Title:

RECURRENCE RISK OF VENOUS THROMBOEMBOLISM AND HORMONE USE IN WOMEN FROM ENGLAND: A COHORT STUDY USING CLINICAL PRACTICE RESEARCH DATALINK

Running Title:

Venous thromboembolism recurrence and hormone use

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SUMMARY

It is vital to identify people with low recurrence risk of venous thromboembolism (VTE) so as to protect them from dangers of prolonged anticoagulation therapy. Among women who develop VTE following hormone use, the evidence as to whether their risk of recurrence is low if they cease this therapy is conflicting. We investigated whether women whose initial VTE event was hormone related have a lower risk of VTE recurrence than women whose initial event had no obvious cause (unprovoked). A cohort study which utilised the Clinical Practice Research Datalink linked to Hospital Episode Statistics data from England was conducted. We selected 4,170 women aged between 15 and 64 years who were diagnosed with a first VTE event between 1997 and 2011. Cox regression models were used to obtain hazard ratios (HR). Hormone users had 29% lower recurrence risk than non-users (adjusted HR=0.71; 95% CI 0.58-0.88), a relationship which existed both in women aged 15-44 years (predominantly OC users) and those aged 45-64 years (predominantly HRT users). In conclusion**, having a hormone-associated VTE is associated with a** lower recurrence risk than **one which is** unprovoked **after discontinuation of the hormone containing preparation. P**rolonged anticoagulation may **therefore** be unjustified in such women.

Key words: Cohort, thromboembolism, recurrence, hormone, women

INTRODUCTION

Globally, the incidence rate of venous thromboembolism (VTE) is estimated to be 1 to 2 per 1000 person years, and it is the third most common cause of cardiovascular death after coronary heart disease and stroke (Anderson *et al*, 1991; Silverstein *et al*, 1998; Cushman M *et al*, 2004; Tagalakis *et al*, 2013; Raskob *et al*, 2014). Besides, VTE has been reported to recur in about 30% of patients after a period of ten years (Prandoni P *et al*, 1996; Heit *et al*, 2001) and the recurrence risk is higher in patients whose index VTE is unprovoked or caused by a risk factor which is non-reversible (Hansson *et al*, 2000; Prandoni *et al*, 2007; Eischer *et al*, 2009; **Iorio *et al*, 2010**). Recently, the incidence rate of VTE recurrence in the UK was estimated to be 4.9 per 100 person years (Martinez *et al*, 2014). Use of oestrogen has been linked to increased risk of VTE (Canonico *et al*, 2008; Vinogradova *et al*, 2015) but it is unclear whether the risk of recurrence is reduced after cessation of oestrogen use. Existing evidence as to whether women whose index VTE is hormone related have lower recurrence than those whose index VTE is unprovoked is still inconclusive. For instance, one large US population based study (Heit *et al*, 2000) comprising 1,244 participants reported a 42% lower VTE recurrence risk in users than non-users of OCs in an unadjusted analysis and a much earlier UK study (Badaracco and Vessey, 1974) also reported significantly lower proportion of VTE recurrences in OC users than in non-users. **This supports a finding from a secondary analysis of pooled data from seven separate cohorts which reported that women with a hormone-associated VTE had a 50% lower risk of VTE recurrence than those who's initial VTE had no obvious cause (Douketis *et al*, 2011) and that hormone use at baseline was found to be an independent term in a subsequent risk calculator using the same studies (Tosetto *et al*, 2012). In contrast**, several smaller studies **which primarily addressed this hypothesis** (Kyrle *et al*, 2004; Christiansen *et al*, 2005; Cushman *et al*, 2006;

Le Gal *et al*, 2010; Le Moigne *et al*, 2013) reported no significant difference in the risk of VTE recurrence between women whose VTE was hormone related and women whose VTE was unprovoked.

Current UK guidelines recommend that patients who develop a venous thromboembolic event receive either oral anticoagulants or low molecular weight heparin for 90 days, and a longer treatment duration is advised if the VTE is related to cancer or is unprovoked (National Institute of health and Clinical Excellence, 2012) . There is however considerable uncertainty as to the optimal duration of anticoagulation following a hormone-related VTE and as such they represent an important and sizeable group for whom VTE management decisions are uncertain (Baglin, 2012; Palareti, 2012). Prolonged use of anticoagulants is risky in that it often results in bleeding in addition to the potential inconvenience of a daily heparin injection (Linkins *et al*, 2003; Kyrle and Eichinger, 2005). Identifying populations with lower VTE recurrence is therefore pertinent in influencing treatment policies to protect patients from the dangers associated with prolonged anticoagulant whilst reducing VTE related healthcare costs which have been estimated at £640 million annually in the United Kingdom (National Institute of health and Clinical Excellence, 2012).

Therefore, we analysed routinely collected data from a large cohort of women from England, to directly compare the VTE recurrence risk between women whose index VTE event was hormone related and women of the same age whose VTE event was considered to be unprovoked. **As a secondary hypothesis we explored whether re-initiation of hormone use during the follow-up period increased the risk of VTE recurrence.**

METHODS

Data source

The Clinical Practice Research Datalink (CPRD) database **currently** contains anonymised primary care data from 6**74** practices **covering 11.3** million patients throughout the UK**, of whom 4.4 million are currently alive and registered with a participating practice (Herrett *et al*, 2015**). The CPRD is subjected to quality checks and a practice's data is only used for time periods where it is of high enough quality for research (Williams *et al*, 2012). This is denoted by defining an up-to-standard (UTS) time period for each practice. The **Hospital Episodes Statistics (**HES**)** database consists of data on primary and secondary discharge diagnoses along with inpatient procedures for patients admitted to hospital (secondary care) from English CPRD practices linked to HES. All diagnoses are coded by use of International Classification of Diseases code system (ICD-10) (Health and Social Care Information Centre, 2014). Using the National Health Service number, post code, date of birth, and sex, CPRD practices were linked to HES (Eaton *et al*, 2008) and for this study period (1997 to 2011) 53% of the CPRD practices had linked data which was used to obtain the study cohort of women from England**, providing an overall study population of 2.33 million people**.

Study population

This study comprised women between the ages of 15 years and 64 years who had a first ever index VTE event between 1997 and 2011. A VTE event was defined by a medical code for venous thromboembolism (ICD 10; I26, I80-I82) in either or both the CPRD and HES. Women were considered to have a valid index VTE if their recording of VTE was supplemented by anticoagulant prescriptions at any time within 90 days of the event. This

algorithm was validated in women of childbearing age with a positive predictive value of 84% (Lawrenson *et al*, 2000).

To minimise the possibility of an existing (prevalent) VTE event being counted as incident, women were excluded if they had a VTE event within 90 days of joining the practice or before their practice's data were judged to be of research quality (up to standard). Also, those whose initial VTE event was related to surgery, pregnancy or malignancy were excluded as were those whose VTE event occurred within 2 weeks of an inpatient hospital admission lasting 3 days or more. This was necessary so as to only retain women whose VTE events were unprovoked (unknown cause) and those whose VTE events were hormone related.

Participant initiation and follow up

The study period commenced on the latest date of either the 15th birthday, when practice became up to standard or 90 days after registration with a participating CPRD practice. Follow up for purposes of our analysis began on the 30th day from the last anticoagulation prescription date following the index VTE event and ended on the earliest date of either VTE recurrence, death, resumption or initiation of hormonal use, transfer from a participating CPRD practice, 65th birthday or end of the study (2011 December 31st). **Censoring upon resumption or initiation of hormonal use was deemed necessary as our focus was on whether a hormone-related VTE would be associated with a low risk of recurrence upon the assumption that this therapy would not be recommenced**.

Definition of hormone use (exposure)

We defined women as hormone users if they had a prescription for oral contraceptives or hormone replacement therapy in the 6 months prior to the date of the index VTE. Both

'progestogen only' and combined OCs as listed under sections 7.3.1 and 7.3.2 of the British National Formulary were included together with all HRT combinations under 6.4.1.1. This group of women were referred to as users in this study. Our comparison group (termed non-users) was defined as women who had no record of OC/HRT use in the 6 months prior to their index VTE. We considered this to be a proxy for unprovoked VTE on the basis that women who's VTE had an identified cause were excluded as described above.

Definition of recurrent VTE event (outcome)

Women were considered to have a recurrent VTE if they had a recording of VTE (either in primary or secondary care data) event at least 30 days after the last prescription for the index VTE. A recurrent VTE event was only considered to be valid if it was either accompanied by a new anticoagulant prescription within 90 days of the event or if a woman died within 30 days of the event.

Statistical analysis

All data management and analyses were performed using STATA version **14**. Absolute rates of VTE recurrence per 1,000 person years and their 95% confidence intervals were computed by dividing the total number of VTE recurrences by the person years of follow up. Recurrence rates between hormone users and non-users were compared using Cox regression models and Hazard ratios were adjusted for age, calendar year (of index VTE), and duration of anticoagulation treatment. The Cox proportional hazard assumption was tested using Schoenfeld's test. Analyses were then conducted in age strata of 15 to 44 years (predominantly OC users) and 45 to 64 years (predominantly HRT users). **For all analyses we used a delayed entry model whereby the time unit in the Cox regression models was time**

since date of the index VTE. This accounts for the differences in the underlying hazard between participants caused by variations in the duration of anticoagulation.

Subgroup and sensitivity analyses

First, given that anticoagulation treatment duration might have an impact on the risk of VTE recurrence and possibly influence the effect of other risk factors on VTE recurrence, we carried out a sub group analysis based on the duration of anticoagulation treatment following the index VTE (<90 days vs. 90 days or more) . Second, a sensitivity analysis was conducted by attuning the start of follow up from 30 days to 180 days following the last anticoagulation prescription, owing to concerns that a new VTE medical code early in the follow-up period may not relate to a new VTE event. Third, owing to the fact that the evidence for a thrombotic effect is weaker for progestogen only compounds than for combined OCs, we reclassified women who only took progestogen only preparations during the 6 months prior to the index date as unexposed. All analyses presented in the paper were rerun with the new exposure groupings and the results were very similar on all occasions (data not presented).

Secondary analyses

For our secondary research question of whether hormone initiation or resumption influenced the risk of VTE recurrence, Cox regression models were fitted in the same way as described above with two exceptions; 1) participants were no longer censored at the time of hormone initiation/resumption, and 2) hormone use was fitted as a time-varying covariate. All patients were therefore unexposed at the commencement of follow-up and became exposed at the time of the first hormone prescription and were assumed to remain exposed for the remainder of the follow-up period. Analyses were stratified by the primary exposure, so for "users" exposure status changed at the time of resumption of hormonal therapy, whilst for "non-users" exposure status

changed at the time of a first prescription for OC/HRT. **Women who did not initiate/resume hormone use were considered to be unexposed for the entire follow-up period.**

Ethical statement

The study was approved by the CPRD's Independent Scientific Advisory Committee (ISAC protocol No.13_211).

RESULTS

Study population

The initial study population comprised 6,598 women between the ages of 15 and 64 years who had a first VTE between 1997 and 2011. A total of 2,428 women were excluded because they also had record of pregnancy (531), surgery (85), previous cancer (1,564) and/or hospitalization (248) at the time of the index event. After exclusion of these potentially provoked VTE events, 4,170 women remained.

The median age of the study population was 48 years (table I). In total, there were 1,196 women (28.7%) whose index VTE was hormone related and 2,974 (71.3%) whose index VTE was unprovoked (non-users). Among women aged 15-44 years, 562 were users of OCs, of which 465 (82.6%) used combined OCs, and 40 were users of HRT at the time of their first VTE. Among women aged 45-64 years, 66 were users of OCs, of which 42 (63.6%) used combined OCs, and 522 were users of HRT.

The median duration of anticoagulation therapy among all participants was 98 (IQR, 70-119) days with the majority of women (60.6%) had receiving anticoagulation therapy for 90 days or more. Users were more likely than non-users to receive anticoagulation for more than 90 days (51% vs. 37%) among women aged 15-44 years. However, the trend was reversed for women aged 45-64 years, where non-users were more likely to receive anticoagulation for more than 90 days (63% v. 49%).

After the end of anticoagulation, there was a total of 12,065 person-years of follow-up with a median follow-up time of 1.8 years (IQR 0.5 to 4.4 years), during which time 497(41.55%)

of the users resumed hormone use and 290 (9.75%) of the non-users commenced hormone use (and were therefore censored from further follow-up at this point).

Recurrent VTE events

Overall, 575 (13.8%) recurrent events were observed, of which 248 and 327 were in women aged 15 to 44 years and 45 to 64 years respectively. The percentage of women with recurrent VTE events was higher in non-users than in users (15.3% versus 9.5%). Recurrence percentages in those who had been prescribed anticoagulation for 90 or more days and those who were prescribed anticoagulation therapy for less than 90 days were 14.2% and 13.5% respectively.

Recurrence rates of VTE

The overall VTE recurrence rate (table II) was 48 (95% CI 43.9-51.8) per 1,000 person years. Non-users had a higher rate of VTE recurrence (51 per 1,000 person-years; 95%CI 46.8-56.2) than users (37 per 1000 person-years; 95% CI 30.8-44.5). The risk of VTE recurrence (Fig. 1) was significantly lower in users than in non-users, with users being 2**8**% less likely to have a VTE recurrence compared to non-users (adjusted HR 0.7**2**, 95% CI 0.58-0.88).

Age stratified VTE recurrence rates in users and non-users

In women aged 15 to 44 years (table III), OC users were **29**% less likely to have a VTE recurrence in comparison with non-users (HR 0.**71**, 95% CI 0.52-0.9**6**). Similarly, in women aged 45 to 64 years HRT users had 29% less likelihood of having a VTE recurrence than non-users (HR 0.71, 95% CI 0.53-0.95).

Sub group Analysis

Subgroup analysis according to anticoagulation therapy duration (table iii) showed that the VTE recurrence rates were not significantly different between users and non-users in women whose treatment lasted for less than 90 days. However, in those who had received anticoagulation therapy for 90 or more days, users were 33% less likely to have a VTE recurrence (95% CI 0.51-0.88) compared with non-users. A test for interaction between hormone therapy and duration of anticoagulation however was not statistically significant.

Sensitivity Analysis

In a sensitivity analysis (table IV), excluding person-time and VTE events in the first 180 days following the last anticoagulant prescription, the magnitude of the difference in recurrence rates between users and non-users was slightly stronger both overall and within the separate age groups.

Secondary Analysis

In this secondary analysis where women were no longer censored at the time of hormone initiation/resumption, there were a total of 634 VTE recurrences in 14,664 person-years of follow-up. Whilst overall rates of VTE recurrence were higher among women who did not resume hormone therapy, once the effect of delayed entry was taken into account in the Cox regression analysis no differences in VTE recurrence were observed (Table V). This was both the case in women classed as "users" in the primary analysis (exposure: resumption of OC/HRT use) and those classed as non-users (exposure: initiation of OC/HRT use).

DISCUSSION

Summary of the main findings

This was the largest study to investigate VTE recurrence risk in women aged 15 to 64 years using routinely collected healthcare data. We found that the VTE recurrence rate in English women aged 15 and 64 years was 48 per 1,000 person years similar to that found in a previous study (Martinez *et al*, 2014) on VTE recurrence using the CPRD.

Overall, in women aged 15 to 64 years, a 29% lower VTE recurrence rate in users compared to non-users was observed, with similar risk reductions reported in the two age groups studied (15 to 44 years and 45 to 64 years). The study also found a significant reduction in hormone users among women whose initial anticoagulation treatment lasted for 90 or more days but not in those whose treatment lasted less than 90 days. **Initiation or resumption of hormonal therapy during the follow-up period was not found to be associated with VTE recurrence.**

Strengths and Limitations

Due to the size of this study the risk of a type II error was small. Furthermore, it was possible to stratify the study population so as to calculate VTE recurrence rates for both OC users and HRT users separately, and compare these risks with their respective comparison groups.

All English women aged 15 to 64 who were registered with CPRD-HES linked practices between 1997 and 2011 were included in this study if they had a VTE event. Although this data covers only 3% of the wider UK population, the distribution of sex and age in the HES-CPRD linked data has been reported (Walker *et al*, 2013) to be comparable to England's

general population. Hence, the study findings may be generalizable to majority of women in England.

In addition, CPRD-HES data is recorded in a prospective manner which negates the possibility of either recall or selection bias. This also enabled us to use person time in computing absolute rates since our study was cohort by design.

This study also had potential limitations. First, we were not able to determine whether hormone use was the definite cause of the VTE in those classed as "users" and some of the events may have been unprovoked. **Similarly, whilst we chose of a window of 6-months to class a woman as having had a hormonal related VTE, it is possible that hormone use prior to this could still play a role in the event.** However, simply noting whether or not women used OCs or HRT in the 6-months preceding a VTE would reflect how these results would be utilised in practice. Second, information on other VTE risk factors was limited in the CPRD-HES database. Therefore, some of the VTE events may have been misclassified as unprovoked instead of being provoked by a recognised factor. For example immobility related VTE might have been considered as **unprovoked** since some causes of immobility such as long haul travel were not recorded. Thus recurrence rates in non-users could have been underestimated and hazard ratios biased towards the null. However, we suspect that women with such other risk factors as a percentage of all VTE events would be relatively small, in which case the impact on the observed results will not be substantial. Third, although VTE recurrence was defined using a standard algorithm, defining VTE recurrence may be difficult due to possibility misclassification between index and recurrent events, a problem previously recognised in studies using routinely collected healthcare data (Schmidt

et al, 2014). However, we accounted for such discrepancy in date by allowing 30 days before an event was considered recurrent. Moreover, in sensitivity analysis where an event was considered recurrent only if it occurred after 180 days, results remained unaltered but rather showed a stronger association. This may be because of either misclassification of first VTE as early recurrent VTEs attenuated the effect size in the first 6 months of follow up or it could simply be that the protection is greater long-term if women cease hormonal use after their first VTE. Fourth, our effect size could have been further attenuated by the fact we observed women with a hormone-related VTE received anticoagulation for a shorter duration than those with an unprovoked VTE. However, adjustment for this variable had little impact on the hazard ratio in our adjusted model due to anticoagulation duration not being associated with recurrence rate in this study. Fifth, we were unable to provide data on the bleeding risk in this population. However, as the purpose of this study was to provide estimates on absolute and relative risks of recurrent VTE as a whole rather than inform individual patient decisions about the appropriate duration of anticoagulation, we do not believe this to be a major limitation. Finally, our results will generalise only to women within the age range studied. Our age bands were carefully chosen *a priori* so that our results would generalise specifically to young women most likely to be using OCs (15-44 years) and women in middle age for which the use of HRT over short periods for relief of menopausal symptoms was anticipated to be high (45-64 years).

In this study, we were able to adjust for possible confounding factors like age which is noted to play a vital role in VTE recurrence (Heit *et al*, 2000). As with any study of this type our results of this study could be influenced by additional unmeasured factors. In particular, we cannot rule out the possibility of the size of our effect reduction being at least in part due to

a healthy user effect whereby women who were using hormones at the time of their VTE were otherwise healthier than those with unprovoked (Ray, 2003), although it will be very difficult to speculate as to the likely magnitude of this effect in the present context.

Comparison with previous studies

Our finding is inconsistent with **data from a trial conducted in Canada and the US** (Cushman *et al*, 2006), which reported no significant difference in three year probability of VTE recurrence between hormonal users (OCs and HRT) and non-users. On the other hand, results from stratified analysis for women aged 15 to 44 years are consistent with a large US based study where users had 42% significantly lower recurrence risk (Heit *et al*, 2000), as well as a significantly lower recurrence proportion in an earlier UK study (Badaracco and Vessey, 1974). A probable reason for the observed results in our study may be due to the reverse effect in that after cessation of hormone use, the VTE risk is decreased. It is not clear whether this phenomenon may be the same for other transient VTE risk factors. This finding however, still disagrees with two other studies (Christiansen *et al*, 2005; Le Moigne *et al*, 2013) which found no differences in VTE recurrence rates between OC users and non-users. Furthermore, findings regarding HRT use are inconsistent with previous studies (Heit *et al*, 2000; Le Gal *et al*, 2010).

One possible explanation for the inconsistent findings may be due to limited statistical power to detect differences in measure of effect in previous studies. For example in the REVERSE study (Le Gal *et al*, 2010), only 18 women out of 314 women had used HRT prior to the initial VTE event and only 4 women got a VTE recurrence. In such a case, there was high possibility of a type II error. **In a pooled secondary analyses of seven existing cohorts, the authors observed at 50% reduction in recurrence (95% confidence interval 20% to 70%) in**

women with a hormone associated VTE, supporting the findings of the present study (Douketis *et al*, 2011). However, the total number of women in the cohorts combined (n=1286) was less than the number in our cohort, whilst this previous analysis did not stratify results according to age and duration of initial anticoagulation in the way in which we were able to.

Clinical and policy implications

Findings from our study imply that in UK, VTE recurrence is an important problem in women aged 15 to 64 years. The reduced risk of VTE recurrence in users compared to non-users does not support prolonged anticoagulation and suggests that 3 rather than 6 months of anticoagulation treatment may be sufficient for women whose initial VTE is related to hormone use in line with current guidelines from the UK and elsewhere.

Furthermore, our findings highlight that among the sub-group of women treated for less than 90 days the absolute risks of VTE were more comparable between hormone users and non-users, indicating that anticoagulation for less than 90 days in women with hormone-related VTE would not be advised.

Using the data we had available, we carried out a secondary analysis to determine whether resumption of hormone therapy once anticoagulation therapy had ceased would influence the risk of VTE recurrence. Whilst our data found this was not the case, this should not be taken to mean that it is safe to resume hormonal therapy in this instance. Our study was not originally powered to explore this hypothesis and whilst this secondary analysis had slightly more person-years of follow-up and outcome events, only a small

number of women (n=797) were in the exposed group. Clinically important real differences may therefore have been missed.

Conclusion

Women whose index VTE is hormone related are at lower risk of VTE recurrence compared to those whose index VTE is unprovoked. Therefore prolonged anticoagulation treatment of more than 90 days appears to be unjustified. Our study also highlights the need for further research both to confirm the findings of the present study and explore whether additional factors need to be taken into account when making treatment decisions concerning women who develop VTE following exposure to hormones.

COMPETING INTERESTS

The authors declare that they have no competing interests and have no relationships with companies that might have an interest in the submitted work.

ROLE OF CONTRIBUTORS

AAS and MJG conceived the study idea and designed the study, with SK making significant contributions. AAS had full access to all the CPRD-HES data and extracted relevant data for the study. AAS and MJG guided the data management. SK carried out the data analysis and wrote the first draft of the paper. All authors participated in data interpretation and manuscript revision.

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Table I: Characteristics of the study population at index VTE

Characteristic (s)	Users		Non-users		
Age group	**15 to 44 years**	**45 to 64 years**	**15 to 44 years**	**45 to 64 years**	**Total, (%)**
Number, n (%)	603 (14.46)	593 (14.22)	1,116 (26.76)	1,858 (44.56)	4,170(100)
Age in years, median(IQR)	32(27-39)	55(50-59)	36(30-41)	55(50-60)	48(37-57)
Type of hormone used, n (%)					
OCs	562(89.49)	66 (10.51)	-	-	628 (15.05)
HRT	40(7.12)	522(92.88)	-	-	562 (13.48)
OCs & HRT	1(16.67)	5(83.33)	-	-	6(0.14)
Time periods, median(IQR)					
Follow up time, years	0.72(0.17-3.01)	1.65(0.24-4.93)	1.96(0.58-4.80)	2.11(0.77-4.34)	1.8 (0.47-4.41)
Person years of follow up	1,308	1,745	3,461	5,543	1,2056
Anticoagulation duration, n (%)					
Less than 90 days	234 (49.68)	237(50.32)	453(38.62)	720(61.38)	1,644 (39.42)
90 or more days	369 (50.90)	356 (49.10)	663(36.81)	1,138(63.19)	2,526 (60.58)
Calendar year					
1997-1999	46(36.22)	81(63.78)	100(40.98)	144(59.02)	371(8.90)
2000-2002	115(39.38)	177(60.62)	203(36.25)	357(63.75)	852(20.43)
2003-2005	126(49.22)	130(50.78)	254(37.52)	423(62.48)	933(22.37)
2006-2008	161(57.30)	120(42.70)	286(36.48)	498(63.52)	1,065(25.54)
2009-2011	155(64.58)	85(35.42)	273(38.50)	436(61.50)	949(22.76)

OCs & HRT refers to women who had prescription of both OCs and HRT in the 6 months preceding the first VTE

Table II: Recurrence rates of VTE stratified by hormonal use, age group and duration of anticoagulant therapy

Characteristic(s)	Number of recurrences/person years	Absolute rates*(95%CI)	Crude HR(95%CI)	Adjusted **HR(95%CI)
Total VTE recurrence	575/12056	47.7(43.9-51.8)	-	-
Hormonal use				
Users	113/3052	37.0(30.8-44.5)	0.73(0.**60**-0.**90**)	0.7**2**(0.58-0.88)
Non-users	462/9004	51.3(46.8-56.2)	reference	reference
Age group				
15 to 44 years	248/4768	52(45.9-58.9)	reference	reference
45 to 64 years	327/7288	44.8(40.3-50)	0.86(0.73-1.01)	0.86(0.73-1.01)
Duration of anticoagulation therapy				
Less than 90 days	233/4763	48.9(43.0-55.6)	reference	reference
90 or more days	342/7293	46.9(42.1-52.1)	**1.18**(0.**99**-1.**41**)	**1.1**7(0.**98**-1.**40**)

***** per 1000 person-years, ** Adjusted for age, calendar year & anticoagulant duration (when not stratified on them), CI- Confidence interval, Age group-≤44 or ≥45 to 64 years at index VTE. Schoenfeld's test for proportional hazards: P=0.3, Log rank test for comparison of survival curves; hormone use P=0.002, age group P=0.78, anticoagulant duration P=0.98.

Table III: Recurrence rates of VTE in users and non-users of hormones stratified by age and duration of anticoagulation

Characteristic(s)	Number of recurrences /person years	Absolute rates*(95%CI)	Crude HR(95%CI)	**Adjusted HR(95%CI)	p-value
		Age			
15 to 44 years					
Total VTE recurrence	248/4768	52(45.9-58.9)	-	-	-
Users	57/1308	43.6(33.6-56.5)	0.**74**(0.**55**-0.**99**)	0.**71**(0.52-0.9**6**)	0.02
Non-users	191/3461	55.2(47.9-63.6)	reference	reference	-
45 to 64 years					
Total VTE recurrence	327/7288	44.8(40.3-50.0)	-	-	-
Users	56/1745	32.1(24.7-41.7)	0.71(0.53-0.94)	0.71(0.53-0.95)	0.02
Non-users	271/5543	48.9(43.4-55.1)	reference	reference	-
		Duration of anticoagulation therapy			
Less than 90 days	233/4763	48.9(43.0-55.6)	-	-	-
Users	47/1109	42.4(31.8-56.4)	0.8**1**(0.5**9**-1.1**2**)	0.7**7**(0.5**6**-1.0**7**)	0.15
Non-users	186/3653	50.9(44.1-58.8)	reference	reference	-
90 or more days	342/7293	46.9(42.2-52.1)	-	-	-
Users	66/1943	33.9(26.7-43.2)	0.68(0.52-0.89)	0.67(0.51-0.88)	0.004
Non-users	276/5349	51.6(45.8-58.1)	reference	reference	-

*****per 1000 person-years, ** Adjusted for age, calendar year, anticoagulant duration (when not stratified on them), CI- Confidence interval, Schoenfeld's test for proportional hazards; ≤44 years P=0.1, >44 years P= 0.9, anticoagulant duration P= 0.8. Log rank test for comparison of survival curves; hormone use P=0.04, anticoagulant duration P=0.64.

Table IV: Recurrence rates of VTE in users and non-users of hormones after 6 months of follow up

Characteristic(s)	Number of recurrences /person years	Absolute rates*(95%CI)	Crude HR(95%CI)	Adjusted **HR(95%CI)	p-value
Total VTE recurrence	310/1200	25.8(23.1-28.9)	-	-	-
15 to 64 years					
Users	47/3041	15.5(11.6-20.6)	0.5**4**(0.4**0**-0.7**4**)	0.54(0.3**9**-0.7**4**)	<0.001
Non-users	263/8968	29.3(25.9-33.1)	reference	reference	-
15 to 44 years					
Users	20/1301	15.4(9.9-23.8)	0.**48**(0.3**0**-0.**79**)	0.4**6**(0.2**8**-0.7**5**)	0.004
Non-users	107/3445	31.1 (25.7-37.5)	reference	reference	-
45 to 64 years					
Users	27/1740	15.5(10.6-22.6)	0.58(0.3**9**-0.8**8**)	0.5**9**(0.39-0.8**9**)	0.011
Non-users	156/5522	28.3(24.1-33.1)	reference	reference	-

* per 1000 person-years, HR-Hazard ratio, CI-confidence interval, **Adjusted for age, anticoagulant duration & calendar year (when not stratified on them), Schoenfeld's test for proportional hazards P= 0.6

Table V Recurrence rates of VTE following resumption of hormone use (15 to 64 years)

Characteristic(s)	Number of recurrences /person years	Absolute rates*(95%CI)	Crude HR(95%CI)	Adjusted **HR(95%CI)	p-value
All women (n=4,170)					
Follow-up Users	66/2601	25.4(19.9-32.3)	0.95(0.72-1.25)	0.97(0.73-1.27)	0.80
Follow-up non-users	572/12063	47.4(43.7-51.4)	reference	reference	-
Hormones non-users at baseline (n=2,973)					
Hormone initiators	23/967	23.8(15.8-35.8)	0.90(0.58-1.38)	0.89(0.58-1.38)	0.61
Non-initiators	460/9011	51.1 (46.6-55.9)	reference	reference	-
Hormone users at baseline (n=1,196)					
Hormone resumption	43/1633	26.3(19.5-35.5)	1.06(0.74-1.53)	1.13(0.78-1.63)	0.52
Non-resumption	112/3052	36.7(30.5-44.2)	reference	reference	-

*** per 1000 person-years, , **Adjusted for age, anticoagulant duration & calendar year. The analysis of all women also adjusts for whether they were hormone-users at baseline. P-values were obtained from the adjusted models.**
HR-Hazard ratio, CI-confidence interval
Hormone resumption/imitation was fitted as a time-varying covariate in all models

Figure 1: Nelson-Aalen cumulative hazard estimates of the probability of VTE recurrence in hormone users and non-users