Hospitalization for Hemorrhage Among Warfarin Recipients Prescribed Amiodarone

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Amiodarone inhibits the hepatic metabolism of warfarin, potentiating its anticoagulant effect. However, the clinical consequences of this are not well established. Our objective in this study was to characterize the risk of hospitalization for a hemorrhage associated with the initiation of amiodarone within a cohort of continuous warfarin users in Ontario. We conducted a population-based retrospective cohort study among Ontario residents aged ≥66 years receiving warfarin. Among patients with at least 6 months of continuous warfarin therapy, we identified those who were newly prescribed amiodarone and an equal number who were not, matching on age, gender, year of cohort entry, and a high-dimensional propensity score. The primary outcome was hospitalization for hemorrhage within 30 days of amiodarone initiation. Between July 1, 1994, and March 31, 2009, we identified 60,497 patients with at least 6 months of continuous warfarin therapy, of whom 11,665 (19%) commenced amiodarone. For 7,124 (61%) of these, we identified a matched control subject who did not receive amiodarone. Overall, 56 (0.8%) amiodarone recipients and 23 (0.3%) control patients were hospitalized for hemorrhage within 30 days of initiating amiodarone (adjusted hazard ratio 2.45; 95% confidence interval, 1.49−4.02). Seven of 56 (12.5%) patients hospitalized for a hemorrhage after starting amiodarone died in hospital. In conclusion, initiation of amiodarone among older patients receiving warfarin is associated with a more than twofold increase in the risk of hospitalization for hemorrhage, with a relatively high fatality rate. Physicians should closely monitor patients who initiate amiodarone while receiving warfarin. **(Am J Cardiol 2013;112:420−423)**

Amiodarone inhibits the hepatic metabolism of (S)-warfarin via cytochrome P450 isoenzyme 2C9, potentially accentuating the response to warfarin.[1,2] Previous studies have shown a dose-dependent increase in the international normalized ratio (INR) following the initiation of amiodarone therapy.[1,3−13] However, few well-designed studies have examined the actual clinically relevant outcomes such as major hemorrhagic events. One small study suggested no increased risk but included a small sample size of 1,260 at-risk patients and a short 7-day follow-up period.[13] The need to better understand this interaction and its impact on clinical outcomes is particularly important as newer analogues such as dronedarone are introduced to the market. We sought to examine the association between initiation of amiodarone and the short-term risk of hemorrhage in a large sample of older patients receiving warfarin.

Methods

We conducted a population-based retrospective cohort study in Ontario, Canada, between July 1, 1994, and March 31, 2009, using administrative health databases. The study was approved by the Research Ethics Board of Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada.

Prescription data were obtained from the Ontario Drug Benefit (ODB) Database, which includes claims for medications reimbursed by the provincial government for residents aged ≥65 years (an estimated 1.7 million people). We obtained data from the Canadian Institute for Health Information Discharge Abstract Database (DAD), which contains detailed diagnostic and procedural information for all hospitalizations in the province. We used the Ontario Health Insurance Plan (OHIP) database to obtain information regarding physicians' claims and the Registered Persons Database (RPDB) to

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See page 423 for disclosure information.

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Table 1
International Statistical Classification of Diseases and Related Health Problems, 9th revision (ICD-9), and 10th enhanced Canadian revision (ICD-10-CA) codes used to identify hemorrhage

Outcome	ICD-9 Code	ICD-10 Code
Intracerebral hemorrhage	430, 431, 432.0, 432.1, 432.9	I60, I61, I62.0, I62.1, I62.9
Upper gastrointestinal hemorrhage	531.0, 531.2, 531.4, 531.6, 532.0, 532.2, 532.4, 532.6, 533.0, 533.2, 533.4, 533.6, 534.0, 534.2, 534.4, 534.6, 578.0, 578.1, 578.9	I85.0, I98.20, I98.3, K22.10, K22.12, K22.14, K22.16, K25.0, K25.2, K25.4, K25.6, K26.0, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.0, K31.80, K63.80
Lower gastrointestinal hemorrhage	569.3, 578.1, 578.9	K55.20, K62.5, K92.2
Other	287.8, 289, 459.0, 596.7, 599.7, 627.1, 719.1, 784.8, 786.3	N020 to N02.9, K61, N93.8, N93.9, N95.0, R04.1, R04.2, R04.8, R04.9, R31.0, R31.1, R31.8, R58, D68.3, H35.6, H43.1, H45.0, M25.0

determine demographic characteristics of the cohort, including age, gender, and socioeconomic status (inferred from the neighborhood income quintile[14]). All records were linked anonymously using an encrypted health card number.

The cohort consisted of Ontario residents aged ≥66 years continuously treated with warfarin for at least 6 months during the study period, with the goal of selecting subjects who were stable on therapy. To ensure continuous warfarin therapy for at least 180 days, patients were required to have at least 1 warfarin prescription in the first 3 months and at least 1 more in the subsequent 3 months before entering the cohort. We did not include patients during their first year of eligibility for prescription drug coverage (age 65) to avoid incomplete medication records. All subjects had access to physician services, hospital care, and prescription drug coverage. We excluded patients who died on the cohort entry date as well as those with an invalid health insurance number, missing information on age or gender, or any previous use of amiodarone in the preceding 365 days.

Patients were followed from the cohort entry date until hospitalization for hemorrhage, death, or 30-day maximum follow-up, whichever occurred first. For exposed individuals, the cohort entry date was the date of the first prescription for amiodarone during the study period. For nonexposed individuals, the cohort entry date was randomly assigned to generate a similar distribution of cohort entry dates as the exposed cohort.

Each exposed patient was matched to an unexposed patient based on age at cohort entry (within 2 years), gender, year of cohort entry, and a high-dimensional propensity score (HDPS) (within 0.2 SD). The HDPS algorithm empirically identifies potential confounders among measured baseline covariates available in administrative databases.[15] The process involves 7 steps: specifying data sources, empirically identifying prevalent covariates within these data sources, assessing recurrence of covariates, prioritizing each covariate based on the amount of confounding it could potentially adjust, selecting the highest ranking covariates in addition to predefined covariates, estimating a propensity score using a multivariable logistic regression model, and incorporating the propensity score into the estimation of the exposure-outcome association. In our study, we identified all records in the DAD, OHIP, and ODB databases in the year before cohort entry for all patients in our cohort and included these as dimensions in the HDPS algorithm, a priori. In total, there were 5 data sets or dimensions created (ODB claims, DAD diagnosis codes, DAD procedural codes, OHIP fee codes, and OHIP diagnosis codes). The 200 most prevalent covariates from each data set were selected and ranked based on the amount of confounding each covariate could reduce in the exposure-outcome association, accomplished by ranking the apparent relative risks of each potentially confounding variable, a multiplicative function that reflects the imbalance in prevalence of the variable between the exposed and nonexposed patients and the independent association between this variable and the outcome of interest.[15,16] We retained the 500 highest-ranking covariates. These empirically derived covariates, in combination with investigator-defined covariates (i.e., age, gender, Charlson Comorbidity Index, hospitalizations for hemorrhage in the previous year, history of congestive heart failure, number of prothrombin time/INR tests in the 30 days before cohort entry date, and number of distinct drugs dispensed in past year) were entered in a propensity score model as independent variables in the multivariable logistic regression model.

The primary outcome was hospitalization for hemorrhage using the Canadian modification of the *International Statistical Classification of Diseases and Related Health Problems, 9th Revision and 10th Revision, Canada* (Table 1). The codes used to identify hemorrhagic events have been previously validated, with specificity, sensitivity, and positive predictive values exceeding 80%.[17–19] We restricted our analysis to hospitalizations in which hemorrhage was present at the time of admission. When subjects experienced multiple outcome events over the study period, only the first was considered.

We used standardized differences to compare the baseline characteristics between groups. This measure is calculated by dividing the difference in mean values of a continuous variable between the exposed and nonexposed group by the pooled standard deviation of the variable.[20] In general, values <0.10 reflect clinically unimportant differences between groups. We used Cox proportional hazards regression to estimate the hazard ratio and 95% confidence interval for the association between initiation of amiodarone and hospitalization for hemorrhage, adjusting for any baseline characteristics that remained substantially different between groups following matching, defined as a standardized difference of ≥0.10. All analyses were performed using SAS version 9.2 (SAS Institute, Cary, North Carolina).

Results

We identified 60,497 patients between July 1, 1994, and March 31, 2009 with at least 6 months of continuous

Table 2
Baseline characteristics after high-dimensional propensity score matching

Variable	Warfarin Alone (n = 7,124)	Warfarin + Amiodarone (n = 7,124)	Standardized Difference of the Mean
Demographics			
Median age at cohort entry, yrs (IQR)	76 (71−81)	76 (71−81)	0
Men	3,674 (52%)	3,674 (52%)	0
Rural location	1,054 (15%)	1,015 (14%)	0.02
Median no. hospitalizations in past yr (IQR)	1 (0−1)	0 (0−1)	0.1
Mean number of PT tests in past 30 days ± SD	1.34 ± 1.35	1.32 ± 1.43	0.01
Charlson Comorbidity Index			
0	2,136 (30%)	2,100 (30%)	0.01
1	1,304 (18%)	1,293 (18%)	0
2	1,067 (15%)	1,021 (14%)	0.02
3	674 (9%)	644 (9%)	0.01
4	862 (12%)	837 (12%)	0.01
Missing	1,081 (15%)	1,229 (17%)	0.06
Hemorrhage in past 1 yr	199 (3%)	194 (3%)	0
Heart failure in past 1 yr	1,537 (22%)	1,535 (22%)	0
Residence in long-term care facility	241 (3%)	312 (4%)	0.05
Median no. of distinct drugs prescribed in past 1 yr (IQR)	11 (8−15)	11 (8−15)	0.02
≤5	694 (10%)	675 (10%)	0.01
6−10	2,462 (35%)	2,586 (36%)	0.04
11−15	2,254 (32%)	2,233 (31%)	0.01
16−20	1,112 (16%)	1,042 (15%)	0.03
21−26	457 (6%)	452 (6%)	0
≥27	145 (2%)	136 (2%)	0.01
Medication use*			
NSAIDs/non COX-2 inhibitor/non-ASA	255 (4%)	310 (4%)	0.04
COX-2 inhibitor	162 (2%)	140 (2%)	0.02
Antiplatelet agents: ASA, ticlopidine, clopidogrel, dipyridamole, dipyridamole/ASA combination)	246 (3%)	216 (3%)	0.02
Acetaminophen and combinations	1,095 (15%)	1,037 (15%)	0.02
Gastroprotective medications (H_2 receptor antagonists, misoprostol, proton pump inhibitors, sucralfate)	1,572 (22%)	1,492 (22%)	0.03
Selective serotonin receptor inhibitors	539 (8%)	437 (6%)	0.06
Corticosteroids†	324 (5%)	339 (5%)	0.01
Statins	1,919 (27%)	1,857 (26%)	0.02
Antibiotic use‡			
Trimethoprim/sulfamethoxazole	21 (0.3%)	23 (0.3%)	0.01
Fluoroquinolone	83 (1%)	100 (1%)	0.02
Metronidazole	6 (0.1%)	13 (0.2%)	0.03

ASA = acetylsalicylic acid (aspirin); COX-2 = cyclooxygenase 2 inhibitor; H_2 = histamine 2 receptor antagonists; IQR = interquartile range; NSAID = nonsteroidal anti-inflammatory drugs; PT = prothrombin time.

* Evidence of ≥1 prescription of the listed medications in the 60 days before cohort entry date.

† Excluding topical or aerosol formulations.

‡ Evidence of ≥1 prescription of the listed medications in the 14 days before cohort entry date.

outpatient warfarin therapy, of whom 11,665 (19%) subsequently initiated amiodarone while receiving warfarin. Of these, 7,124 (61%) were successfully matched to a subject who was not exposed to amiodarone while receiving warfarin therapy. Following matching, exposed and unexposed individuals were similar on baseline characteristics (Table 2), with the exception of the median number of hospitalizations during the year preceding cohort entry (standardized difference = 0.11). The median age was 76 years, with approximately equal percentages of men and women (52% male).

Among the 7,124 patients who commenced amiodarone while receiving warfarin, 50 (0.8%) were hospitalized for hemorrhage within the subsequent 30 days. In the matched control group, 23 (0.3%) patients were hospitalized for hemorrhage within 30 days (Table 3). We observed a significantly greater risk of hemorrhage among patients who received amiodarone compared with patients receiving warfarin alone (adjusted hazard ratio 2.45; 95% confidence interval, 1.49 to 4.02; Table 2). In terms of absolute risk, this difference corresponds to a number needed to treat to harm of 216. In total, 7 (12.5%) patients hospitalized for hemorrhage following the initiation of amiodarone, died in hospital.

Discussion

In this population-based cohort study spanning 15 years, we found that patients receiving warfarin were also frequently prescribed amiodarone. This is not surprising given the utility of both drugs for atrial fibrillation. However, the prevalence

Table 3
Primary outcome: patients admitted hemorrhagic event (primary event)

	Warfarin Alone	Warfarin + Amiodarone
No. of individuals	N = 7,124	N = 7,124
Total follow-up (person yrs)	581	577
Follow-up (days ± SD)	30 ± 2	30 ± 3
Number of patients with a hemorrhage	23	56
Incidence	0.3%	0.8%
No. needed to harm	Reference	216
Unadjusted HR (95% CI)	1.0	2.43 (1.50−3.96)
Adjusted HR (95% CI)	1.0	2.45 (1.49−4.02)

HRs were adjusted for hospitalizations prior to cohort entry.
CI = confidence interval; HR = hazard ratio.

of concomitant use does mandate a better understanding of the potential for an adverse drug interaction between warfarin and amiodarone. Our results suggest that patients receiving chronic warfarin therapy face a more than twofold-increased risk of hospitalization for hemorrhage within 30 days of starting amiodarone. Overall, roughly 1% of patients started on amiodarone during warfarin therapy were hospitalized for hemorrhage in the subsequent 30 days.

Our findings have strong biologic plausibility but differ from those of previous research by Zhang et al.[13] Our cohort was >10 times larger, we followed patients for a longer period of time, and we compared amiodarone users with a well-matched reference group. Furthermore, our results are consistent with evidence showing that that this interaction exaggerates the hypoprothrombinemic response to warfarin.[1−13] Although hemorrhage can occur at therapeutic INR levels, INRs above the therapeutic range are associated with a higher risk of major hemorrhage.[21]

Some limitations of our study merit emphasis. First, we could not assess unmeasured variables such as use of nonprescription medications or diets that interact with warfarin. Although exposed and unexposed patients were closely matched on measured characteristics, it is impossible in an observational study to achieve the level of balance for unmeasured characteristics attainable in a randomized controlled trial.[22] Second, although we were able to determine the frequency of INR testing using OHIP billing codes, we could not directly obtain the values and so were unable to measure INR control to identify patients at risk of bleeding or determine a correlation between hospitalization for bleeding and supratherapeutic INR values. Our results derive from patients aged ≥66 years, and the generalizability to younger patients is unknown. Also, we could not account for less severe bleeds that did not lead to hospital admission or very severe bleeds that led to death in the prehospital setting. Finally, our study was not designed to describe or control for the indication of warfarin or amiodarone therapy.

Disclosures

Mr. Lam is currently an employee at Eli Lilly Canada Inc. However, at the time of study design, analysis, and manuscript writing, Mr. Lam was not associated with this company or any of its affiliates. Dr. Muhammad Mamdani has received honoraria from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Hoffman LaRoche, Novartis, Novo Nordisk, and Pfizer. All other authors report no conflicts of interest.

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