

In assessing the impact of PCCK9i in subgroups, we observed much larger absolute risk reductions in subgroups, such as those with diabetes mellitus, stroke, and PAD, than in the overall cohort. This is not unexpected because the impact of any cardiovascular evidence-based therapy in the population is predominantly dependent on patients' baseline risk of future adverse cardiovascular events.[28] Furthermore, the hazard ratio reduction associated with evolocumab was larger in patients with PAD and stroke.[4] Given that these subgroups had higher hazard reductions and a substantially smaller number of eligible patients, the budget impact of adopting treatment among these subgroups was substantially lower than in the overall cohort.

The present study should be interpreted in the context of several limitations that merit further discussion. First, we assumed all patients aged <65 years were prescribed statins because we did not have prescription medication data for this group of patients. Thus, it is possible that we might have overestimated the eligibility proportion of PCSK9i. To evaluate the potential impact of our estimate, we performed additional simulation on this younger cohort if statin was used among 80% and 90% of patients. We chose these targets because we observed a statin use rate of 83% for patients with ASCVD aged >65 years. We found that the eligibility estimate would have been altered to 2.5% of the overall population, 46.8% of patients with ASCVD for 80% use; and 2.6% of the overall population, 49.3% of patients with ASCVD for 90% use. Second, we used the Kaplan-Meier method to estimate incidence of the clinical outcomes. Because the outcomes of interest had competing risks of death, a cumulative incidence function should be ideally used to generate a survival function for the hypothetically treated cohort. We were unable to do so because the FOURIER trial only provided hazard ratios for treatment derived from a Cox model and not a subdistribution hazard model. Accordingly, it is possible that we have overestimated the incidence of the outcome compared with the competing risk method. We also assumed that all patients included in our cohort would be eligible for PCSK9i and have similar benefit as in the clinical

trials, and we did not make adjustment or use matching to compare these patients. Finally, we were only able to examine PCSK9i adoptions among patients who had lipid testing in our population. Despite this, our initial cohort of >2 million individuals is likely representative of the entire population.

In summary, our study uses data from routine clinical practice to provide the real-world implication of adopting PCSK9i. Given the relatively low baseline risk of an average patient with ASCVD, adoption of PCSK9i is unlikely to be feasible for many healthcare systems. Selective adoption of PCSK9i to those at highest baseline risk may be a reasonable initial approach for many health systems.

Acknowledgments

Parts of this material are based on data and information compiled and provided by the Canadian Institute for Health Information (CIHI). The analyses, conclusions, opinions, and statements expressed herein are those of the authors, and not necessarily those of the CIHI. Coauthor Jack V. Tu, MD, PhD, died May 30, 2018.

Sources of Funding

This study was supported by the Institute for Clinical Evaluative Sciences (ICES), which is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC). The opinions, results, and conclusions reported in this article are those of the authors and are independent from the funding sources. No endorsement by ICES, or the MOHLTC, is intended or should be inferred. This study was funded by a foundation grant (FDN-154333 and 143313) from the Canadian Institutes of Health Research.

Disclosures

Ko and Austin are supported by a Mid-Career Investigator award from the Heart and Stroke Foundation of Canada (HSFC), Ontario Provincial Office. Wijeysundera received a Distinguished Clinical Scientist Award from HSFC. Tu was funded by a Tier 1 Canada Research Chair in Health Services Research and an Eaton Scholar Award from the Department of Medicine, University of Toronto. The remaining authors have no disclosures to report.

References

1. Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, Greenland P, Lackland DT, Levy D, O'Donnell CJ, Robinson JG, Schwartz JS, Shero ST, Smith SC Jr, Sorlie P, Stone NJ, Wilson PW, Jordan HS, Nevo L, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Smith SC Jr, Tomaselli GF; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129:S49–S73.
2. Sampson UK, Fazio S, Linton MF. Residual cardiovascular risk despite optimal LDL cholesterol reduction with statins: the evidence, etiology, and therapeutic challenges. *Curr Atheroscler Rep*. 2012;14:1–10.
3. Giugliano RP, Sabatine MS. Are PCSK9 inhibitors the next breakthrough in the cardiovascular field? *J Am Coll Cardiol*. 2015;65:2638–2651.
4. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, Kuder JF, Wang H, Liu T, Wasserman SM, Sever PS, Pedersen TR; FOURIER Steering Committee and Investigators. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med*. 2017;376:1713–1722.
5. Schulman KA, Balu S, Reed SD. Specialty pharmaceuticals for hyperlipidemia: impact on insurance premiums. *N Engl J Med*. 2015;373:1591–1593.
6. Britton A, McKee M, Black N, McPherson K, Sanderson C, Bain C. Threats to applicability of randomised trials: exclusions and selective participation. *J Health Serv Res Policy*. 1999;4:112–121.
7. Rothwell PM. External validity of randomised controlled trials: "to whom do the results of this trial apply?" *Lancet*. 2005;365:82–93.
8. Kazi DS, Moran AE, Coxson PG, Penko J, Ollendorf DA, Pearson SD, Tice JA, Guzman D, Bibbins-Domingo K. Cost-effectiveness of PCSK9 inhibitor therapy in patients with heterozygous familial hypercholesterolemia or atherosclerotic cardiovascular disease. *JAMA*. 2016;316:743–753.
9. Kazi DS, Penko J, Coxson PG, Moran AE, Ollendorf DA, Tice JA, Bibbins-Domingo K. Updated cost-effectiveness analysis of PCSK9 inhibitors based on the results of the FOURIER trial. *JAMA*. 2017;318:748–750.
10. Cannon CP, Khan I, Klimchak AC, Reynolds MR, Sanchez RJ, Sasiela WJ. Simulation of lipid-lowering therapy intensification in a population with atherosclerotic cardiovascular disease. *JAMA Cardiol*. 2017;2:959–966.
11. McPherson R, Frohlich J, Fodor G, Genest J; Canadian Cardiovascular Society. Canadian Cardiovascular Society position statement: recommendations for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease. *Can J Cardiol*. 2006;22:913–927.
12. Jackevicius CA, Tu JV, Krumholz HM, Austin PC, Ross JS, Stukel TA, Koh M, Chong A, Ko DT. Comparative effectiveness of generic atorvastatin and lipitor (R) in patients hospitalized with an acute coronary syndrome. *J Am Heart Assoc*. 2016;5:e003350. DOI: 10.1161/JAHA.116.003350.
13. Tu JV, Chu A, Donovan LR, Ko DT, Booth GL, Tu K, Maclagan LC, Guo H, Austin PC, Hogg W, Kapral MK, Wijeysundera HC, Atzema CL, Gershon AS, Alter DA, Lee DS, Jackevicius CA, Bhatia RS, Udell JA, Rezai MR, Stukel TA. The Cardiovascular Health in Ambulatory Care Research Team (CANHEART): using big data to measure and improve cardiovascular health and healthcare services. *Circ Cardiovasc Qual Outcomes*. 2015;8:204–212.
14. Yan AT, Koh M, Chan KK, Guo H, Alter DA, Austin PC, Tu JV, Wijeysundera HC, Ko DT. Association between cardiovascular risk factors and aortic stenosis: the CANHEART Aortic Stenosis Study. *J Am Coll Cardiol*. 2017;69:1523–1532.
15. Sabatine MS, Giugliano RP, Keech A, Honarpour N, Wang H, Liu T, Wasserman SM, Scott R, Sever PS, Pedersen TR. Rationale and design of the Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk trial. *Am Heart J*. 2016;173:94–101.
16. Ko DT, Alter DA, Guo H, Koh M, Lau G, Austin PC, Booth GL, Hogg W, Jackevicius CA, Lee DS, Wijeysundera HC, Wilkins JT, Tu JV. High-density lipoprotein cholesterol and cause-specific mortality in individuals without previous cardiovascular conditions: the CANHEART study. *J Am Coll Cardiol*. 2016;68:2073–2083.
17. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC Jr, Watson K, Wilson PW, Eddleman KM, Jarrett NM, LaBresh K, Nevo L, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Smith SC Jr, Tomaselli GF; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129:S1–S45.
18. Jacobs P, Yim R. *Using Canadian Administrative Databases to Derive Economic Data for Health Technology Assessments*. Ottawa, Ontario, Canada: Canadian Agency for Drugs and Technologies in Health; 2009.
19. Szpakowski N, Qiu F, Masih S, Kurdyak P, Wijeysundera HC. Economic impact of subsequent depression in patients with a new diagnosis of stable angina: a population-based study. *J Am Heart Assoc*. 2017;6:e006911. DOI: 10.1161/JAHA.117.006911.
20. Wodchis WP, Bushmeneva K, Nikitovic M, McKillop I. Guidelines on person-level costing using administrative databases in Ontario. Working Paper Series.

Vol 1. 2013.Toronto, Ontario, Canada. Available at: www.hsprn.ca/uploads/files/Guidelines_on_PersonLevel_Costing_May_2013.pdf. Accessed September 1, 2018.

21. Ko DT, Krumholz HM, Wang Y, Foody JM, Masoudi FA, Havranek EP, You JJ, Alter DA, Stukel TA, Newman AM, Tu JV. Regional differences in process of care and outcomes for older acute myocardial infarction patients in the United States and Ontario, Canada. *Circulation*. 2007;115:196–203.
22. Ko DT, Tu JV, Austin PC, Wijeysundera HC, Samadashvili Z, Guo H, Cantor WJ, Hannan EL. Prevalence and extent of obstructive coronary artery disease among patients undergoing elective coronary catheterization in New York State and Ontario. *JAMA*. 2013;310:163–169.
23. Virani SS, Akeroyd JM, Nambi V, Heidenreich PA, Morris PB, Nasir K, Michos ED, Bittner VA, Petersen LA, Ballantyne CM. Estimation of eligibility for PCSK9 inhibitors and associated costs based on the FOURIER trial: insights from the Department of Veterans Affairs. *Circulation*. 2017;135:2572–2574.
24. Kennedy-Martin T, Curtis S, Faries D, Robinson S, Johnston J. A literature review on the representativeness of randomized controlled trial samples and implications for the external validity of trial results. *Trials*. 2015;16:495.
25. Steg PG, Lopez-Sendon J, Lopez de Sa E, Goodman SG, Gore JM, Anderson FA Jr, Himbert D, Allegrone J, Van de Werf F; GRACE Investigators. External validity of clinical trials in acute myocardial infarction. *Arch Intern Med*. 2007;167:68–73.
26. 2015/16 report card for the Ontario drug benefit program. http://www.health.gov.on.ca/en/pro/programs/drugs/pub_drugs.aspx. Accessed August 1, 2018.
27. Lee TC, Kaouache M, Grover SA. Evaluation of the cost-effectiveness of evolocumab in the FOURIER study: a Canadian analysis. *CMAJ Open*. 2018;6:E162–E167.
28. Ko DT, Mamdani M, Alter DA. Lipid-lowering therapy with statins in high-risk elderly patients: the treatment-risk paradox. *JAMA*. 2004;291:1864–1870.