Concurrent use of statins and hormone therapy and risk of venous thromboembolism in post-menopausal women: a population-based case-controlled study

Running head: Statins, HT and VTE

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Abstract

Objective: Statins and hormone therapy (HT), often used concurrently in post-menopausal women, have antagonist effects on the risk of venous thromboembolism (VTE). The aim of this study was to determine if statins attenuate the increased VTE risk associated with HT.

Methods: Nested case-control study within a population-based cohort of women aged 50 to 79 years between January 1st, 1987 and March 1st, 2008, identified from the UK General Practice Research Database. Cases of VTE occurring during follow-up were identified and matched with up to ten controls from the cohort. Odds ratios (OR) of the effect of concurrent HT and statin use on the risk of VTE were estimated using conditional logistic regression with interaction terms.

Results: The cohort included 955,582 postmenopausal women, with 32,505 cases of VTE matched with 231,562 controls. Regardless of any HT use, current use of statins was associated with a decreased risk of VTE (OR 0.83, 95% CI 0.78-0.87). The interaction between statin use and HT use was of borderline significance (p=0.053). The risk of VTE was elevated with current use of oral oestrogen and progestogen combinations among non-users of statins (OR 1.55; 95% CI: 1.45-1.66), while it was not among users of statins (OR 0.9[illegible] 95%CI 1.56-1.[illegible]). There was no such modification in OR with other HT types and formulations.

Conclusions: Statins could potentially attenuate the increase in risk associated with HT combinations of oral oestrogens and progestogens. This observation needs further confirmation in other large cohorts.

Key words

Hormone therapy, statins, pulmonary embolism, venous thrombosis, drug interactions

Introduction

HMG-CoA reductase inhibitors (statins) and hormone therapy (HT) are commonly used medications that both have effects on the risk of venous thromboembolism (VTE). Statins have pleiotropic effects on coagulation and inflammation that could contribute to a protective effect on VTE [1,2]. An observational study even suggested that this decrease in risk could be dose-dependent [3]. A meta-analysis of observational studies has assessed this protective effect to be more modest than initially described [4]. The meta-analysis of randomized controlled trial of Rahimi *et al.* even found an insignificant association between statin use and VTE, though a moderate reduction in risk could not be ruled out [5].

On the other hand, VTE is a well-documented complication of the use of HT for the treatment of menopausal symptoms [6,7]. The increase in risk appears to vary according to several factors related to HT [8]: type of formulation, route of administration, dose of oral oestrogens or type of progestogens. Our team previously reported this increased risk in women using oral oestrogens, alone or in combinations with progestogens, with no increased risk in user of transdermal HT [9].

Although statins and HT are often used concurrently in post-menopausal women, it is unclear whether the concomitant use of statins could attenuate the increased VTE risk associated with HT, especially when administered orally. We investigated this question in a secondary analysis of a large population-based case-control study previously reporting on the risk of VTE associated with HT use [9].

Methods

Study design

We performed a nested case-control study within a population-based cohort of post-menopausal women identified from a general practice database from the United Kingdom. The cohort, used for a previous study of HT and VTE risk, is described in greater detail elsewhere [9]. The case-control analysis of the cohort was necessary because of the time-dependent nature of the statin and HT exposures and the large size of the cohort.

Data source

We used data from the Clinical Practice Research Datalink (CPRD) the world's largest computerized database of longitudinal patient records. The patients registered in the CPRD are a representative sample of around 6% of the entire UK population. The CPRD records information on diagnoses, prescriptions, referrals to specialists, as well as information from discharges letters, lifestyle habits (smoking, alcohol excess use) or body mass index (BMI). All information is regularly updated and estimated to be highly valid [10,11]. In particular, diagnoses of VTE have been demonstrated highly valid for use in epidemiologic studies [12].

Participant selection

The cohort consisted of women aged 50 to 79 years between January 1st, 1987 and March 1st, 2008. All women with a diagnosis of VTE prior cohort entry were excluded. Similarly to a previous study on VTE that used the CPRD, a computerized algorithm was used to identify ´definite´ or ´probable' cases of VTE (deep venous thrombosis or pulmonary embolism) [9]. 'Definite' cases consisted of women with a diagnostic code referring to VTE associated with the initiation of antivitamin K treatment, therapeutic procedure related to VTE or hospitalization, or death in the case of pulmonary embolism. 'Probable 'cases were defined by a diagnostic code for VTE without mention of related treatment or hospitalization. 'Possible 'cases included diagnostic codes of phlebitis without further information, therefore possibly including superficial thrombophlebitis, and were not considered in the analysis. The computerized algorithm was validated after complete agreement with diagnosis retained after manual review of a random sample of 264 potential cases. Cases were matched to up to ten controls on age (± two years), general practice and year of registration with the practice (± two years). The date of diagnosis of VTE was used as the index date of the case and of its matched controls who had to be registered, alive, contributing data and not have had VTE before this index date.

Exposure

Exposure to HT was assessed in the year prior to the index date, using details on the dosing and the quantity prescribed. HT was categorized according to formulation (plain oestrogens, combined oestrogens and progestogens, progestogens only or tibolone) and route of administration (oral or transdermal). Women were classified as current users if their most recent HT prescription lasted at least until the index date. Use of statins was classified as current when the last prescription was issued in less than 90 days before the index date. Statins were classified as standard-dose or high-dose according to their therapeutic potency. Daily statin use of <80 mg of fluvastatin or pravastatin, <40 mg of lovastatin, simvastatin, or atorvastatin, and <10 mg of rosuvastatin were classified as standard-dose usage. Daily statin use ≥10 mg of rosuvastatin and ≥40 mg of pravastatin, simvastatin, or atorvastatin were classified as high-dose usage.

Statistical analyses

We estimated unadjusted and adjusted odds ratios (OR) with 95% confidence intervals (95% CI) for the associations between HT and statin use and VTE using conditional logistic regression for matched case-control data. In addition to matching on age, practice, duration of follow-up and calendar time, all models were adjusted for all the following potential confounders: BMI (obese and non-obese), smoking status (current, never, and former smoker), history of treatment of varicose veins, inherited thrombophilia and screening for thrombophilia, anti-phospholipid syndrome (Hughes' syndrome), immobilization, invasive surgery, trauma and fracture (in the month before index date), myeloproliferative disorders, cancer (in the year before index date), inflammatory bowel disease, nephrotic syndrome, hypertension, cardiovascular and cerebrovascular diseases, use of tamoxifen and NSAIDs. Variables with missing data were coded with an 'unknown' category. The concurrent effect of HT and statins was assessed using interaction terms between statin use (current use/no statin use) and HT use (classified as oral oestrogen alone, oral estrogen combined to progestogen, non-oral estrogen, non-oral estrogen and progestogen, other, and no HT use) and presented by

stratified analyses. All computations were performed using the SAS software version 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

From the study cohort of 955,582 eligible women, 23,505 'definite' or 'probable' cases of VTE were identified (18,927 cases of deep venous thrombosis and 4,578 cases of pulmonary embolism) during a mean 6.7 years of follow-up. They were matched to 231,562 controls. General characteristics, distribution of comorbidities and co-medications in cases and controls were reported previously [9], with more frequent VTE risk factors in cases than in controls (overweight, varicose veins, immobilization, trauma or fracture in the month prior index date, cancer, or tamoxifen). Cases were more often current users of HT (15.6% *vs.* 12.8% in controls), and statins (9.4% *vs.* 8.7%). The statins most commonly used in cases were simvastatin (50.9%), atorvastatin (33.4%), pravastatin (9.8%), fluvastatin (2.8%), rosuvastatin (2.3%), and cerivastatin (0.8%). Controls used simvastatin (52.3%), atorvastatin (34.0), pravastatin (8.0), rosuvastatin (2.5%), fluvastatin (2.3%) and cerivastatin (1.0%). Among current statin users, 71.2% of cases and 75.1% of controls were at standard-doses.

Regardless of any HT use, current use of statins was associated with a decreased risk of VTE (OR 0.83, 95% CI 0.78-0.87). This decrease in risk was not different among users of standard-doses statins (OR 0.81; 95% CI 0.76-0.86) and high-dose statins (OR 0.89; 95% CI 0.81-0.97).

The interaction between statin use and HT use was of borderline statistical significance (p=0.053). Table 1 shows the crude and adjusted OR for associations of HT (by formulation and route of administration) and statins. Risk of VTE was elevated for oral HT (OR 1.52; 95% CI 1.44- 1.65), including oral estrogens and progestogens (OR 1.54; 95% CI 1.44-1.64) and oral plain estrogens (OR 1.49; 95% CI 1.37-1.62), regardless of statin use. In non-users of statins, the risk of VTE was elevated with current use of oral oestrogens and progestogens (OR 1.55; 95%CI 1.45-1.66), while it was not

(OR 0.98; 95%CI 0.56-1.73) among users of statins There was no such modification of OR with other types and formulations of HRT and statins.

Discussion

Our study results confirm that statins use is associated with decrease in risk of VTE in postmenopausal women [13]. The 20% reduction in risk is consistent with a recent meta-analysis of observational studies [4] and randomized controlled trials [5]. Our results do not support the dose-response effect of statins on VTE previously described [3], although we used a similar classification of statin potency [14]. Similarly, in a recent cohort study on the effects of statins on the risk of recurrent VTE, no difference was found between standard-dose statin use (HR 0.76; 95% CI 0.68-0.85) and high-dose statin use (HR 0.71; 95% CI 0.64-0.79) [15]. Further studies are required to confirm the hypothesis of dose-response protective effect of statins on VTE.

Our study adds new insights as it seems that statins may specifically attenuate the increase in risk associated with HT combination of oral oestrogens and progestogens. Our results should be interpreted with caution as plausible mechanisms for this phenomenon are uncertain. Statins have pleiotropic effects on coagulation [16,17]. Their anti-inflammatory and anticoagulants properties could contribute to the reduction of unfavourable changes in activated protein C and C-reactive protein observed in oral HT users, compared to transdermal HT users [18]. However, these biological mechanisms could not entirely support our data, as no interaction was found in the users of oral oestrogens only. Other factors that might explain our results (type of progestogens, duration of use) could not be assessed in our dataset, due to insufficient subgroup size. Also, one should take into account that in the CPRD prescriptions represent those written by general practitioners, and thus it is unknown whether patients complied with HT or statin treatment. Moreover, the study results should be interpreted with caution, since we were not able to take into account potential healthy user bias in statin users. Restricting our analysis to incident users of statins would not bring sufficient

power to the subgroup analysis. Finally, the interaction analysis reached borderline statistical significance so that random error cannot be ruled out.

Conclusions

To our knowledge, the ability of statins to attenuate the risk of VTE related to HT has not been reported. Our data suggest that these potential drug interactions could be considered more thoroughly in further studies.

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Tables

Table 1- Odds ratio for VTE associated with type of hormonal therapy (formulation and route of administration) and statins.

Exposure	Cases (n= 23 505)	Controls (n= 231 562)	Odds Ratio* (95% CI) Crude	Odds Ratio* (95% CI) Adjusted†
Overall effects				
No HT	19849	201985	1	1.00 (Reference)
Oral HT (any)	2006	14447	1.50	1.53 (1.44 – 1.61)
Oral oestrogens and progestogens‡	1277	9343	1.48	1.54 (1.44 – 1.64)
Oral plain oestrogens‡	729	3905	1.53	1.49 (1.37 – 1.62)
Stratified effects				
No Statins				
No use of HT	17823	183457	1	1.00 (Reference)
Oral HT (any)	1880	13792	1.49	1.51 (1.43 – 1.60)
Oral oestrogens and progestogens‡	1227	9006	1.49	1.55 (1.45 – 1.66)
Oral plain oestrogens‡	653	4786	1.48	1.45 (1.33 – 1.59)
Statins§				
No use of HT	2026	18528	1	1.00 (Reference)
Oral HT (any)	126	655	1.19	1.21 (0.83 – 1.76)
Oral oestrogens and progestogens‡	50	336	0.94	0.98 (0.56 – 1.73)
Oral plain oestrogens‡	76	319	1.40	1.41 (0.88 – 2.26)

HT: Hormonal Therapy

* Full model takes into account other formulations and routes of administration of HT (transdermal oestrogens and progestogens, transdermal plain oestrogens, progestogens only, and tibolone).