Hormone Replacement Therapy and the Risk of Hospitalization for Venous Thromboembolism: A Population-based Study in Southern Europe

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The authors evaluated the risk of venous thromboembolism associated with hormone replacement therapy in a cohort of 265,431 women aged 45–79 years who did not have major risk factors for venous thromboembolism. Through review of hospital charts, 171 cases were confirmed (pulmonary embolism = 77; deep vein thrombosis = 94). Ten thousand controls were randomly sampled. The risk of venous thromboembolism among nonusers of hormone replacement therapy was 1.3 per 10,000 women per year. Current users of hormone replacement therapy had 2.3 times higher risk of venous thromboembolism (95 percent confidence interval 1.0–5.3) compared with nonusers. The increased risk was restricted to the first year of treatment. Am J Epidemiol 1998;147:387–90.

Recent observational studies conducted in the United Kingdom and the United States have reported an increased risk of venous thromboembolism associated with the use of hormone replacement therapy (1–4). Few of these studies have provided data on the use of transdermal route of administration (1, 4). To evaluate the risk in a southern European population where hormone replacement therapy has been recently introduced with predominant use of transdermal preparations, we conducted a population-based case-control study using the Regional Health Databases of Friuli-Venezia Giulia in Italy.

MATERIALS AND METHODS

Source population

The region of Friuli-Venezia Giulia, Italy, keeps complete and accurate records in various computerized databases on the utilization of health care re-

Received for publication June 18, 1997, and accepted for publication October 10, 1997.

Abbreviations: CI, confidence interval; OR, odds ratio.

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occurrence of one of the following endpoints: a hospitalization with a first discharge diagnosis code of venous thromboembolism or one of the exclusion conditions; death; emigration; attainment of age 80 years; or end of the study period.

**Case ascertainment**

A total of 519 patients with a hospital discharge code (International Classification of Diseases, Ninth Revision (5)) for deep venous thrombosis or pulmonary embolism and no hospitalization in the preceding 6 months were identified. By protocol, we eliminated 51 women who had a subsequent hospitalization with a discharge diagnosis of cancer, alcohol abuse, vasculitis, or coagulopathy in the 2 months after the index date (admission date). Hospital records for the remainder (n = 468) were obtained for all but three cases and reviewed by two investigators blinded to exposure status. A woman was confirmed as a definite case if she presented with typical clinical signs and symptoms of deep venous thrombosis or pulmonary embolism and had a positive diagnostic procedure (ventilation/perfusion scan, pulmonary angiography or a positive venogram, or ultrasonography for deep venous thrombosis) or necropsy or if she was treated with anticoagulants for more than 2 months after hospital discharge. She was classified as a probable case if she had no information on diagnostic tests recorded in the hospital charts but presented with typical clinical signs and symptoms of deep venous thrombosis, was treated with anticoagulants only in the hospital, and had no evidence for an alternative diagnosis. After review of the hospital records, 171 women were considered to have idiopathic incident cases of venous thromboembolism. A total of 149 had venous thromboembolism but presented with one of our exclusion criteria, and 145 did not have a confirmed episode of venous thromboembolism.

**Selection of controls**

Ten thousand women were randomly sampled from the study cohort with a random date included in the individual’s follow-up period. The random date served as index date (6). All eligibility criteria used among cases were applied to the controls.

**Exposure and other risk factors assessment**

Hormone replacement therapy preparations were listed from the Italian Drug Formulary. Use of transdermal estradiol, oral conjugated equine estrogens, and other regimens was identified from the prescription database, either opposed or unopposed to synthetic progestogen. Women whose last prescription was filled up to 6 months before the index date and those whose last prescription was issued more than 6 months before were classified as current users and past users of hormone replacement therapy, respectively. Women with no hormone replacement therapy prescription were classified as nonusers. Duration of hormone replacement therapy use was the time period since the beginning of therapy defined by consecutive supplies (refill gap of less than 6 months).

Information on other potential risk factors for venous thromboembolism was obtained from the Hospital Services and the Outpatient Prescription Databases.

**Analysis**

Adjusted odds ratios and 95 percent confidence intervals were estimated by unconditional logistic regression. This analysis was performed by the LOGISTIC procedure of SAS release 6.08 (7).

**RESULTS**

Among the 171 cases of idiopathic venous thromboembolism, 166 (97 percent) were classified as definite and five (3 percent) as probable. Seventy-seven (45 percent) were cases of pulmonary embolism (31 also presented with confirmed deep venous thrombosis), and 94 (55 percent) were cases of deep venous thrombosis.

History of varicose veins or superficial phlebitis and obesity were the two most important independent risk factors for venous thromboembolism (table 1). Six women (4 percent) among 171 cases of venous thromboembolism and 232 women (2 percent) among the controls were current users of hormone replacement therapy. Seventy-nine percent of use was with transdermal therapy. Compared with the crude odds ratio for nonusers, that for venous thromboembolism in current users was 1.5 (95 percent confidence interval (CI) 0.7–3.5). This risk increased after controlling for age and remained unchanged after adjustment for additional risk factors (odds ratio (OR) = 2.3, 95 percent CI 1.0–5.3). Past use of hormone replacement therapy was not associated with an increased risk of venous thromboembolism (OR = 0.4, 95 percent CI 0.1–2.8). A similar risk among current users was observed (OR = 2.1, 95 percent CI 0.7–5.9) when a narrower definition was applied (last supply of hormone replacement therapy within 30 days of index date) (data not shown). The risk of venous thromboembolism associated with current use of hormone replacement therapy among women aged 50 years or older was 2.7 (95 percent CI 1.2–6.5) (data not shown).

The increased risk of venous thromboembolism appeared to be restricted to the first year of use (OR = 2.9, 95 percent CI 1.2–6.9) (table 2). Women on opposed therapy presented a somewhat higher relative risk of venous thromboembolism than did women on
TABLE 1. Association of venous thromboembolism with hormone replacement therapy use and other risk factors, Friuli-Venezia Giulia, Italy, 1991-1995

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Cases (n = 171)</th>
<th>Controls (n = 10,000)</th>
<th>Crude OR*</th>
<th>95% Cl*</th>
<th>Adjusted OR†</th>
<th>95% Cl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>45-64</td>
<td>70</td>
<td>6,685</td>
<td>1</td>
<td>2.1-3.9</td>
<td>2.3</td>
<td>1.6-3.2</td>
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<tr>
<td>65-80</td>
<td>101</td>
<td>3,315</td>
<td>2.9</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Hormone replacement therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonuse</td>
<td>164</td>
<td>9,601</td>
<td>1</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Current use (&lt;180 days)</td>
<td>6</td>
<td>222</td>
<td>1.5</td>
<td>0.7-3.5</td>
<td>2.3</td>
<td>1.0-5.3</td>
</tr>
<tr>
<td>Past use (&gt;180 days)</td>
<td>1</td>
<td>167</td>
<td>0.4</td>
<td>0.1-2.5</td>
<td>0.4</td>
<td>0.1-2.8</td>
</tr>
<tr>
<td>Obesity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>161</td>
<td>9,935</td>
<td>1</td>
<td>4.8-18.8</td>
<td>4.6</td>
<td>2.2-9.7</td>
</tr>
<tr>
<td>Yes</td>
<td>10</td>
<td>65</td>
<td>9.5</td>
<td></td>
<td></td>
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<tr>
<td>Varicose veins‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>147</td>
<td>9,746</td>
<td>1</td>
<td>3.9-9.8</td>
<td>6.9</td>
<td>4.3-11.0</td>
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<tr>
<td>Yes</td>
<td>24</td>
<td>254</td>
<td>6.3</td>
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<tr>
<td>Diabetes</td>
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<td></td>
</tr>
<tr>
<td>No</td>
<td>148</td>
<td>9,568</td>
<td>1</td>
<td>2.2-5.4</td>
<td>1.9</td>
<td>1.2-3.1</td>
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<tr>
<td>Yes</td>
<td>23</td>
<td>432</td>
<td>3.4</td>
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<td></td>
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<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>No</td>
<td>108</td>
<td>8,182</td>
<td>1</td>
<td>1.9-3.6</td>
<td>1.6</td>
<td>1.2-2.3</td>
</tr>
<tr>
<td>Yes</td>
<td>63</td>
<td>1,818</td>
<td>2.6</td>
<td></td>
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<tr>
<td>Osteoarthrosis</td>
<td></td>
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<td></td>
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<td></td>
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<tr>
<td>No</td>
<td>113</td>
<td>8,758</td>
<td>1</td>
<td>2.6-4.9</td>
<td>2.4</td>
<td>1.7-3.3</td>
</tr>
<tr>
<td>Yes</td>
<td>58</td>
<td>1,242</td>
<td>3.6</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* OR, odds ratio; CI, confidence interval.
† Estimates of odds ratios were obtained from a model that included all variables presented in this table.
‡ Varicose veins or superficial phlebitis.

unopposed therapy, but data were limited in order to obtain precise confidence intervals. We could not analyze the dose-effect relation, since most cases and controls were exposed to the same dose category.

The crude incidence rate of venous thromboembolism in our cohort of relatively healthy women was 1.3 per 10,000 person-years. The overall case-fatality rate was 1.8 percent. Among cases with pulmonary embolism, the case fatality rate was 3.9 percent.

DISCUSSION

The objective of this study was to examine the risk of idiopathic venous thromboembolism associated


<table>
<thead>
<tr>
<th>Duration of therapy</th>
<th>Cases (n = 171)</th>
<th>Controls (n = 10,000)</th>
<th>Crude OR*</th>
<th>95% Cl*</th>
<th>Adjusted OR†</th>
<th>95% Cl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonuse</td>
<td>164</td>
<td>9,601</td>
<td>1</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>1 month to 1 year</td>
<td>6</td>
<td>177</td>
<td>1.9</td>
<td>0.9-4.6</td>
<td>2.9</td>
<td>1.2-6.9</td>
</tr>
<tr>
<td>&gt;1 year</td>
<td>0</td>
<td>55</td>
<td>0.0</td>
<td>0.0-4.1</td>
<td>0.0</td>
<td>0.0-4.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of regimen</th>
<th>Cases (n = 171)</th>
<th>Controls (n = 10,000)</th>
<th>Crude OR*</th>
<th>95% Cl*</th>
<th>Adjusted OR†</th>
<th>95% Cl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonuse</td>
<td>164</td>
<td>9,601</td>
<td>1</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Unopposed</td>
<td>3</td>
<td>169</td>
<td>1.1</td>
<td>0.3-3.3</td>
<td>1.4</td>
<td>0.4-4.8</td>
</tr>
<tr>
<td>Opposed</td>
<td>3</td>
<td>63</td>
<td>2.8</td>
<td>0.9-8.9</td>
<td>5.0</td>
<td>1.5-16.7</td>
</tr>
</tbody>
</table>

* OR, odds ratio; CI, confidence interval.
† Odds ratios were adjusted for age and prior history of hypertension, diabetes mellitus, obesity, varicose veins, and superficial phlebitis and osteoarthrosis.
with current use of hormone replacement therapy in a
general population of women in a southern European
country where this treatment has been recently intro-
duced. In our study population, a low prevalence of
hormone replacement therapy use and preferentially of
transdermal preparations (79 percent) was observed
with respect to other northern European and North
American populations. The results suggest that women
who are current users of hormone replacement therapy
have two to three times higher risk of being hospital-
ized for venous thromboembolism compared with
those women who never use this therapy. Overall, the
risk seems to be restricted to users in their first year of
treatment. After this initial period, the estimate of risk
is compatible with the background risk in nonusers.
However, our risk estimators are based on a small
number of exposed cases, resulting in relatively wide
confidence intervals. Results also confirmed the prog-
nostic value of known risk factors such as varicose
veins, superficial phlebitis, and obesity (8).

These results are of similar direction and magnitude
as those reported in recent studies (1–4) conducted in
populations in which women were taking mainly oral
estrogen therapy. In these studies, overall risks esti-
mated for current users relative to nonusers ranged
from 2.1 to 3.6. Relative to nonusers, the risks esti-
mated for oral preparations ranged from 2.1 to 4.6
(1–4). At present, this study and two others (1, 4) have
provided data on transdermal preparations, and the
relative risks range from 2.0 to 2.3.
The possibility that women exposed to hormone
replacement therapy might be more likely to be sent to
the hospital for a diagnosis of venous thromboembo-
lism would tend to overestimate the risk of venous
thromboembolism associated with the use of this ther-
apy (diagnostic bias). Overall, 77 percent of cases had
a positive result for one of the specific diagnostic tests.
Corresponding numbers in nonusers and ever users of
hormone replacement therapy were 78 and 57 percent,
respectively. Thus, only a minor overestimation of the
risk associated with hormone replacement therapy
could be present in our results. In our study popula-
tion, a high quality of diagnostic workup during hospi-
talization for deep venous thrombosis resulted in a
high percentage of definite venous thromboembolism
cases according to the case definition. In addition, the
accessibility to hospital records was excellent, and the
validity of the recorded information was high, con-
firming the usefulness of Friuli Health Care Databases
for epidemiologic research purposes (9).

Although other potential risk factors were taken into
account, age was the only one that was related to both
the risk of venous thromboembolism and use of hor-
mone replacement therapy. We used only information
on risk factors recorded in the automated database to
account for in the analyses. We also abstracted infor-
mation for certain risk factors from the hospital
records of cases. Distribution of these risk factors
based on this source of information (likely to be more
complete) was similar in exposed and nonexposed
cases (data not shown), further confirming the lack of
confounding by these variables.

In this study, the absolute risk of idiopathic venous
thromboembolism among healthy women who had
never used hormone replacement therapy was esti-
mated to be rare, below 2 per 10,000 women per year.
Among current users of hormone replacement therapy,
this risk was increased by a factor close to three in the
first year of treatment. This would result in two addi-
tional cases of venous thromboembolism among
10,000 women using hormone replacement therapy
during a year. The magnitude of this excess risk of
venous thromboembolism and the implications for
women on hormone replacement therapy are similar to
those reported recently (1–4).

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Am J Epidemiol Vol. 147, No. 4, 1998