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Recent Epidemiological Studies of the Association Between Hormone Replacement Therapy and Venous Thromboembolism

A Review

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Contents

Summary

The association between use of hormone replacement therapy (HRT) and the risk of venous thromboembolism (VTE) has been assessed in relatively few epidemiological studies. Evidence from the earliest studies did not support an increased risk of VTE among HRT users. However, methodological limitations in most studies, including small sample size and inadequate control of confounding, did not allow firm conclusions to be made.

Most of these limitations have been overcome in 5 recent studies which consistently show that the risk of VTE among women currently using HRT is 2 to 3 times higher than among women not using HRT. The overall relative risk of VTE for women currently using HRT obtained from these studies was 2.6 (95% confidence interval 1.6 to 4.2). This association is unlikely to be explained by confounding or other potential biases affecting observational studies. The risk appears to be more prominent during the first year of HRT use, and in 2 studies the risk disappeared after the first year of therapy. A dose-response relationship, with a doubling of risk among users of high doses of estrogens, was shown in 2 of these studies. No major differences were observed with the different types of

therapy, but users of unopposed estrogen therapy and transdermal therapy might be at lower risk than users of opposed regimens and oral preparations.

Evidence from these new studies indicates that, among healthy postmenopausal women, between 1 and 2 additional cases of VTE per 10 000 women can be annually attributed to current use of HRT. The Committee on Safety of Medicines in the UK evaluated this risk as small and considered that it does not change the overall benefit-risk profile of HRT for most women.

Relatively few epidemiological studies have examined the effect of hormone replacement therapy (HRT) on the risk of venous thromboembolism (VTE). Although early studies failed to show an association between HRT use and the occurrence of VTE, limitations in study design, including lack of statistical power, inadequate control of confounding and inclusion of highly selected populations, did not rule out such an association. Most of these limitations have been overcome in new observational studies which, using a variety of methodological approaches, consistently show a moderate increase in the risk of VTE among current users of HRT. In the following article, we review and quantitatively summarise the available epidemiological data and the public health impact of the use of HRT on the risk of idiopathic VTE.

1. Early Epidemiological Studies: 1974-1992

The association between use of HRT and the risk of VTE was first examined in studies conducted in the US mainly during the 1980s. These studies included 4 case-control studies,[1-4] one retrospective cohort study,[5] and one small clinical trial.[6] The only evidence of an increased risk of VTE was found in a study conducted by the Boston Collaborative Drug Surveillance Program.[1] In this case-control study, 14% of the current users of HRT experienced a VTE, whereas only 8% of women not using HRT experienced a VTE. The analysis of these raw data yields an age-adjusted relative risk of VTE in current users of HRT of 1.9 [95% confidence interval (CI) 0.7 to 5.2]. Until very recently, these were the only available data suggesting that HRT could increase the risk of VTE. None of these studies examined the effect of duration of therapy, estrogen dose, or type of HRT regimen.

The validity of these first studies was limited by important methodological drawbacks. Most studies lacked enough power to detect moderate associations. Two of the case-control studies were based on less than 20 cases.[1,2] The largest study, with 121 cases and a relative risk of 0.8 (95% CI 0.3 to 2.1), did not have enough power to detect a 2-fold risk increase.[3] Inadequate or lack of control of confounding was another limitation. Some authors reported only crude associations[4,5] and others were unable to adjust for several potential confounders at the same time, which possibly led to residual confounding.[1,3] Finally, inclusion of highly selected populations such as long term estrogen users,[5] women with long term hospitalisation for chronic disease[6] or women with suspected pulmonary embolism[4] restricted the validity of some of these studies.

2. New Epidemiological Studies: 1996-1997

Limitations of the early studies have been overcome in 5 recently conducted observational studies: 4 case-control[7-10] and 1 prospective cohort study.[11] These studies consistently showed a moderate increase in the risk of idiopathic VTE associated with current use of HRT. Although the number of women evaluated was too small for more detailed analyses, for the first time these studies provided data on the risk of VTE according to duration of HRT use, estrogen dose, type of regimen and route of administration.

2.1 Study Design

Methodological features of each study are pre-

sented in table I. Three of the case-control studies used information recorded in automated health databases, including the Group Health Cooperative of Puget Sound in Seattle, Washington, US,[8] the General Practice Research Database (GPRD) in the UK,[9] and the Friuli-Venezia Giulia Health Databases in Italy.[10] The other case-control study involved data obtained from interviews with women admitted to hospitals in the area of the Oxford Regional Health Authority in the UK.[7] The cohort study was conducted using data from the ongoing Nurses' Health Study in the US.[11]

All the studies examined the risk of a first occurrence of VTE among women without major risk factors for this condition such as a history of VTE, cancer and recent trauma or surgery. Women with VTE occurring during hospitalisation were similarly excluded. Whereas all 4 case-control studies examined the risk of either deep venous thrombosis (DVT) or pulmonary embolism (PE), the Nurses' Health Study was limited to the risk of PE.

The GPRD study was a case-control nested in a cohort of 347 253 women aged 50 to 79. The study included 292 cases of idiopathic VTE and 10 000 controls randomly selected from the source cohort. The studies from Oxford and the Group Health Cooperative of Puget Sound were matched case-control studies. In the Oxford study, 103 cases of idiopathic VTE were matched to 178 hospital controls for age-group, and date and district of admission. Matched controls were selected among women admitted to hospital with a diagnosis considered as unrelated to HRT use. In the Group Health Cooperative study each of the 42 cases identified was matched, by age, duration of Cooperative membership and calendar year, to 4 healthy individuals selected from the Cooperative enrollees. The study from Friuli-Venezia Giulia was a case-control study nested in a cohort of 265 431 women, and included 171 cases and 10 000 controls. In the Nurses' Health Study, 68 cases of idiopathic PE occurred during 633 817 person-years of follow-up.

2.2 Risk of Venous Thromboembolism Associated with Current Hormone Replacement Therapy Use

Time windows used to define current use of HRT were 1,[7] 6[8-10] and up to 24 months.[11] Prevalence of current HRT use varied largely among the different populations of women studied. The lowest prevalence was in Italy (2.3% of controls) and the highest (25%) in the populations of Oxford and Group Health Cooperative of Puget Sound. The prevalence of current HRT use in controls from GPRD was 12%. Differences in the prevalence of

Table I. Characteristics of recent epidemiological studies on hormone replacement therapy and the risk of first hospitalisation for idiopathic venous thromboembolism (VTE)

Author	Population	Study period	Design	Age range (y)	Number of cases of VTE	End-point
Daly et al.[7]	Hospitals in the Oxford Regional Health Authority, UK	1993-1994	Matched hospital based case-control	45-64	103	DVT or PE
Grodstein et al.[11]	Nurses' Health Study, US	1978-1992	Cohort of registered nurses	Postmenopausal	68	PE
Jick et al.[8]	Group Health Cooperative of Puget Sound, US	1980-1994	Matched population based case-control	50-74	42	DVT or PE
Pérez-Gutthann et al.[9]	General Practice Research Database, UK	1991-1994	Population based nested case-control	50-79	292	DVT or PE
Varas et al.[10]	Friuli-Venezia Giulia Health Databases, Italy	1991-1995	Population based nested case-control	45-79	171	DVT or PE

Abbreviations: DVT = deep venous thrombosis; PE = pulmonary embolism.

Table II. Relative risk (95% confidence intervals) of venous thromboembolism according to type of hormone replacement therapy (HRT) among current users

Author	Type of current HRT regimen				
	any	unopposed	opposed	oral	transdermal
Daly et al.[7]	3.6 (1.8-7.3)	3.2 (1.4-7.4)	5.3 (1.9-14.6)	4.6 (2.1-10.1)	2.0 (0.5-7.6)
Grodstein et al.[11]	2.1 (1.2-3.8)a			2.1 (1.2-3.8)	
Jick et al.[8]	3.6 (1.6-7.8)a	4.1 (1.8-9.3)	2.4 (0.8-7.3)	3.6 (1.6-7.8)	
Pérez-Gutthann et al.[9]	2.1 (1.4-3.2)	1.9 (1.0-3.8)	2.2 (1.4-3.5)	2.1 (1.3-3.6)	2.1 (0.9-4.6)
Varas et al.[10]	2.3 (1.0-5.3)b	1.4 (0.4-4.6)	5.0 (1.5-16.7)		2.3 (1.0-5.3)
Overall relative risk	2.6 (1.6-4.2)	2.5 (1.3-4.8)	3.1 (1.6-5.8)	2.8 (1.6-4.8)	2.1 (1.0-4.7)

a All exposed women used oral HRT preparations.

b 79% of exposed women used transdermal therapy.

use among the studies conducted in the UK result principally from the different age distribution of women included in the 2 studies.[7,9] Indeed, the prevalence of current use among women aged 50 to 60 years included in the GPRD study was 23%, similar to the prevalence in the Oxford study.

The risk of VTE in current HRT users was compared with the risk in women who never used HRT or to the combined risk in never users and past users. None of the studies showed an increased risk among women who had used HRT in the past. In all studies, women currently using HRT were found to be at a moderately increased risk of VTE than women not using HRT. Estimates of relative risk varied from 2.1[9,11] to 3.6[7,8] (table II). We calculated an overall estimate of the relative risk by pooling the results from the 5 studies and weighting each of them by the inverse of the variance of the log relative risk.[12] The overall relative risk of VTE for women currently using HRT was 2.6 (95% CI 1.6 to 4.2) [table II].

The risk of VTE did not differ to any considerable extent among current users of different HRT regimens in most studies (table II). The overall relative risks of VTE for users of unopposed and opposed estrogens were 2.5 (95% CI 1.3 to 4.8) and 3.1 (95% CI 1.6 to 5.8), respectively. Regarding the route of administration, the overall relative risk for users of oral preparations was 2.8 (95% CI 1.6 to 4.8) and for users of transdermal therapy 2.1 (95% CI 1.0 to 4.7) [table II].

2.3 Effect of Duration of Therapy and Dose of Estrogens

Results from these studies suggest that the risk of VTE is higher in the first year of therapy and that after that period of time the risk decreases considerably (table III). In 2 studies the risk of VTE after the first year of treatment was similar to the risk for women who had never used HRT.[9,10] We combined the results from the 4 studies that had separately estimated the risk of VTE during and after the first year of therapy.[7-10] The overall relative risk during the first year of treatment was 4.2 (95% CI 2.3 to 7.6) and this risk decreased to 2.2 (95% CI 1.3 to 3.8) after 1 year.

The risk associated with current dose of estrogens was inconsistent among studies, although the number of women exposed to a high estrogen dose was low in all of them. A dose-response relationship, with a doubling of risk among users of 0.625 mg/day or more of estrogens, was found in 2 studies,[7,8] whereas no dose effect was found in the other 2.[9,11] Because of the low prevalence of HRT use, the dose-effect was not examined in the study of Friuli-Venezia Giulia.[10]

3. Methodological Issues

The results from these epidemiological studies indicate that current use of HRT is associated with an increased risk of idiopathic VTE. The observed association appears to be real. This is supported by the consistency of the findings among studies that

were conducted with different methodological approaches and in different populations of women.

Recall bias, a potential limitation of field based case-control studies, is not present in cohort studies or in studies conducted with information routinely recorded in automated health databases. Thus, this type of bias was avoided in the cohort of the Nurses' Health Study[11] and in the case-control studies that used data from Puget Sound, GPRD and Friuli-Venezia Giulia.[8-10]

The use of hospital controls in case-control studies might introduce bias if the exposure of interest is related to the disease for which controls are hospitalised. This type of bias was unlikely in the Oxford study,[7] since controls were selected among women hospitalised for diseases thought to be unrelated to the use of HRT. Also, the prevalence of current use of HRT in the Oxford hospital controls (25%)[7] was similar to the prevalence found among the community controls (23%) included in the GPRD study.[9]

Diagnostic or referral bias could be present if physicians examined women exposed to HRT more closely than women not exposed to HRT. This could result in an overestimation of the association between VTE and HRT. However, results from the Nurses' Health study,[11] which examined the risk of PE, a more severe condition than DVT, and studied a rather homogeneous population (registered nurses), indicate that the effect of this bias, if any, would be very small. This is further supported by the similar risk of DVT and PE shown in the 2 studies that examined these end-points separately.[8,9]

Confounding is unlikely to explain the findings from these studies, since all of them controlled for selected known or suspected confounding factors including age, body mass index, smoking, hypertension and diabetes mellitus, among others.

4. Biological Plausibility

The effects of estrogens on the coagulation system are complex and not fully understood. Some studies have shown that estrogens can increase the level of coagulation factors or decrease the level of inhibitors of the coagulation, but the clinical relevance of these changes is still controversial, and some authors have pointed out that they may not reflect the complex balance of the haemostatic system.[13]

Table III. Risk of venous thromboembolism (VTE) according to duration of hormone replacement therapy among current users

Duration of therapy (months)	Number of cases of VTE	Relative risk	95% confidence intervals
Daly et al.[7]			
≤12	14	6.7	2.1-21.3
13-24	16	4.4	1.6-11.9
25-60	4	1.9	0.5-7.8
>60	10	2.1	0.8-6.1
Grodstein et al.[11]			
≤60	12	2.6	1.2-5.2
>60	10	1.9	0.9-4.0
Jick et al.[8]			
≤12	4	6.7	1.5-30.8
12-60	3	2.8	0.6-11.7
>60	11	4.4	1.6-12.2
Pérez-Gutthann et al.[9]			
≤6	14	4.6	2.5-8.4
7-12	8	3.0	1.4-6.5
>12	13	1.1	0.6-2.1
Varas et al.[10]			
≤12	6	2.9	1.2-6.9
>12	0	0.0	0.0-4.1

Table IV. Risk of venous thromboembolism (VTE) attributable to current use of hormone replacement therapy (HRT) in postmenopausal women without major risk factors for VTE

Author	Incidence rates (per 10 000 women per year)		
	non-users of HRT	current HRT users	risk attributable to current HRT use
Daly et al.[7]	1.1	2.7	1.6
Grodstein et al.[11] a	0.8	1.4	0.6
Jick et al.[8]	0.9	3.2	2.3
Pérez-Gutthann et al.[9]	1.3	2.7	1.4
Varas et al.[10]	1.3	2.9	1.6

a Only cases of pulmonary embolism were included.

In these recent epidemiological studies, the risk of VTE was either more prominent in, or restricted to, the first year of therapy, which suggests that women with some underlying characteristic may be particularly at risk for developing VTE. It has been shown recently that the risk of VTE is higher among carriers of a specific mutation in the factor V Leiden and that the presence of this mutation potentiates the risk of VTE attributed to oral contraceptives.[14] Factor V Leiden induces resistance to activated protein C, a natural anticoagulant that inhibits the conversion of factor X to factor Xa and of prothrombin to thrombin. A recent study has shown a significantly increased resistance to activated protein C among users of third-generation oral contraceptives[15] and this has been proposed as the biological explanation for the increased risk of VTE in this population of oral contraceptive users.[16] No information is currently available about the role of factor V Leiden, or about other inborn abnormalities of the haemostatic system, in the risk of VTE among women using HRT.

5. Public Health Impact

Estimates from the recent epidemiological studies show that the incidence of idiopathic VTE in postmenopausal healthy women not using HRT is approximately 1 case per 10 000 women per year (table IV). The estimated incidence in current users of HRT varies from 1.4[11] to 3.2[8] cases per 10 000 women per year. Therefore, between 1 and 2 cases of idiopathic VTE per 10 000 women per year can be attributed to current use of HRT (table IV). The UK Committee on Safety of Medicines evaluated this risk as small and considered that it does not change the overall positive balance between the benefits and risks of HRT for most women.[17]

6. Conclusions

Although early studies failed to demonstrate an association between HRT and VTE, evidence from 5 recent epidemiological studies consistently indicates that the risk of VTE among current users of HRT is about 2 to 3 times higher than the risk of VTE among women who are not using HRT. The risk is more prominent in, or restricted to, the first year of therapy and appears to be estrogen–dose-dependent. The risk is not markedly different among the different HRT regimens, but users of unopposed estrogens and transdermal therapy might be at lower risk than users of opposed regimens and oral preparations.

These studies indicate that, annually, between 1 and 2 additional cases of VTE can occur among 10 000 women treated with HRT. According to the UK Committee on Safety of Medicine, this risk is small and does not appear to change the overall benefit-risk profile of HRT for most women.

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Erratum

Vol 17 No.4, page 256: Last row in table III has the Wheatley & Kramer reference listed as 65; it should be 37. It also gives 160 as the number of patients; this should be 37 patients.

[Kasper S, Praschak-Rieder N, Tauscher J, Wolf R. A Risk-Benefit Assessment of Mirtazapine in the Treatment of Depression. Drug Safety; 17 (4): 251-264]