RESEARCH

Association between statin use and ischemic stroke or major hemorrhage in patients taking dabigatran for atrial fibrillation

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ABSTRACT

BACKGROUND: Dabigatran etexilate is a prodrug whose absorption is opposed by intestinal P-glycoprotein and which is converted by carboxylesterase to its active form, dabigatran. Unlike other statins, simvastatin and lovastatin are potent inhibitors of P-glycoprotein and carboxylesterase, and might either increase the risk of hemorrhage with dabigatran etexilate or decrease its effectiveness.

METHODS: We conducted 2 population-based, nested case–control studies involving Ontario residents 66 years of age and older who started dabigatran etexilate between May 1, 2012, and Mar. 31, 2014. In the first study, cases were patients with ischemic stroke; in the second, cases were patients with major hemorrhage. Each case was matched with up to 4 controls by age and sex. All cases and controls received a single statin in the 60 days preceding the index date. We determined the association between each outcome and the use of simvastatin or lovastatin, relative to other statins.

RESULTS: Among 45 991 patients taking dabigatran etexilate, we identified 397 cases with ischemic stroke and 1117 cases with major hemorrhage. After multivariable adjustment, use of simvastatin or lovastatin was not associated with an increased risk of stroke (adjusted odds ratio [OR] 1.33, 95% confidence interval [CI] 0.88 to 2.01). In contrast, use of simvastatin and lovastatin were associated with a higher risk of major hemorrhage (adjusted OR 1.46, 95% CI 1.17 to 1.82).

INTERPRETATION: In patients receiving dabigatran etexilate, simvastatin and lovastatin were associated with a higher risk of major hemorrhage relative to other statins. Preferential use of the other statins should be considered in these patients.

Dabigatran etexilate is a direct-acting anticoagulant used for the prevention of stroke in patients with nonvalvular atrial fibrillation.[1] Once absorbed, dabigatran etexilate is metabolized to the pharmacologically active direct thrombin inhibitor dabigatran by carboxylesterase enzymes.[2,3] The bioavailability of dabigatran is low (6.5%), in part because intestinal absorption of the prodrug is opposed by P-glycoprotein, a multidrug efflux transporter.[4] Importantly, P-glycoprotein and carboxylesterase are subject to inhibition by other drugs in the same manner as hepatic cytochrome P450 enzymes.[5,6] It is therefore conceivable that coadministration of drugs that inhibit either P-glycoprotein or carboxylesterase could increase the absorption of dabigatran etexilate and/or prevent its bioactivation to dabigatran, thereby increasing the risk of hemorrhage or decreasing the drug's effectiveness.

3′-Hydroxymethylglutaryl–coenzyme A reductase inhibitors, generically referred to as statins, are among the most widely prescribed drugs worldwide. Unlike other statins, simvastatin and lovastatin are administered as lactone prodrugs that are subsequently metabolized to their pharmacologically active hydroxy forms. In contrast, the remaining marketed statins are administered as the active hydroxy acid. Emerging evidence from in vitro studies suggests that statins administered in their lactone forms (i.e., simvastatin and lovastatin) are potent inhibitors of P-glycoprotein and carboxylesterase enzyme activity, whereas other statins are not.[7–10] Because hypothetical intestinal concentrations of simvastatin and lovastatin likely exceed those required to inhibit intestinal P-glycoprotein,[11] coadministration with dabigatran etexilate could increase the absorption of dabigatran and the resultant risk of hemorrhage. Conversely, inhibition of the carboxy-

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lesterase enzyme could decrease the effectiveness of dabigatran etexilate in clinical practice.

However, apart from a small pharmacokinetic study involving healthy volunteers that found that use of atorvastatin reduced systemic dabigatran exposure by 18% without affecting the pharmacodynamic properties of the drug,[12] data are lacking on the potential interaction between statins and dabigatran etexilate in patients with atrial fibrillation. This is important because the safety and efficacy of dabigatran etexilate are related to its plasma concentrations, single-nucleotide polymorphisms in the gene encoding P-glycoprotein are associated with a 12% increase in peak dabigatran concentration per minor allele carried, studies with other P-glycoprotein inhibitors have found increases in dabigatran exposure ranging from 30% to 171%, and the likelihood of concomitant statin use among these patients is high.[13–16]

We examined the association between statin use and subsequent hospital admissions or emergency department visits for ischemic stroke or major hemorrhage in patients with atrial fibrillation treated with dabigatran etexilate. Owing to their inhibitory effects on P-glycoprotein, we hypothesized that simvastatin and lovastatin would increase the risk of major hemorrhage in patients taking dabigatran. We also reasoned that inhibition of carboxylesterase enzymes by simvastatin or lovastatin would prevent bioactivation of dabigatran etexilate, thereby increasing the risk of stroke relative to other statins. Because intestinal concentrations of the lactone forms of simvastatin and lovastatin would be expected to exceed hepatic concentrations of these drugs, we anticipated that inhibition of P-glycoprotein and the resultant elevated risk of major hemorrhage would be the more important interaction.

Methods

Setting

We conducted 2 population-based, nested case–control studies involving Ontario residents 66 years of age and older who started dabigatran etexilate between May 1, 2012, and Mar. 31, 2014. These individuals had universal access to physician services, hospital care and prescription drug coverage.

Data sources

We used Ontario's administrative health databases, which are held securely in linkable files without direct personal identifiers. We identified prescription drug records using the Ontario Drug Benefit database, which contains comprehensive records of prescription drugs dispensed to Ontario residents aged 65 years and older. Patients receiving medications under the Ontario Drug Benefit program may obtain a maximum of 100 days of treatment for each prescription. We obtained hospital admission and emergency department data from the Canadian Institute for Health Information's Discharge Abstract Database and National Ambulatory Care Reporting System, respectively. We used the Ontario Health Insurance Plan database to identify claims for physician services, and we used validated disease registries to ascertain the presence of comorbid diabetes, hypertension, myocardial infarction and congestive heart failure.[17–20] We obtained basic demographic data from the Registered Persons Database, a registry of all Ontario residents eligible for health insurance. These databases were linked in an anonymous fashion using encrypted health card numbers, and are routinely used to study the consequences of drug interactions.[21–23]

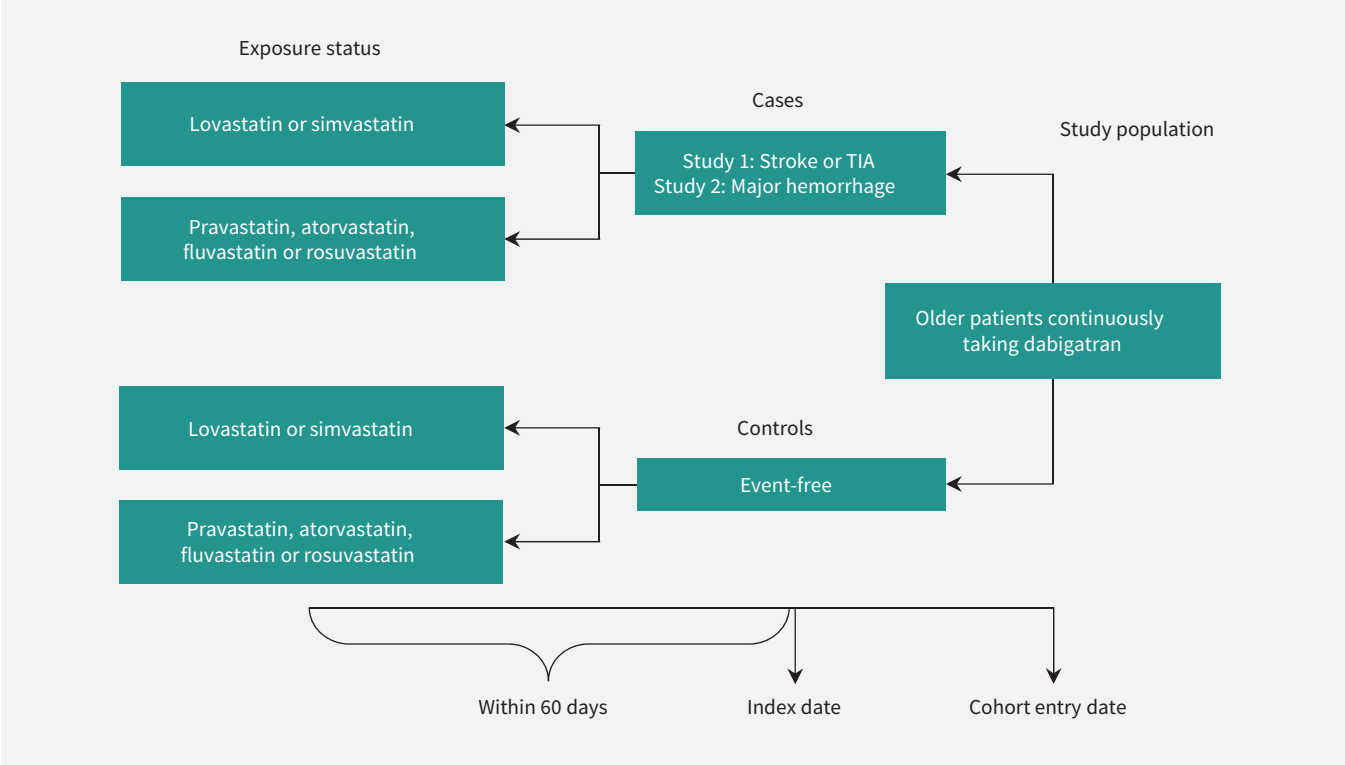

Figure 1: Study design. TIA = transient ischemic attack.

Study design and participants

We identified a cohort of patients treated with dabigatran etexilate between May 1, 2012, and Mar. 31, 2014. Use of this drug is restricted by the Ontario Drug Benefit formulary for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. For each patient, we defined a period of continuous use of dabigatran etexilate beginning with the first prescription after the patient's 66th birthday. We defined ongoing use as receipt of a prescription refill within 1.5 times the days covered by the previous prescription. We excluded the first year of eligibility for prescription drug coverage (age 65) to avoid incomplete medication records. Observation ended with the first occurrence of a study outcome, death, the end of the study period, or cessation of dabigatran etexilate treatment, defined by the date of the final prescription plus 1.5 times the prescription days' supply.

In the first study, we defined cases as patients with a hospital admission or emergency department visit for ischemic stroke (see Appendix 1, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.160303/-/DC1, for International Statistical Classification of Diseases and Related Health Problems, 10th revision [ICD-10] codes) during a period of continuous dabigatran therapy within 60 days of receiving a prescription for 1 of the following: lovastatin, simvastatin, atorvastatin, pravastatin, fluvastatin or rosuvastatin. The codes used to identify stroke were previously validated against patient records from 18 hospitals across Ontario.[24] The date of hospital admission or emergency department visit for stroke served as the index date for all analyses. For patients with recurrent ischemic strokes, we considered only the first occurrence. We excluded from the analysis patients who received prescriptions for multiple statins in the 60 days preceding the index date.

For each case, we selected up to 4 controls from the same cohort of patients receiving dabigatran etexilate. Controls were randomly assigned index dates to match the distribution of index dates among cases, and were then matched to cases by age at the index date (within 3 yr) and sex. Controls were required to be event-free at the index date and like cases were required to have received a single statin within 60 days preceding the index date. We excluded controls who received prescriptions for multiple statins in the 60 days preceding the index date. Consequently, all cases and controls were older patients receiving dabigatran etexilate who had also received treatment with only 1 of the study statins in the past 60 days. When fewer than 4 controls were available for each case, we analyzed only those controls and maintained the matching process. We excluded cases that could not be matched to at least 1 control, and controls were permitted to become cases at a later date. In summary, cases were patients taking dabigatran etexilate who had a hospital admission or emergency department visit for ischemic stroke within 60 days of receiving a statin. Controls were patients taking dabigatran etexilate who had not experienced a stroke as of the index date and, like the cases, had been prescribed a study statin in the 60 days preceding the index date (Figure 1).

In the second study, we defined cases as patients with major hemorrhage (i.e., any hemorrhagic event resulting in hospital admission or visit to an emergency department; see Appendix 1 for ICD-10 codes). The codes used to identify hemorrhage have been previously validated using patient charts from a tertiary care hospital in Ontario, with specificity, sensitivity and positive predictive values exceeding 80%, and have been used in earlier studies.[25–27] The design and analysis were otherwise identical to those described above (Figure 1). Specifically, cases were patients taking dabigatran etexilate who had a hospital admission or emergency department visit for major hemorrhage within 60 days of receiving a statin. Controls were patients taking dabigatran etexilate who had not experienced a hemorrhagic event as of the index date and, like the cases, had been prescribed a study statin in the 60 days preceding the index date.

Statistical analysis

We used standardized differences to compare baseline demographic and clinical characteristics of cases and controls. Standardized differences less than 0.1 indicate good balance between the cases and controls for a given covariate.[28]

We used multivariable conditional logistic regression to estimate the odds ratio (OR) and 95% confidence intervals (CI) for the association between stroke or transient ischemic attack and exposure to lovastatin or simvastatin relative to other statins. Because transient ischemic attack is coded less accurately than stroke in administrative data sets, we replicated our analysis by considering only cases with ischemic stroke.[29] We adjusted our models for all baseline variables with a standardized difference exceeding 0.1 between cases and controls. We conducted a similar analysis for the association between statins and major hemorrhage. We replicated our analyses by considering the effects of simvastatin and lovastatin separately. Because chronic kidney disease and recent use of warfarin could act as effect modifiers in the association between simvastatin or lovastatin and our study outcomes, we tested for interactions between these variables and study group in separate models. All analyses were performed using SAS version 9.3 (SAS Institute).

Ethics approval

The Research Ethics Board of Sunnybrook Health Sciences Centre, Toronto, approved this study.

Table 1: Numbers of patients taking each statin, by diagnosis of ischemic stroke or transient ischemic attack, or major hemorrhage

	No. (%)	
Statin	Stroke or TIA *n* = 1985*	Major hemorrhage *n* = 5582*
Atorvastatin	986 (49.7)	2778 (49.8)
Fluvastatin	6 (0.3)	26 (0.5)
Lovastatin	12 (0.6)	27 (0.5)
Pravastatin	61 (3.1)	190 (3.4)
Rosuvastatin	743 (37.4)	2059 (36.9)
Simvastatin	177 (8.9)	502 (9.0)

Note: TIA = transient ischemic attack.
*Stroke or TIA: 397 cases + 1588 controls; major hemorrhage: 1117 cases + 4465 controls.

Results

During the study period, we identified 45 991 patients treated with dabigatran etexilate. Within this cohort, 836 patients were diagnosed with an ischemic stroke or transient ischemic attack. Of these, 397 (47.5%) cases received a statin in the 60 days preceding their index date. All cases were matched to 4 controls (n = 1588). For the second study, we identified 2406 patients taking dabigatran who were diagnosed with major hemorrhage. Of these, 1117 (46.4%) received a statin in the 60 days preceding their index date. The overwhelming majority (n = 1114 [99.7%]) were matched to 4 controls (total no. of controls 4465). The numbers of patients receiving each statin are summarized in Table 1. As expected, comorbidities were more prevalent among cases than among controls (Table 2).

After multivariable adjustment, use of simvastatin or lovastatin was not associated with an increased risk of stroke or transient ischemic attack relative to other statins in patients receiving dabigatran etexilate (adjusted OR 1.33, 95% CI 0.88–2.01) (Table 3). The results did not change appreciably when considering cases with stroke only (adjusted OR 1.44, 95% CI 0.87–2.39). In contrast, use of simvastatin or lovastatin was associated with a higher risk of major hemorrhage than comparator statins in these same patients (adjusted OR 1.46, 95% CI 1.17–1.82) (Table 4). We found similar results for individual comparisons of simvastatin (adjusted OR 1.44, 95% CI 1.14–1.81) and lovastatin (adjusted OR 1.90, 95% CI 0.78–4.61) with comparator statins, although a lack of statistical power resulted in a less precise

Table 2 (part 1 of 2): Characteristics of study patients

Characteristic	Study 1 (stroke or TIA), no. (%)*			Study 2 (major hemorrhage), no. (%)*		
	Cases n = 397	Controls n = 1588	Standardized difference†	Cases n = 1117	Controls n = 4465	Standardized difference†
Age, yr						
Median (IQR)	82 (77–86)	81 (77–86)	0.02	82 (77–86)	82 (77–86)	0.03
66–74	74 (18.6)	301 (19.0)	0.01	214 (19.2)	863 (19.3)	0.00
75–84	203 (51.1)	833 (52.5)	0.03	561 (50.2)	2229 (49.9)	0.01
≥ 85	120 (30.2)	454 (28.6)	0.04	342 (30.6)	1373 (30.8)	0.00
Sex, female	209 (52.6)	836 (52.6)	0.00	468 (41.9)	1872 (41.9)	0.00
Stroke or transient ischemic attack in previous 5 years	144 (36.3)	197 (12.4)	0.65	170 (15.2)	598 (13.4)	0.05
Charlson Comorbidity Index score						
No hospital admission	109 (27.5)	811 (51.1)	0.48	337 (30.2)	2230 (49.9)	0.40
0	44 (11.1)	219 (13.8)	0.08	159 (14.2)	668 (15.0)	0.02
1	70 (17.6)	223 (14.0)	0.10	188 (16.8)	638 (14.3)	0.07
≥ 2	174 (43.8)	335 (21.1)	0.53	433 (38.8)	929 (20.8)	0.42
History of congestive heart failure	172 (43.3)	586 (36.9)	0.13	579 (51.8)	1664 (37.3)	0.30
History of angina	67 (16.9)	241 (15.2)	0.05	257 (23.0)	704 (15.8)	0.19
History of diabetes	198 (49.9)	693 (43.6)	0.13	528 (47.3)	1906 (42.7)	0.09
History of hypertension	379 (95.5)	1467 (92.4)	0.12	1057 (94.6)	4132 (92.5)	0.08
History of acute MI	81 (20.4)	244 (15.4)	0.14	270 (24.2)	731 (16.4)	0.19
History of chronic alcohol use (3 yr)	7 (1.8)	19 (1.2)	0.05	29 (2.6)	69 (1.5)	0.08
History of chronic kidney disease (3 yr)	16 (4.0)	27 (1.7)	0.16	48 (4.3)	74 (1.7)	0.18
History of chronic liver disease (3 yr)	11 (2.8)	35 (2.2)	0.04	36 (3.2)	71 (1.6)	0.12
Residence in a long-term care facility	12 (3.0)	50 (3.1)	0.01	66 (5.9)	151 (3.4)	0.13
No. of prescription drugs in previous year, median (IQR)	15 (11–19)	12 (9–16)	0.41	15 (12–20)	12 (9–16)	0.55
Use of medications that increase risk of hemorrhage in preceding 120 days						
ASA	≤ 5	6 (0.4)	0.02	14 (1.3)	24 (0.5)	0.09
ASA–dipyridamole	≤ 5	≤ 5	0.11	≤ 5	6 (0.1)	0.05
Clopidogrel	23 (5.8)	36 (2.3)	0.21	49 (4.4)	116 (2.6)	0.11
Warfarin	62 (15.6)	80 (5.0)	0.42	210 (18.8)	289 (6.5)	0.44
NSAIDs	32 (8.1)	122 (7.7)	0.01	98 (8.8)	368 (8.2)	0.02

estimate of risk for lovastatin. In sensitivity analyses, the presence of chronic kidney disease (p for interaction = 0.09) or prior warfarin use (p for interaction = 0.83) did not influence the association between statin group and major hemorrhage.

Interpretation

We found that simvastatin and lovastatin were associated with an increased risk of major hemorrhage among older patients taking dabigatran etexilate. We did not, however, observe a heightened risk of stroke relative to statins that do not inhibit carboxylesterase. This may in part reflect the smaller number of stroke cases and insufficient power to detect a significant association. In light of the expected association with major hemorrhage, our findings suggest that simvastatin and lovastatin should be avoided in patients taking dabigatran etexilate who require statin therapy.

Our finding that patients taking simvastatin or lovastatin with dabigatran etexilate face a higher risk of major hemorrhage is consis-

Table 2 (part 2 of 2): Characteristics of study patients

Characteristic	Study 1 (stroke or TIA), no. (%)*			Study 2 (major hemorrhage), no. (%)*		
	Cases n = 397	Controls n = 1588	Standardized difference†	Cases n = 1117	Controls n = 4465	Standardized difference†
Other medication use in preceding 120 days						
β-adrenergic receptor antagonists	265 (66.8)	944 (59.4)	0.15	729 (65.3)	2667 (59.7)	0.11
ACE inhibitors	174 (43.8)	639 (40.2)	0.07	494 (44.2)	1862 (41.7)	0.05
Angiotensin-receptor blockers	100 (25.2)	356 (22.4)	0.07	251 (22.5)	995 (22.3)	0.00
Calcium-channel blockers	167 (42.1)	683 (43.0)	0.02	438 (39.2)	1811 (40.6)	0.03
Digoxin	71 (17.9)	275 (17.3)	0.01	209 (18.7)	717 (16.1)	0.07
Antiarrhythmics	22 (5.5)	143 (9.0)	0.13	101 (9.0)	357 (8.0)	0.04
Nitrates	53 (13.4)	153 (9.6)	0.12	184 (16.5)	428 (9.6)	0.22
P-glycoprotein inhibitors	38 (9.6)	146 (9.2)	0.01	114 (10.2)	360 (8.1)	0.08
P-glycoprotein inducers	14 (3.5)	21 (1.3)	0.17	27 (2.4)	65 (1.5)	0.08
Cytochrome P450 3A4 inhibitors	< 5	< 5	0.01	≤ 5	10 (0.2)	0.04
Formulation of dabigatran etexilate dispensed						
110 mg only	288 (72.5)	1100 (69.3)	0.07	814 (72.9)	3098 (69.4)	0.08
150 mg only	93 (23.4)	407 (25.6)	0.05	252 (22.6)	1136 (25.4)	0.07
Both	16 (4.0)	81 (5.1)	0.05	51 (4.6)	231 (5.2)	0.03
Procedures in previous 5 years						
Angiography	61 (15.4)	274 (17.3)	0.05	250 (22.4)	782 (17.5)	0.13
Carotid Doppler ultrasonography	209 (52.6)	469 (29.5)	0.50	386 (34.6)	1354 (30.3)	0.09
Carotid endarterectomy	6 (1.5)	10 (0.6)	0.10	7 (0.6)	18 (0.4)	0.03
Coronary artery bypass	8 (2.0)	40 (2.5)	0.03	44 (3.9)	137 (3.1)	0.05
Pacemaker insertion	25 (6.3)	178 (11.2)	0.16	120 (10.7)	434 (9.7)	0.03
Percutaneous coronary angioplasty	24 (6.0)	85 (5.4)	0.03	90 (8.1)	243 (5.4)	0.11
Valve surgery	12 (3.0)	54 (3.4)	0.02	56 (5.0)	174 (3.9)	0.06
Income quintile						
1 (lowest)	87 (21.9)	290 (18.3)	0.09	225 (20.1)	777 (17.4)	0.07
2	74 (18.6)	328 (20.7)	0.05	253 (22.6)	868 (19.4)	0.08
3	80 (20.2)	330 (20.8)	0.02	200 (17.9)	874 (19.6)	0.04
4	82 (20.7)	311 (19.6)	0.03	212 (19.0)	904 (20.2)	0.03
5 (highest)	73 (18.4)	324 (20.4)	0.05	225 (20.1)	1030 (23.1)	0.074
Major hemorrhage in previous 5 years	–	–	–	222 (19.9)	441 (9.9)	0.31
Duration of statin use, median (IQR), yr	3.6 (1.1–7.0)	4.0 (1.9–7.9)	0.14	4.6 (1.8–8.5)	4.4 (1.9–7.9)	0.05

Note: ACE = angiotensin-converting-enzyme, ASA = acetylsalicylic acid, IQR = interquartile range, MI = myocardial infarction, NSAID = nonsteroidal anti-inflammatory drug, TIA = transient ischemic attack.
*Unless stated otherwise.
†Difference between cases and controls divided by standard deviation.

tent with the observation that these drugs inhibit intestinal P-glycoprotein, thereby increasing systemic dabigatran exposure.[9] Unlike other statins, simvastatin and lovastatin are administered in their lactone forms, which are nearly 10-fold more potent as inhibitors of P-glycoprotein than the hydroxy acid metabolites of these drugs.[9] In contrast, the remaining statins are administered as hydroxy acids, which are relatively weak P-glycoprotein inhibitors. Consequently, a clinically important interaction between dabigatran etexilate and these statins would not be expected; this assertion is supported by findings of a small decrease in dabigatran concentrations with the concomitant use of atorvastatin.[12] Although increased dabigatran absorption might also be expected to improve drug efficacy, previous studies have found a stronger relation between dabigatran concentrations and major hemorrhage than for ischemic events.[13]

Another possible explanation for the lack of association between simvastatin or lovastatin and the risk of stroke relates to postabsorption hydrolysis of the lactone form of these drugs to their pharmacologically active hydroxy acid forms, which do not inhibit carboxylesterase.[7,8] Consequently, the bioactivation of dabigatran would not be inhibited, and no influence on dabigatran efficacy would be observed. This reasoning may also explain the lack of a clinically relevant drug interaction between simvastatin and angiotensin-converting-enzyme inhibitors that require carboxylesterase enzymes for bioactivation.[30]

Table 3: Association between statin use and stroke or transient ischemic attack

Statin	No. (%) Cases *n* = 397	No. (%) Controls *n* = 1588	OR (95% CI)	Adjusted OR* (95% CI)
Atorvastatin, pravastatin, fluvastatin or rosuvastatin (ref)	358 (90.2)	1438 (90.6)	1.00	1.00
Simvastatin or lovastatin	39 (9.8)	150 (9.4)	1.04 (0.72–1.51)	1.33 (0.88–2.01)

Note: CI = confidence interval, OR = odds ratio, ref = reference category.
*Adjusted for history of stroke or transient ischemic attack in preceding 5 years, Charlson Comorbidity Index score, diabetes, hypertension, myocardial infarction, congestive heart failure, chronic kidney disease, number of prescription drugs in previous year, medications (β-adrenergic receptor blockers, nitrates, acetylsalicylic acid and dipyridamole, antiarrhythmics, clopidogrel, warfarin, nonsteroidal anti-inflammatory drugs, P-glycoprotein inhibitors, cytochrome P450 3A4 inhibitors), carotid Doppler ultrasonography, pacemaker insertion and duration of statin use.

Table 4: Association between statin use and major hemorrhage

Statin	No. (%) Cases *n* = 1117	No. (%) Controls *n* = 4465	OR (95% CI)	Adjusted OR* (95% CI)
Atorvastatin, pravastatin, fluvastatin or rosuvastatin (ref)	984 (88.1)	4069 (91.1)	1.00	1.00
Simvastatin or lovastatin	133 (11.9)	396 (8.9)	1.39 (1.13–1.71)	1.46 (1.17–1.82)

Note: CI = confidence interval, OR = odds ratio, ref = reference category.
*Adjusted for history of major hemorrhage, Charlson Comorbidity Index score, myocardial infarction, angina, congestive heart failure, chronic kidney disease, chronic liver disease, residence in long-term care facility, number of prescription drugs in previous year, medications (β-adrenergic receptor blockers, nitrates, clopidogrel, warfarin, nonsteroidal anti-inflammatory drugs, P-glycoprotein inhibitors, P-glycoprotein inducers, cytochrome P450 3A4 inhibitors), angiography and percutaneous coronary angioplasty.

Limitations

Some limitations of our work merit emphasis. We used administrative data and had no access to laboratory data or information about indices of renal function, smoking, nonprescription use of acetylsalicylic acid and nonsteroidal anti-inflammatory drugs, and adequacy of blood pressure and diabetes control. We could not ascertain the extent of medication adherence to dabigatran etexilate or statins. Although we used previously validated codes for outcome ascertainment, outcome misclassification is possible. However, these limitations apply equally to all statins studied. In addition, some imbalance in baseline characteristics was apparent between cases and controls. However, this is expected in a case–control study when cases are defined by an adverse outcome. Importantly, the key comparison in our analysis is not between cases and controls, but between statin types. We could not ascertain whether doses of dabigatran were adjusted in patients with chronic kidney disease. However, chronic kidney disease was not an effect modifier in the association between statin type and major hemorrhage. We had no data on when dabigatran etexilate was taken in relation to lovastatin or simvastatin, because it is possible that separation of these drugs may mitigate the effect of this interaction. However, the phenomenon of competitive P-glycoprotein inhibition and spacing of medication should attenuate any observed effect in our analysis. The number of cases receiving lovastatin and simvastatin in each study was small; this may have influenced our power to detect an association between these drugs and stroke, and may have limited our ability to establish whether event risk varies according to statin dose. Although we defined major hemorrhage using hospital admission and emergency department data, not all anticoagulation patients presenting to the emergency department have major bleeding. Finally, our findings may not apply to younger patients, who may have fewer risk factors for stroke or major hemorrhage.

Conclusion

We found that among older patients taking dabigatran etexilate, simvastatin and lovastatin were not associated with an increased risk of stroke relative to other statins, suggesting that carboxylesterase inhibition is of little clinical relevance in this setting. However, this finding may reflect a lack of power for detecting an association. In contrast, simvastatin and lovastatin were associated with an increased risk of major hemorrhage in these patients, which may reflect increased dabigatran absorption as a result of P-glycoprotein inhibition. Clinicians should consider avoiding simvastatin and lovastatin in older patients receiving dabigatran etexilate who require statin therapy.

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