

Rates of rebleeding, thrombosis and mortality associated with resumption of anticoagulant therapy after anticoagulant-related bleeding

Derek H.W. Little MD, Rinku Sutradhar PhD, Joshua O. Cerasuolo MSc, Richard Perez MSc, James Douketis MD, Anne Holbrook MD PharmD MSc, J. Michael Paterson MSc, Tara Gomes PhD MHSc, Deborah M. Siegal MD MSc

■ Cite as: *CMAJ* 2021 March 1;193:E304-9. doi: 10.1503/cmaj.201433

ABSTRACT

BACKGROUND: Data on resuming oral anticoagulants (OACs) after bleeding are primarily from studies involving patients given warfarin, with few data on direct OACs (DOACs). We aimed to characterize prescribing patterns for OACs after OAC-related bleeding and compare the rates of bleeding, thrombosis and mortality in patients who resumed either type of OAC with those who did not.

METHODS: We conducted a population-based cohort study of adults aged 66 years or older who were admitted to hospital for bleeding while receiving OACs from Apr. 1, 2012, to Mar. 31, 2017, using linked administrative health databases from Ontario. We used competing

risk methods to calculate cause-specific adjusted hazard ratios (HRs) for thrombosis, bleeding and mortality with resumption of OACs adjusted as a time-varying covariate. We determined time to OAC resumption using the Kaplan-Meier method.

RESULTS: We included 6793 patients with gastrointestinal ($n = 4297$, 63.3%), intracranial ($n = 805$, 11.9%) or other bleeding ($n = 1691$, 25.0%). At cohort entry, 3874 patients (57.0%) were prescribed warfarin and 2919 patients (43.0%) were prescribed a DOAC. The most common indication for OAC was atrial fibrillation ($n = 5557$, 81.8%), followed by venous thromboembolism ($n = 1367$, 20.1%). Oral anticoagulants were

resumed in 4792 patients (70.5%) within 365 days of the index bleed. The median time to resumption was 46 (interquartile range 6–550) days. We found that resuming OAC was associated with reduced rates of thrombosis (adjusted HR 0.60, 95% confidence interval [CI] 0.50–0.72) and mortality (adjusted HR 0.54, 95% CI 0.48–0.60), and an increased rate of rebleeding (adjusted HR 1.88, 95% CI 1.64–2.17).

INTERPRETATION: We found that resuming OAC is associated with a reduction in thrombosis and mortality but an increase in bleeding. Randomized controlled trials that evaluate the net benefit of strategies for resumption of OAC after a bleeding event are warranted.

Oral anticoagulants (OACs) are used to prevent and treat arterial and venous thrombosis. Bleeding associated with OACs is the most common adverse drug event that leads to visits to the emergency department, hospital admissions and death.^{1,2} When OACs are withheld after a bleed, patients are exposed to an increased risk of thrombosis and possibly death. A challenging clinical problem is determining whether OACs should be resumed after a bleed and, if so, the optimal strategy for resumption.

Oral anticoagulant therapy is stopped permanently in a substantial proportion of patients after gastrointestinal (GI) or intracranial bleeding (50% and 64%, respectively)^{3,4} despite evidence that suggests a benefit to restarting.^{3,5-9} Direct OACs (DOACs) are

now recommended for stroke prevention in patients with atrial fibrillation (AF) and for the treatment of venous thromboembolism (VTE) based on substantial evidence.¹⁰⁻¹² However, resumption of OACs after bleeding has been assessed primarily in small studies of patients treated with warfarin that did not report on extracranial non-GI bleeding.^{3,4,13}

Using population-based data, we aimed to characterize prescribing patterns for OACs and compare outcomes between patients who resumed OAC with those who did not after OAC-related bleeding. Our secondary aims were to compare outcomes separately after OAC-related GI bleeding, intracranial hemorrhage, extracranial non-GI bleeding and any bleeding.

Methods

Study design

We conducted a population-based, retrospective cohort study involving adults with a bleeding event while receiving OAC therapy between Apr. 1, 2012, and Mar. 31, 2017, using linked administrative data from Ontario. We obtained data on prescription drug claims from the Ontario Drug Benefit (ODB) Database, records of hospital discharges from the Discharge Abstract Database (Canadian Institute for Health Information), records of visits to emergency departments from the National Ambulatory Care Reporting System, physician service claims from the Ontario Health Insurance Plan Claims History Database, and demographic and vital status information from the Registered Persons Database. We linked data sources using unique encoded identifiers and analyzed data at ICES. Results were reported using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.¹⁴

Study population

We included adults aged 66 years or older with a hospital admission for bleeding and a prescription for warfarin, apixaban, rivaroxaban or dabigatran that was dispensed in the preceding 100 days. Ontario residents receive coverage for prescription drugs through the ODB plan as of age 65 years. We defined bleeding as an admission to hospital with the most responsible diagnosis of intracranial hemorrhage, GI bleeding (upper or lower) or other bleeds (primarily genitourinary or respiratory) present on admission using *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* (ICD-10) codes. This method has a sensitivity of 94% and a specificity of 83% for determining major bleeding events for warfarin.¹⁵ We excluded patients who died during the index admission. We also excluded patients with a bleed within the previous 5 years because these patients are at increased risk for rebleeding and permanent discontinuation of OAC therapy. We excluded patients who were designated palliative (using physician service palliative care codes¹⁶ and data sources¹⁷) because their limited life expectancy would affect ascertainment of outcomes and prescribing practices. For patients with multiple admissions for bleeding during the study accrual period, we used the first eligible bleeding event. We followed patients until the occurrence of an outcome, loss of health insurance coverage, death or the end of the study period.

Study outcomes

Our primary outcomes were bleeding, thrombosis, and all-cause mortality. We defined bleeding events using ICD-10 codes associated with hospital admission or a visit to the emergency department and included intracranial hemorrhage, GI bleeding and other bleeds (e.g., respiratory or genitourinary). We defined thrombotic events using ICD-10 codes for ischemic stroke, transient ischemic attack, deep vein thrombosis, pulmonary embolism, myocardial infarction, percutaneous coronary intervention, and coronary artery bypass grafting (Appendix 1, Supplementary Table S1, available at www.cmaj.ca/lookup/doi/10.1503/cmaj.201433/tab-related-content).

We collected the following baseline patient characteristics: age, sex, site of bleeding, indication for OAC, type of OAC, antiplatelet

or nonsteroidal anti-inflammatory drug (NSAID) use within 100 days of the index bleed, duration of index hospital admission, socioeconomic status (neighbourhood income quintile) and residence in a long-term care facility. We determined baseline comorbidities using codes for physician service claims, emergency department records and hospital discharge abstracts.

For the analysis of outcomes, we implemented a blanking period of 100 days after hospital discharge with follow-up starting after 100 days. This was done to address uncertainty about whether patients continued their home supply of OACs after hospital discharge (the maximum supply under ODB is 100 d) and to address immortal time bias by starting follow-up at the same time point in both groups. Therefore, events that occurred within the blanking period were excluded from the main analysis. The blanking period was not applied to the descriptive analysis or timing of resumption analysis. Using a time-varying approach, exposure status was updated throughout the observation window that began after the blanking period and ended when the patient experienced an outcome, competing event or was censored. We determined OAC resumption status from prescription drug claims.

Statistical analysis

We reported categorical data as counts and proportions. We reported continuous data as means with standard deviations (SDs) or medians with interquartile ranges (IQRs). We used the standardized difference to compare baseline characteristics between those who resumed OAC at some point during their observation period and those who did not.¹⁸ We considered a standardized difference of greater than 0.1 to be meaningful. We treated thrombosis, bleeding and death as competing events. We used multivariable cause-specific hazards regression models to calculate adjusted hazard ratios (HRs) for subsequent thrombosis, bleeding and mortality, and adjusted for prespecified covariates for the whole cohort and separately by index bleed type.^{19,20} We adjusted the models for the following variables measured at the time of the index bleed: age, sex, index bleed type, OAC at index bleed, antiplatelet or NSAID therapy dispensed 100 days preceding the index bleed, Charlson Comorbidity Index, and history of hypertension, diabetes, liver disease, renal disease, dementia and congestive heart failure. We included exposure to OAC as a binary time-varying covariate. We calculated time to OAC resumption using the Kaplan–Meier method.

Ethics approval

The study was approved by the Hamilton Integrated Research Ethics Board.

Results

We identified 26 501 patients who were admitted to hospital for bleeding between Apr. 1, 2012, and Mar. 31, 2017, after we excluded 4824 patients who died during admission. Of these, 6793 patients were dispensed OAC in the 100 days preceding the index bleed and composed the study cohort. Baseline characteristics are shown in Table 1. The median age of these patients was 82 (IQR 76–87) years and 52% were male. Gastrointestinal bleeding occurred in 4297 patients (63.3%), intracranial hemorrhage in

805 patients (11.9%) and other bleeding in 1691 patients (25.0%). At the time of the index bleed, 3874 patients (57.0%) were taking warfarin and 2919 (43.0%) were taking a DOAC.

Resumption of OACs

Treatment using an OAC was resumed in 4792 patients (70.5%) within 365 days of the admission date of the index bleed (GI bleeding 71.6%, intracranial hemorrhage 45.6%). The median length of

follow-up was 82 (IQR 41–146) weeks and 83 (IQR 40–149) weeks for those who resumed and did not resume OAC, respectively.

Associated factors

Patients who did not resume OAC were significantly older (median 83 [IQR 77–88] v. 81 [IQR 75–86] yr), more likely to have dementia (22.6% v. 14.5%) and more likely to reside in a long-term care facility (14.9% v. 6.7%) than patients who resumed OAC. Patients with

Table 1: Baseline characteristics of the study cohort*

Characteristic	No. (%) of patients† who did not resume OAC treatment‡ n = 2001	No. (%) of patients† who resumed OAC treatment§ n = 4792	Standardized difference¶
Age, yr; median (IQR)	83 (77–88)	81 (75–86)	0.25
Sex, male	967 (48.3)	2596 (54.2)	0.12
Location of index bleed			
Upper GI	1077 (53.8)	2682 (56.0)	0.04
Lower GI	142 (7.1)	396 (8.3)	0.04
Intracranial hemorrhage	438 (21.9)	367 (7.7)	0.41
Other	344 (17.2)	1347 (28.1)	–
Type of OAC			
Apixaban	165 (8.2)	430 (9.0)	0.03
Dabigatran	270 (13.5)	587 (12.2)	0.04
Rivaroxaban	494 (24.7)	973 (20.3)	0.11
Warfarin	1072 (53.6)	2802 (58.5)	0.1
Indication for OAC**			
Atrial fibrillation	1476 (73.8)	4081 (85.2)	0.29
Venous thromboembolism	396 (19.8)	971 (20.3)	0.01
Prosthetic heart valve	49 (2.4)	214 (4.5)	0.11
Charlson Comorbidity Index, mean ± SD	2.0 ± 1.9	2.0 ± 1.8	0.01
CHA ₂ DS ₂ -VASC score, mean ± SD††	5.0 ± 1.5	5.0 ± 1.5	0.01
HAS-BLED score, mean ± SD††	3.3 ± 0.7	3.3 ± 0.7	0.01
Resident of LTC at time of bleed	299 (14.9)	320 (6.7)	0.27
Comorbidity			
Active malignant disease	96 (4.8)	161 (3.4)	0.07
Myocardial infarction	165 (8.2)	389 (8.1)	0.00
Congestive heart failure	891 (44.5)	2433 (50.8)	0.13
Ischemic stroke or TIA	108 (5.4)	262 (5.5)	0.00
Venous thromboembolism	315 (15.7)	754 (15.7)	0.00
Dementia	452 (22.6)	696 (14.5)	0.21
Hypertension	1776 (88.8)	4409 (92.0)	0.11
Chronic kidney disease	360 (18.0)	800 (16.7)	0.03
Diabetes	794 (39.7)	2053 (42.8)	0.06

Note: GI = gastrointestinal, IQR = interquartile range, LTC = long-term care, OAC = oral anticoagulant, SD = standard deviation, TIA = transient ischemic attack.

*The presentation of OAC exposure is for descriptive purposes only; in the analysis, we treated it as a time-varying measure.

†Unless specified otherwise.

‡Did not resume OAC within 365 days of index bleed.

§Resumed OAC within 365 days of the index bleed.

¶We considered a standardized difference greater than 0.1 to be significant.

**Percentages do not add to 100% because patients may have had multiple indications for OAC.

††Patients with atrial fibrillation only.

Table 2: Type of oral anticoagulant dispensed prebleed and postbleed

Type of OAC dispensed (prebleed)	No. of patients who received an OAC before index bleed	No. (%) of patients given an OAC postbleed				
		Warfarin	Apixaban	Dabigatran	Rivaroxaban	None*
Warfarin (n = 3874)	3874	2458 (63.4)	243 (6.3)	79 (2.0)	127 (3.3)	967 (25.0)
Apixaban (n = 595)	595	36 (6.1)	388 (65.2)	6 (1.0)	16 (2.7)	149 (25.0)
Dabigatran (n = 857)	857	114 (13.3)	121 (14.1)	342 (39.9)	38 (4.4)	242 (28.2)
Rivaroxaban (n = 1467)	1467	121 (8.2)	189 (12.9)	28 (1.9)	705 (48.1)	424 (28.9)

Note: OAC = oral anticoagulant.
*Did not resume OAC within 365 days of the index bleed.

a prosthetic heart valve and those with AF were significantly more likely to resume OAC than not resume OAC (4.5% v. 2.4% and 85.2% v. 73.8%, respectively). For patients with AF, we determined that the mean CHA₂DS₂-VASc and HAS-BLED scores were similar between patients who resumed OAC and those who did not (5.0 v. 5.0 and 3.3 v. 3.3, respectively). The mean Charlson Comorbidity Index was similar between patients who resumed OAC and those who did not (2.0 v. 2.0).

Drug type

Treatment using OACs was resumed in 2907 patients (75.0%) with bleeding while on warfarin (Table 2), of whom 2458 (84.6%) resumed warfarin and 449 (15.4%) switched to a DOAC. Apixaban was the most commonly used DOAC in patients who were switched from warfarin. Of the 2104 patients (72.4%) who resumed OAC therapy after bleeding while on a DOAC, 1833 (87.1%) resumed a DOAC and 271 (12.9%) switched to warfarin.

Timing

The median time to first OAC prescription after the index bleed for all patients throughout the study period was 46 (IQR 6–550) days. Among those who resumed OAC within 365 days of the index bleed, the median time to resumption was 26 (IQR 10–64) days from the index bleed, with 53% resuming OACs within 30 days. Among those who resumed OAC within 365 days, the median time to resumption was 63 (IQR 29–114) days for those with intracranial hemorrhage and 24 (IQR 9–60) days for those with GI bleeding.

Outcomes by type of index bleed

All bleed types

We included 5278 patients in the time-varying analysis after we excluded 1515 patients who had an event during the blanking period. The cause-specific HRs are shown in Table 3. There were 2018 deaths over the study period, with 1332 as the first outcome and 686 after bleeding or thrombosis. Of 1087 patients with bleeding as the first outcome, 472 (43.4%) died afterward. Of 463 patients with thrombosis as the first outcome, 214 (46.2%) died afterward. The rates of bleeding were higher in patients who resumed OACs than in those who did not (35.2% v. 16.4%; adjusted HR 1.88, 95% confidence interval [CI] 1.64–2.17). Resuming OACs was associated with a lower rate of thrombosis (10.0% v. 14.9%; adjusted HR 0.60, 95% CI 0.50–0.72)

Table 3: Unadjusted and adjusted* cause-specific hazard ratios for resuming oral anticoagulants versus not resuming oral anticoagulants†

Index bleed type	Bleeding HR (95%CI)	Thrombosis HR (95%CI)	Mortality HR (95%CI)
All			
Unadjusted	1.98 (1.72–2.27)	0.60 (0.50–0.72)	0.50 (0.45–0.56)
Adjusted	1.88 (1.64–2.17)	0.60 (0.50–0.72)	0.54 (0.48–0.60)
GI			
Unadjusted	1.99 (1.68–2.37)	0.58 (0.46–0.74)	0.49 (0.42–0.56)
Adjusted	2.02 (1.69–2.40)	0.56 (0.44–0.71)	0.54 (0.47–0.62)
Intracranial			
Unadjusted	2.39 (1.50–3.80)	0.72 (0.43–1.19)	0.49 (0.34–0.71)
Adjusted	2.20 (1.36–3.56)	0.73 (0.44–1.23)	0.54 (0.37–0.79)
Extracranial non-GI bleeding			
Unadjusted	1.52 (1.16–2.00)	0.60 (0.41–0.88)	0.51 (0.41–0.64)
Adjusted	1.50 (1.15–1.98)	0.60 (0.41–0.89)	0.54 (0.43–0.68)

Note: CI = confidence interval, GI = gastrointestinal, HR = hazard ratio, OAC = oral anticoagulant.
*Adjusted for age; sex; index bleed type; OAC at index bleed; antiplatelet or nonsteroidal anti-inflammatory therapy given 100 days preceding the index bleed; Charlson Comorbidity Index; and medical history of hypertension, diabetes, liver disease, renal disease, dementia or congestive heart failure.
†Not resuming OACs was the reference category.

and mortality for all index bleed types (31% v. 54%, adjusted HR 0.54, 95% CI 0.48–0.60). Types of thrombotic events are shown in Appendix 2, Supplementary Table S2, available at www.cmaj.ca/lookup/doi/10.1503/cmaj.201433/tab-related-content. Compared with patients who did not resume OACs, outcomes were similar whether patients resumed warfarin or a DOAC for all bleed types (Appendix 3, Supplementary Table S3, available at www.cmaj.ca/lookup/doi/10.1503/cmaj.201433/tab-related-content).

Gastrointestinal bleeding

Among 3369 patients with an index GI bleed, we found that resuming OACs was associated with an increased rate of bleeding (adjusted HR 2.02, 95% CI 1.69–2.40), which was most frequently recurrent GI bleeding (64.5%). The rate of thrombosis was reduced in patients who resumed OACs compared with

those who did not (adjusted HR 0.56, 95% CI 0.44–0.71). There was a similar reduction in mortality in patients with GI bleeding (adjusted HR 0.54, 95% CI 0.47–0.62).

Intracranial hemorrhage

Among 612 patients with an index intracranial hemorrhage, we found that resuming OACs was associated with an increased rate of bleeding (adjusted HR 2.20, 95% CI 1.36–3.56). The type of bleeding event was a recurrent intracranial hemorrhage in 32.5% of these patients and a GI bleed in 31.2%. Resuming OACs was associated with a lower rate of mortality (adjusted HR 0.54, 95% CI 0.37–0.79), whereas the rate of thrombosis was not significantly different (adjusted HR 0.73, 95% CI 0.44–1.23).

Extracranial nongastrointestinal bleeding

We determined that resuming OACs in patients with extracranial non-GI bleeding ($n = 1297$) was associated with an increased rate of bleeding (adjusted HR 1.50, 95% CI 1.15–1.98), a reduced rate of thrombosis (adjusted HR 0.60, 95% CI 0.41–0.89) and a reduced rate of mortality (adjusted HR 0.54, 95% CI 0.43–0.68).

Interpretation

We found that patients who resumed OACs had important relative reductions in the rates of both thrombosis (39.9%) and mortality (45.9%) but with an increase in the relative rate of subsequent bleeding (88.4%). These findings were generally consistent across subgroups of patients presenting with GI bleeding, intracranial hemorrhage and extracranial non-GI bleeding, although the reduction in thrombosis in patients with intracranial hemorrhage was not statistically significant.

We analyzed a large, population-based cohort that included many patients taking DOACs. We used a competing risks analysis, which is appropriate because bleeding and thrombosis have shared risk factors and, therefore, are not independent events. We treated resumption of OACs as a time-varying covariate to account for OAC exposure over time, thereby reducing the possibility of misclassification bias in assuming that patients who resume OAC remain on it. Because OAC exposure was a function of time, absolute risks were not attainable. Finally, we provided evidence of a benefit to resuming OAC in patients with extracranial, non-GI bleeding, a population seldom studied.

Our study more closely reflects current practice than previous studies in that 43.0% of patients were taking a DOAC during the index bleed. For example, patients who were taking DOACs comprised 2% and less than 1% of the study populations in 2 meta-analyses of OAC-associated GI bleeding³ and intracranial hemorrhage,⁴ respectively. Our results suggest that the benefits and harms of resuming OACs apply to a population of patients on warfarin or DOACs in contemporary clinical practice.

In our study, resuming OAC after intracranial hemorrhage was associated with the highest rate of rebleeding compared with other index bleed types and included nonintracranial bleeding, which may be explained in part by the older age and multiple comorbidities of the patients in this subpopulation, both of which increase the risk of bleeding.²¹ When we accounted for the competing risks of

bleeding and mortality, resuming OACs after an intracranial hemorrhage was associated with a nonsignificant reduction in thrombosis. This differs from a 2017 study that reported a 66% reduction in thrombosis with OAC resumption.⁴ This discrepancy may be related to the time-varying risk of bleeding and thrombosis, with the highest risk for bleeding occurring soon after the index bleed.²² The 2017 study used a time-to-event analysis, which estimates the probability of the event of interest assuming the absence of competing risks and generally estimates are larger.²³

Treatment with an OAC was resumed in 71.6% of patients with GI bleeding and 45.6% of patients with intracranial hemorrhage within 365 days of the index bleed in our study. In earlier studies, OACs were resumed in 34%–59% of patients after GI bleeding^{6,7,24} and 24%–35% of patients after intracranial hemorrhage.^{5,8,25} These lower rates may be explained in part by the definition of OAC resumption being at or shortly after hospital discharge in some studies. In addition, the potential benefits of resuming OACs after bleeding have become more recognized and guidelines have recently recommended resumption of OAC after GI bleeding and intracranial hemorrhage.^{12,26,27}

Limitations

Although our analyses were adjusted for covariates, it is possible that residual unmeasured confounding was present and that baseline patient and provider characteristics influenced OAC management (i.e., OACs were withheld in sicker patients). This may have affected mortality, and we were unable to determine causes of death. In addition, our results were limited to events associated with hospital admission, which are clinically relevant but likely represent a spectrum of severity, and we were unable to define severity of bleeding further. With respect to treatment using OACs, we assumed that prescriptions claimed were taken by the patient and were unable to fully account for the use of acetylsalicylic acid and NSAIDs, which can be purchased over the counter. The blanking period was another limitation because it excluded patients who had an event within 100 days. However, it reduced the uncertainty about whether patients continued their home supply of an OAC at discharge and addressed the issue of immortal time bias as follow-up began at the same time for both groups. In addition, our focus was on longer- rather than shorter-term risks. As we included adults aged 66 years and older, our results may not be generalizable to younger populations. Finally, we were unable to evaluate outcomes based on the timing of resumption because we treated resumption of OACs as a time-varying covariate.

Conclusion

In our large cohort of older adults on warfarin or a DOAC predominantly for AF, resuming OACs after OAC-associated bleeding appeared to be associated with an increased rate of bleeding, but with important reductions in thrombosis and mortality, findings that were generally consistent across types of bleeding. We found that the net benefit of OAC use after intracranial hemorrhage is more uncertain than after other types of bleeding. Our results support individualized, shared decision-making that involves a discussion of the harms and benefits of resuming OACs after bleeding. Future randomized controlled trials are needed to reduce confounding and identify the optimal resumption strategy.

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Competing interests: James Douketis has received consultant fees from Pfizer, Bayer, Bristol-Myers Squibb, Sanofi and Servier Canada. Deborah Siegal has received honoraria from Aspen Pharmacare, BMS-Pfizer, Bayer, Leo Pharma, Portola Pharmaceutical, Servier and Novartis. No other competing interests were declared.

This article has been peer reviewed.

Affiliations: Department of Medicine (Little, Douketis, Holbrook) and ICES McMaster (Cerasuolo, Perez), Faculty of Health Sciences, McMaster University, Hamilton, Ont.; ICES Central (Sutradhar, Paterson), Toronto, Ont.; Department of Medicine (Little); Division of Biostatistics (Sutradhar), Dalla Lana School of Public Health; Institute of Health Policy, Management and Evaluation (Paterson); Leslie Dan Faculty of Pharmacy (Gomes), University of Toronto; Unity Health Toronto (Gomes), Toronto, Ont.; Department of Medicine (Siegal), University of Ottawa, Ottawa, Ont.

Contributors: Deborah Siegal conceived the study. Deborah Siegal, Derek Little, J. Paterson, Joshua Cerasuolo and Rinku Sutradhar designed the study. Joshua Cerasuolo and Rinku Sutradhar performed the data analysis. Derek Little drafted the manuscript. Deborah Siegal, James Douketis and Anne Holbrook provided critical revisions for important intellectual content. All of the authors revised the manuscript, gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

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Funding: Tara Gomes received a grant from the Ontario Ministry of Health. Deborah Siegal received a CanVECTOR/Heart and Stroke Foundation of Canada ERLI Grant and a Hamilton Health Sciences Research Early Career Award. The funding sources were not involved in the design, conduct, analysis or preparation of the study.

Data sharing: None of the data included in this manuscript is available to others outside of the study authors. The data will be available and accessible only in the *Canadian Medical Association Journal*. The data set from this study is held securely in coded form at ICES. While legal data-sharing agreements between ICES and data providers (e.g., health care organizations, government) prohibit ICES from making the data set publicly available, access may be granted to those who meet prespecified criteria for confidential access, available at www.ices.on.ca/DAS (email: das@ices.on.ca). The full data set creation plan and underlying analytic code are available from the authors on request, with the understanding that the computer programs rely upon coding templates and macros that are unique to ICES and therefore may be inaccessible or may require modification.

Disclaimer: This study was supported by ICES, which is funded by an annual grant from the Ontario Ministry of Health. Parts of this material are based on data and information compiled and provided by the Ontario Ministry of Health, the Canadian Institute for Health Information and IQVIA Solutions Canada, Inc. The analyses, conclusions, opinions, and statements expressed herein are those of the authors and do not necessarily reflect those of the funding or data sources; no endorsement is intended or should be inferred.

Accepted: Dec. 21, 2020

Correspondence to: Deborah Siegal, siegald@mcmaster.ca