Use of Statins and the Subsequent Development of Deep Vein Thrombosis

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Background: Some of the benefit of statins for the prevention of cardiovascular disease may be due to their antithrombotic properties. Little is known about the effect of these drugs on the development of deep vein thrombosis.

Materials and Methods: We conducted a retrospective cohort study over an 8-year period by linking Ontario provincial health care administrative databases covering more than 1.4 million Ontario residents aged 65 years or older. We excluded those with a documented history of atherosclerosis, venous thromboembolism, or cancer within 36 months prior to study enrollment, as well as those prescribed warfarin sodium within 12 months before enrollment. In the primary cohort, we evaluated the subsequent risk of deep vein thrombosis (DVT) among men and women prescribed thyroid replacement therapy, nonstatin lipid-lowering agents, or statins. A second cohort of women only was evaluated in a similar fashion, but estrogen use was added as a third comparison drug group.

Results: There were 125862 men and women in the primary cohort. After adjusting for age; sex; prior hospitalization; newly diagnosed cancer; or prescribed aspirin, warfarin, or estrogen, statin users (n=77993) had an associated decreased risk of DVT relative to those prescribed thyroid replacement therapy (n=35978) (adjusted hazard ratio [HR], 0.78; 95% confidence interval [CI], 0.69-0.87). Compared with thyroid replacement therapy, users of nonstatin lipid-lowering agents (n=11891) did not seem to be at lower risk for deep vein thrombosis (HR, 0.97; 95% CI, 0.79-1.18). In the secondary cohort of 89508 women, after adjusting for age, prior hospitalization, newly diagnosed cancer, or prescribed aspirin or warfarin, estrogen users (n=29165) had an associated increased risk for DVT compared with those receiving thyroid replacement therapy (n=22118) (HR, 1.16; 95% CI, 1.01-1.33), while statin users had an associated decreased risk (HR, 0.68; 95% CI, 0.59-0.79). Nonstatin lipid-lowering agents (n=5155) were not associated with a reduced risk of DVT compared with thyroid replacement therapy (HR, 0.84; 95% CI, 0.63-1.12).

Conclusion: Among selected individuals aged 65 years or older, statins were associated with a 22% relative risk reduction in the risk of DVT. A randomized clinical trial is needed to evaluate the efficacy of statins for the primary and secondary prevention of DVT.

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PARTICIPANTS, MATERIALS, AND METHODS

STUDY POPULATION

We conducted a retrospective cohort study by linking Ontario provincial health care administrative databases covering more than 1.4 million senior residents of Ontario over an 8-year period. All persons aged 65 years or older and enrolled with the Ontario Health Insurance Plan for the province of Ontario were considered eligible. The Ontario Health Insurance Plan covers all medical care and prescription drug costs for every Ontario senior citizen. For the primary cohort of men and women, the following mutually exclusive drug groups were studied: (1) statins, the exposure of interest; (2) thyroid replacement hormones, the referent control group, selected because of their lack of known association with VTE; and (3) nonstatin lipid-lowering agents (ie, fibrates, niacin, or bile acid sequestrants), a biological comparison group.

We also studied a second cohort of women only, derived from the same Ontario population as the primary cohort, but included estrogen users as a third, positive comparison drug group. This secondary cohort of women was added to test our study design, in that we expected there to be a positive association between estrogen use and DVT. Because the primary cohort consisted of both men and women, and since men are not prescribed estrogens, an estrogen drug comparison group would have been impossible. Finally, since estrogen use in the secondary cohort had to be “mutually exclusive” (ie, no concomitant use of statins, thyroid replacement hormones, or nonstatin lipid-lowering agents), secondary cohort participants may have differed slightly from women in the primary cohort.

Within each drug class, men were more likely to be hospitalized or diagnosed as having cancer during the period of observation (P<.001), and had a higher rate of both concurrent aspirin and warfarin use compared with women (P<.001) (Table 1).

During the period of observation, statin users experienced a lower rate of DVT (7.4 per 1000 person-years) than those prescribed thyroid replacement therapy (10.9 per 1000 person-years) (HR, 0.78; 95% CI, 0.69-0.87) (Table 1 and Figure). No significant difference was observed between those prescribed nonstatin lipid-lowering agents vs thyroid replacement drugs (HR, 0.97; 95% CI, 0.79-1.18).

Women experienced a higher rate of DVT than men in the thyroid replacement group (12.0 per 1000 person-years vs 7.8 per 1000 person-years), nonstatin lipid-lowering group (10.1 per 1000 person-years vs 8.4 per 1000 person-years), and statin group (8.1 per 1000 person-years vs 6.7 per 1000 person-years) (Table 1). Furthermore, statins were associated with a lower risk of DVT compared with both concurrent aspirin and warfarin use compared with women (P<.001) (Table 1). During the period of observation, statin users experienced a lower rate of DVT (7.4 per 1000 person-years) than those prescribed thyroid replacement therapy (10.9 per 1000 person-years) (HR, 0.78; 95% CI, 0.69-0.87) (Table 1 and Figure). No significant difference was observed between those prescribed nonstatin lipid-lowering agents vs thyroid replacement drugs (HR, 0.97; 95% CI, 0.79-1.18).

Women experienced a higher rate of DVT than men in the thyroid replacement group (12.0 per 1000 person-years vs 7.8 per 1000 person-years), nonstatin lipid-lowering group (10.1 per 1000 person-years vs 8.4 per 1000 person-years), and statin group (8.1 per 1000 person-years vs 6.7 per 1000 person-years) (Table 1). Furthermore, statins were associated with a lower risk of DVT compared with both concurrent aspirin and warfarin use compared with women (P<.001) (Table 1). During the period of observation, statin users experienced a lower rate of DVT (7.4 per 1000 person-years) than those prescribed thyroid replacement therapy (10.9 per 1000 person-years) (HR, 0.78; 95% CI, 0.69-0.87) (Table 1 and Figure). No significant difference was observed between those prescribed nonstatin lipid-lowering agents vs thyroid replacement drugs (HR, 0.97; 95% CI, 0.79-1.18).

SECONDARY COHORT OF WOMEN ONLY

There were 89,508 women included in the secondary cohort, for a total of 124,568 person-years of drug use (Table 2). Their overall mean age was 73.5 years. The rate of concurrent aspirin use was highest among those prescribed statins (35.6%) and lowest in the estrogen replacement therapy group (18.9%), while warfarin use was highest among those prescribed thyroid replacement therapy (8.3%) and lowest among estrogen recipients (3.9%).

Women prescribed estrogen replacement therapy were at increased risk for DVT compared with those receiving thyroid replacement therapy (HR, 1.16; 95% CI, 1.01-1.33). Relative to thyroid replacement therapy, statins were associated with a statistically significant reduced risk for DVT (HR, 0.68; 95% CI, 0.59-0.79), while nonstatin lipid-lowering agents were not (HR, 0.84; 95% CI 0.63-1.12).

COMMENT

In a large retrospective cohort of individuals aged 65 years or older, prescribed statins were associated with a 22% relative reduction in the risk for DVT compared with control. This benefit seemed to be only significant in women. Prescription of nonstatin lipid-lowering agents was not associated with a decrease in DVT.

We excluded all individuals with a history of a malignant neoplasm within 36 months prior to study enrollment and further adjusted for prior hospital admis-
having reached the end of follow-up to March 31, 1999. An individual was also censored if he or she was prescribed a drug from another study drug group (ie, contamination effect). At least 2 consecutive study drug prescriptions were required to select individuals who were more likely to continue receiving their medications. It has been demonstrated that 60% of patients discontinue their lipid-lowering medications over a 12-month period, most within 3 months of starting treatment. Individuals older than 65 years are more likely to continue receiving their medications, including statins, further increasing the likelihood that our defined sample would continue receiving their prescribed agent throughout the period of analysis.

The Ontario Drug Benefits database was used to identify the medications each elderly participant was prescribed during the observation period. This database is maintained by the Ontario Ministry of Health, Ottawa, and includes encrypted patient identifiers, prescription dates, and drug information for all residents of Ontario 65 years or older. Participants who received medications from any of the study drug groups during the year prior to cohort enrollment were excluded, allowing only new users of the medications to be included. There is little missing information in the Ontario databases (<1%), while there is a high degree of coding accuracy. Hospitalizations, identified using the Canadian Institute for Health Information Discharge Abstract Database, were used to characterize subsequent events and comorbid illnesses. The discharge abstracts contain the unique health care number, age, and sex of the participant, date of admission, and up to 16 diagnoses, as coded by the International Classification of Diseases, Ninth Revision (ICD-9). The Ontario Health Insurance Plan database, which contains records of all outpatient visits by Ontario residents, including a service date and diagnosis field, was used to capture outpatient diagnoses of VTE. Participant age and sex were retrieved from the Registered Persons Database. This database contains demographic information and health care numbers for all individuals eligible for the Ontario Health Insurance Plan. All data at Institute for Clinical Evaluative Sciences are maintained in an anonymous fashion to ensure confidentiality.

**STATISTICAL ANALYSIS**

Time-to-event analyses were conducted using the Cox proportional hazards regression model. For the analysis of the primary cohort, adjustments were made for age, sex, hospitalization within 1 year prior to study enrollment, newly diagnosed cancer, or concurrent prescription of aspirin, warfarin, or estrogen during the observation period. For the analysis of the secondary cohort of women, since conjugated estrogen was added as a third comparison agent, no adjustment was made for its use. All participants were identified as being exposed to a potential confounder if the confounding event occurred at any time between 100 days prior to study enrollment and the end of follow-up. The comparative risk for DVT between drug classes was expressed as the adjusted hazard ratio (HR) along with its 95% confidence interval (CI).

Baseline characteristics between men and women were compared within each drug group using either an analysis of variance for continuous variables or the chi-squared test for categorical data. All P values were 2-sided and a statistical significance level of .05 was set a priori. All statistical analyses were performed using SAS for UNIX, Version 6.12 (SAS Institute, Cary, NC).
may have resulted in a diminution of any potential protective effect from statins. Our overall findings are supported by those of the HERS investigators, who observed an even greater reduction in DVT or PE with statin use (adjusted HR, 0.5; 95% CI, 0.2-0.9).6 We chose to not evaluate the effect of statins on the risk for PE since testing strategies for PE are often less accurate than for DVT.19,20 Thus, even though they are part of the same spec-

### Table 1. Characteristics of the Primary Cohort and the Risk for Deep Vein Thrombosis (DVT) According to Drug Class

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Men and Women</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of participants</td>
<td>35978</td>
<td>11891</td>
<td>77993</td>
</tr>
<tr>
<td>Males, %</td>
<td>26.9</td>
<td>48.9</td>
<td>100.0</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>75.9 (7.5)</td>
<td>72.0 (5.5)</td>
<td>71.6 (4.7)</td>
</tr>
<tr>
<td>Duration of drug use, mean (SD), d</td>
<td>664 (505)</td>
<td>397 (386)</td>
<td>526 (421)</td>
</tr>
<tr>
<td>Duration of follow-up, person-years</td>
<td>65435</td>
<td>12910</td>
<td>112256</td>
</tr>
<tr>
<td>Concurrent hospital admissions, %</td>
<td>17.3</td>
<td>17.7</td>
<td>17.6</td>
</tr>
<tr>
<td>Concurrent cancer diagnosis, %</td>
<td>6.4</td>
<td>4.9</td>
<td>6.4</td>
</tr>
<tr>
<td>Concurrent estrogen use, %</td>
<td>13.1</td>
<td>9.2</td>
<td>8.3</td>
</tr>
<tr>
<td>Concurrent aspirin use, %</td>
<td>26.1</td>
<td>39.9</td>
<td>31.5</td>
</tr>
<tr>
<td>Concurrent warfarin sodium use, %</td>
<td>9.8</td>
<td>8.4</td>
<td>8.9</td>
</tr>
<tr>
<td>No. of cases of DVT per 1000 person-years</td>
<td>10.9</td>
<td>9.3</td>
<td>7.4</td>
</tr>
<tr>
<td>Adjusted hazard ratio (95% CI) for DVT*</td>
<td>1.0</td>
<td>0.97</td>
<td>0.78</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, concurrent hospitalization or diagnosis of cancer, and concurrent prescription of aspirin, warfarin, or estrogen. No adjustment was made for sex within the male and female subgroups. CI indicates confidence interval.
Intravenous disease, it remains to be established whether these drugs appear protective against PE.

There is some biological basis to explain how statins may attenuate the risk for VTE. Data from 2 case-control studies have demonstrated a strong association between combined hypercholesterolemia and hypertriglyceridermia and DVT in middle-aged adults (crude odds ratio, 5.1; 95% CI, 2.0-13.0), as well as elevated lipoprotein(a) levels and VTE in children (adjusted odds ratio, 7.2; 95% CI, 3.7-14.5). Circulating lipids seem to have both prothrombotic and endothelial altering properties. For example, ingestion of a fatty meal seems to cause venous endothelial dysfunction, manifested by reduced acetylcholine-mediated venodilatation in healthy adults. Thus, it is conceivable that specific circulating agents, we speculate that statins may also possess other protective properties.

In the Post Coronary Artery Bypass Graft Trial, aggressive lipid-lowering with lovastatin effectively reduced both the rate of progression of atherosclerosis in saphenous vein coronary artery bypass grafts, as well as the need for coronary revascularization. Beyond their lipid-reducing ability, statins also seem to alter elements within the vascular endothelium and coagulation cascade, consistent with an antithrombotic effect. For example, 6 months of pravastatin treatment significantly lowered levels of prothrombin fragment 1 + 2 in women, indicating reduced thrombin generation, while simvastatin produced the same effect in men. Others hypothesize that these drugs may inhibit platelet-derived protease-activated receptor 1 and tissue factor up-regulation that leads to thrombin generation, in addition to reducing the levels of both factor VIIc and soluble thrombomodulin. Collaborative research among those who study lipid-related disorders and arterial and venous thrombotic disease could help to clarify whether it is their lipid-reducing or antithrombotic properties, or both, that best explain the beneficial role of statins in the treatment of atherosclerosis, and their potential to do the same for VTE.

We believe that these preliminary data provide the rationale for a randomized clinical trial of statins for the secondary prevention of recurrent VTE. Consenting individuals who have completed 3 months of anticoagulant therapy following a first idiopathic VTE event could be randomized to either continue warfarin therapy for another 12 to 18 months, or to stop warfarin therapy and begin taking a statin drug for the same duration. The major end point in this trial would be the development of recurrent VTE, balanced against major bleeding. Current or future clinical trials designed to examine the effect of statins on cardiovascular disease might consider collecting secondary data on VTE events as well, which could be combined in a systematic overview. Future observational studies may provide greater insight as to which statins and what dose is there a maximal reduction in primary or secondary VTE events, including PE.

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This study is in memory of Christa Bos, MD, whose encouragement to pursue new ideas was not forgotten.

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REFERENCES

Table 2. Characteristics of the Secondary Cohort of Women and the Risk for Deep Vein Thrombosis (DVT) According to Drug Class

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Subjects Receiving Thyroid Replacement Therapy</th>
<th>Subjects Receiving Nonstatin Lipid-Lowering Agents</th>
<th>Subjects Receiving Statins Therapy</th>
<th>Subjects Receiving Estrogen Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of women</td>
<td>22118</td>
<td>5155</td>
<td>33070</td>
<td>29165</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>76.4 (7.7)</td>
<td>73.0 (6.0)</td>
<td>72.1 (4.9)</td>
<td>73.0 (6.3)</td>
</tr>
<tr>
<td>Duration of drug use, mean (SD), d</td>
<td>660 (505)</td>
<td>381 (376)</td>
<td>503 (416)</td>
<td>422 (417)</td>
</tr>
<tr>
<td>Concurrent hospital admissions, %</td>
<td>16.6</td>
<td>16.5</td>
<td>14.7</td>
<td>13.0</td>
</tr>
<tr>
<td>Concurrent cancer diagnosis, %</td>
<td>8.0</td>
<td>4.1</td>
<td>4.7</td>
<td>4.6</td>
</tr>
<tr>
<td>Concurrent estrogen use, %</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Concurrent aspirin use, %</td>
<td>24.4</td>
<td>28.1</td>
<td>35.6</td>
<td>18.9</td>
</tr>
<tr>
<td>Concurrent warfarin sodium use, %</td>
<td>8.3</td>
<td>6.6</td>
<td>6.7</td>
<td>3.9</td>
</tr>
<tr>
<td>No. of DVT per 1000 person-years</td>
<td>11.9</td>
<td>9.5</td>
<td>7.6</td>
<td>12.6</td>
</tr>
<tr>
<td>Adjusted hazard ratio (95% CI) for DVT*</td>
<td>1.0 (Referent)</td>
<td>0.84 (0.63-1.12)</td>
<td>0.68 (0.59-0.79)</td>
<td>1.16 (1.01-1.33)</td>
</tr>
</tbody>
</table>

* Adjusted for age, sex, concurrent hospitalization or diagnosis of cancer, and concurrent prescription of aspirin or warfarin. CI indicates confidence interval.