Conclusions—Increases were observed in resistance to APC, which were more pronounced in the oral treatment groups using ethynylestradiol in combination with so-called third-generation progestogens (desogestrel or gestodene) than among women oral contraceptive users. The increase in resistance to APC might be explained by a differential effect of the progestogens on resistance to activated protein C (APC), a risk factor for venous thrombosis. It is plausible that the observed increased risk of venous thrombosis in hormone replacement users can also, at least in part, be explained by an increase in resistance to APC.

Key Words: resistance to activated protein C ■ protein S ■ protein C ■ estrogen replacement therapy ■ venous thrombosis

W omen using oral estrogen containing hormone replacement therapy or oral contraceptives have an increased risk of developing venous thrombosis. The risk for oral contraceptive users is higher in women who use ethynylestradiol in combination with so-called third-generation progestogens (desogestrel or gestodene) than among women using ethynylestradiol in combination with the second-generation progestogen levonorgestrel. This difference might be explained by a differential effect of the progestogens on resistance to activated protein C (APC), a risk factor for venous thrombosis. It is plausible that the observed increased risk of venous thrombosis in hormone replacement users can also, at least in part, be explained by an increase in resistance to APC.

The effect of hormone replacement therapy on resistance to APC, on protein S, and on protein C has been investigated in several studies. However, only few had a randomized, placebo-controlled design. Only uncontrolled and cross-sectional studies on the effect of transdermal estradiol on resistance to APC have been published to date.

The effect of hormone replacement therapy on risk factors for venous thrombosis may be modified by the route of administration and the type of estrogen, which can be administered either unopposed or combined with a progestogen. As far as we know, there are no reports on the effect of oral 17\(\beta\)-estradiol combined with the third-generation progestogen gestodene and on the direct comparison of unopposed transdermal and oral 17\(\beta\)-estradiol on resistance to...
APC and on the plasma levels of the hemostatic variables protein S, protein C, and prothrombin, changes of which are associated with an increased risk of venous thrombosis.

Therefore, we performed a randomized, placebo-controlled, double-blind study in healthy postmenopausal women to gain more insight into the short- and long-term effects of unopposed transdermal 17β-estradiol and oral 17β-estradiol, either unopposed or combined with the progestogen gestodene, on resistance to APC and on plasma levels of protein S, protein C, and prothrombin.

Methods

Study Population

The design of this study has been published previously.20 Briefly, after screening, 152 eligible healthy postmenopausal women who had undergone a hysterectomy were enrolled in this multicenter study. The investigation conformed to the principles outlined in the Declaration of Helsinki. All Institutional Review Boards approved the protocol. Written informed consent was obtained from each participant before entering the study.

Participants were 45 to 65 years old, smoked fewer than 6 cigarettes per day, had blood pressures below 160/100 mm Hg, and had a body mass index ≤30 kg/m². Postmenopausal status was defined as a serum follicle-stimulating hormone concentration greater than 40 IU/L and an estradiol concentration lower than 110 pmol/L on each of 2 different visits in the screening period. None of the women had received hormone replacement therapy within 6 months before randomization, and none took cardiovascular medication. Exclusion criteria included a personal history of cardiovascular, thromboembolic, metabolic, endocrinological, and malignant disease, as well as clinically relevant abnormalities in laboratory tests.

To maintain blinding of the study medication, a double-dummy approach was used. Eligible women were randomly assigned to either a placebo tablet and placebo patch (placebo group, n=49); transdermal 17β-estradiol 50 μg daily (Climara) and a placebo tablet (tE2 group, n=33); oral micronized 17β-estradiol 1 mg daily and a placebo patch (oE2 group, n=37); or oral micronized 17β-estradiol 1 mg and gestodene 25 μg daily (1 tablet) and a placebo patch (oE2+G group, n=33) given for the first 13 28-day cycles for each group followed by 4 cycles of placebo tablets and placebo patches. Medication was manufactured by Schering AG, SBU Fertility Control & Hormone Therapy, Berlin, Germany. We included more women in the placebo group than in the other groups, because we expected more dropouts in this group.

Laboratory Measurements

At baseline and in cycles 4, 13, and 17 of follow-up, venous blood was collected in a fasting state in cooled tubes containing trisodium citrate (1:9 vol/vol; 0.129 mol/L) (Becton Dickinson) between 8:00 AM and 10:00 AM. The tubes were immediately placed on ice and centrifuged within 1 hour after blood collection (3000g, 4°C, 30 minutes). Plasma was snap-frozen and stored at −80°C. Normal pooled plasma was obtained from healthy volunteers (6 women not using oral contraceptives and 9 men, mean age 33 years) and collected in the same manner as described above.

Assays

Normalized APC sensitivity ratios (nAPCsr) were determined with an APC resistance test21 that quantifies the effect of APC on the time integral of thrombin generation (the endogenous thrombin potential) under well-defined conditions.6 Briefly, thrombin generation was initiated in plasma with 0.4 μg/L recombinant tissue factor (Dade Innovin), 16 mmol/L CaCl₂, and 15 μmol/L phospholipid vesicles containing 20 mol % 1,2-dioleoyl-sn-glycero-3-phosphoserine, 20 mol % 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine, and 60 mol % 1,2-dioleoyl-sn-glycerol-3-phosphocholine (Avanti Polar Lipids) either in the absence or presence of 5 pmol/L APC. Concentrations given are final concentrations present in plasma mixtures. The amidolytic activity of the α1-macroglobulin-thrombin complex (α-M-IIa) was used as an end point marker to quantify thrombin generation.21 The nAPCsr was defined as the ratio of the amounts α-M-IIa in APC/α-M-IIa,APC)plasma sample/(α-M-IIa,APC)/α-M-IIa,APC;normal plasma. In this assay, an increase in nAPCsr represents an increase in resistance to APC. Total protein S22 and free protein S23 were determined by ELISA. Protein C activity,23 prothrombin,25 and C-reactive protein20 were measured as described before. We used C-reactive protein concentrations to test whether the pathways that mediate estradiol-associated increases in C-reactive protein are similar to those that mediate estradiol-associated changes in hemostatic variables. Serum estradiol was quantified by using a double-antibody radioimmunoassay (Sorin Biomedica) with a lower limit of detection of 18 pmol/L. All samples for a given variable of each participant were assayed in a single run. The intra-assay coefficient of variation for measuring nAPCsr was 6.9%; for total and free protein S, 11.7% and 12.1%, respectively; for protein C, 4.2%; for prothrombin, 5.8%; for C-reactive protein, 2.4%; and for estradiol, 8.5%. All women were tested for the factor VLeiden mutation. Because no DNA was available, we used a functional test that fully discriminates homozygous and heterozygous carriers of the factor VLeiden mutation from noncarriers.26

| TABLE 1. Descriptive Characteristics of the Four Groups at Baseline |
|-------------------------|-----------------|-----------------|-----------------|
|                         | Placebo         | tE₂             | oE₂             |
| N                       | 49              | 33              | 37              |
| Age, y                  | 55.0±4.7        | 55.5±4.8        | 54.4±4.3        |
| Body mass index, kg/m²  | 25.7±3.0        | 26.0±2.4        | 25.0±3.2        |
| Blood pressure, mm Hg   | 126±17          | 134±14          | 127±12          |
|                         | 79±6            | 83±9            | 81±10           |
| Systolic                | 7 (14)          | 1 (3)           | 3 (8)           |
| Diastolic               | 5.9±0.9         | 6.1±0.9         | 6.2±1.0         |
| Serum cholesterol, mmol/L| 62±20          | 63±23           | 67±28           |
| Serum FSH, U/L          | 29 (25–41)      | 28 (23–47)      | 29 (24–38)      |

Values are given as mean±SD, as number (%) with percentage in parentheses, or as median (25th–75th percentile).

FSH indicates follicle-stimulating hormone; E₂, 17β-estradiol.
TABLE 2. Hemostatic Variables During the Study

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Cycle 4</th>
<th>Cycle 13</th>
<th>∆13–0 (%)*</th>
<th>ANCOVA†</th>
<th>ANCOVA‡</th>
<th>Cycle 17 (After Washout)</th>
</tr>
</thead>
<tbody>
<tr>
<td>nAPCsr</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>0.77 (0.45 to 1.05)</td>
<td>0.73 (0.43 to 1.18)</td>
<td>0.70 (0.57 to 1.08)</td>
<td>0.84 (-12.5 to 16.1)</td>
<td>&lt;0.001</td>
<td>0.69 (0.55 to 0.95)</td>
<td></td>
</tr>
<tr>
<td>tE₂</td>
<td>0.66 (0.43 to 1.05)</td>
<td>0.82 (0.40 to 1.12)</td>
<td>0.83 (0.50 to 1.39)</td>
<td>27.7 (8.6 to 50.2)§</td>
<td>0.07</td>
<td>0.64 (0.36 to 1.05)</td>
<td></td>
</tr>
<tr>
<td>oE₂</td>
<td>0.73 (0.43 to 1.01)</td>
<td>1.22 (1.00 to 1.77)</td>
<td>1.38 (1.07 to 1.90)</td>
<td>103.5 (80.5 to 129.5)¶</td>
<td>&lt;0.001</td>
<td>0.74 (0.54 to 1.24)</td>
<td></td>
</tr>
<tr>
<td>oE₂+G</td>
<td>0.87 (0.57 to 1.30)</td>
<td>1.54 (0.96 to 1.96)</td>
<td>1.49 (1.07 to 2.22)</td>
<td>70.7 (41.0 to 106.6)¶</td>
<td>&lt;0.001</td>
<td>0.95 (0.68 to 1.57)</td>
<td></td>
</tr>
</tbody>
</table>

Total protein S, %

|                  |          |         |          |            |         |         |                         |
| Placebo          | 110 ± 24 | 112 ± 31 | 110 ± 22 | 0.0 (-2.8 to 2.8) | <0.001 | 110 ± 23 |
| tE₂             | 107 ± 23 | 103 ± 23 | 103 ± 24 | -4.1 (-7.6 to -0.5) | 0.02 | 114 ± 24 |
| oE₂             | 114 ± 26 | 103 ± 25 | 105 ± 26 | -7.9 (-11.5 to -4.2)¶ | <0.001 | 116 ± 28 |
| oE₂+G           | 113 ± 30 | 104 ± 32 | 106 ± 28 | -5.8 (-9.6 to -2.0)§ | <0.001 | 115 ± 33 |

Free protein S, %

|                  |          |         |          |            |         |         |                         |
| Placebo          | 106 ± 31 | 110 ± 41 | 107 ± 28 | 1.1 (-2.7 to 4.8) | 0.001 | 108 ± 28 |
| tE₂             | 108 ± 28 | 102 ± 28 | 102 ± 28 | -6.0 (-10.0 to -2.0)§ | 0.005 | 113 ± 33 |
| oE₂             | 112 ± 29 | 102 ± 25 | 105 ± 28 | -7.3 (-10.9 to -3.7)¶ | 0.009 | 113 ± 32 |
| oE₂+G           | 110 ± 36 | 104 ± 37 | 104 ± 31 | -4.1 (-8.1 to -0.5)¶ | <0.001 | 110 ± 33 |

Protein C, %

|                  |          |         |          |            |         |         |                         |
| Placebo          | 107 ± 16 | 107 ± 16 | 109 ± 18 | 2.2 (-0.7 to 5.2) | <0.001 | 109 ± 17 |
| tE₂             | 103 ± 17 | 103 ± 12 | 103 ± 13 | 0.0 (-4.6 to 4.5) | 0.18 | 112 ± 14 |
| oE₂             | 113 ± 18 | 114 ± 21 | 116 ± 18 | 3.3 (-0.2 to 6.8) | 0.25 | 116 ± 19 |
| oE₂+G           | 109 ± 20 | 101 ± 17 | 104 ± 18 | -4.2 (-8.0 to -0.4)¶ | 0.001 | 108 ± 22 |

Prothrombin, %

|                  |          |         |          |            |         |         |                         |
| Placebo          | 104 ± 14 | 104 ± 14 | 104 ± 15 | 0.6 (-1.8 to 3.0) | 0.22 | 106 ± 15 |
| tE₂             | 102 ± 16 | 99 ± 14 | 100 ± 14 | -1.1 (-5.5 to 3.2) | 0.04 | 107 ± 15 |
| oE₂             | 105 ± 12 | 103 ± 11 | 105 ± 13 | -0.1 (-3.1 to 2.9) | 0.46 | 106 ± 13 |
| oE₂+G           | 103 ± 17 | 102 ± 15 | 105 ± 13 | 1.6 (-1.7 to 4.9) | 0.71 | 107 ± 13 |

Values are given as median (25th to 75th percentile) or as mean±SD at baseline and in cycle 4, cycle 13, and cycle 17.

*Mean and 95% confidence interval of the individual percentage changes in cycle 13 compared to baseline (geometric values are given for nAPCsr).

†P<0.05, ‡P<0.01, †P<0.001. Test for between-group differences compared with placebo. ANCOVA with the baseline value of the variable as covariate for between-group differences over the 13-cycle study period. §ANCOVA over the 13-cycle study period, treatment vs placebo. Other significant between-group differences are as follows: nAPCsr: tE₂ vs oE₂ group (P<0.001) and tE₂ vs oE₂+G group (P<0.001); protein C: tE₂ vs oE₂ group (P=0.02) and oE₂ vs oE₂+G group (P<0.001).

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences + 4.0 and 9.0 (SPSS Inc). Baseline characteristics are given as mean±SD when normally distributed or as median and interquartile range (25th and 75th percentile) when the distribution was skewed. The means of the individual percentage changes are given as mean and 95% confidence interval (geometric values for data with a skewed distribution). Standard parametric tests were performed (after log transformation for data with a skewed distribution). ANCOVA for repeated measurements with the baseline value of the variable under consideration as covariate was used for comparisons between and among the groups. A 2-tailed P<0.05 was accepted as the level of significance.

Women with only baseline samples were excluded from the analyses. In addition, for the missing results at cycle 13 (7 women), the last-observation-carried-forward procedure was applied using the results obtained at cycle 4. Therefore, the analyses of the first year were based on 146 women (placebo, n=47; tE₂, n=32; oE₂, n=37; and oE₂+G, n=30 women). The analyses of the washout-period were based on 134 women completing the trial (placebo, n=40; tE₂, n=29; oE₂, n=36; and oE₂+G, n=29 women).

Results

Table 1 shows baseline demographic characteristics of the 4 groups. At baseline, no significant differences were found between the groups in either demographic characteristics (Table 1) or in any of the variables investigated (Table 2). All women had undergone a hysterectomy for benign diseases (eg, bleeding problems, symptomatic myomas, polyps, or prolapse). None of the women was homozygous for the factor VLeiden mutation, whereas 7 women were heterozygous carriers (placebo group, n=1; tE₂ group, n=1; oE₂ group, n=3; and oE₂+G group, n=2). Baseline nAPCsr of these 7 women ranged from 1.13 to 3.55. Neither reasons for dropout²⁰ nor (serious) adverse events (Table 3) were related to venous thromboembolic disease.

Table 2 summarizes the values of the hemostatic variables investigated during the study. The Figure shows box-and-whisker plots of the nAPCsr of all 4 groups at baseline, cycle 13, and cycle 17, as well as individual nAPCsr of the women who were heterozygous carriers of the factor VLeiden mutation. Compared with placebo, 4 and 13 cycles of treatment with oE₂ and oE₂+G were associated with significant increases in nAPCsr. The percentage change in nAPCsr in the tE₂ group versus baseline and placebo was significant only after 13 cycles. This led to a nonsignificant difference (P=0.07) between the tE₂ and placebo group in the ANCOVA. Over the 13-cycle study period,
a significant difference in nAPCsr was found between the tE2 group and the groups treated orally (Table 2).

During the 13-cycle study period, plasma levels of total protein S and free protein S decreased in all actively treated groups. Plasma levels of protein C decreased in the oE2 group, whereas no changes were observed in the tE2 group and in the oE2 group. Analyses of covariance over the first 13 cycles showed a significant difference in prothrombin between the placebo group and the tE2 group.

Compared with placebo, the change in nAPCsr from baseline to cycle 17 (after 13 treatment cycles and 4 washout cycles with placebo) was statistically significant only in the oE2 group (17.6%, \( P = 0.04 \)). A significant increase in protein C was found in the tE2 group in cycle 17 compared with baseline and placebo (+7.9%, \( P = 0.02 \)). Levels of total protein S, free protein S, and prothrombin returned to baseline levels after the washout period.

In cycle 13, serum estradiol levels in the placebo group were 28 (25 to 39) pmol/L (median and interquartile range); in the tE2 group, 122 (85 to 187) pmol/L; in the oE2 group, 153 (100 to 192) pmol/L; and in the oE2+G group, 120 (71 to 188) pmol/L. After 13 cycles, the ANCOVA showed statistically significant differences between the placebo group and the 3 actively treated groups (all \( P < 0.001 \)) and significant differences between the tE2 and oE2 group \( (P = 0.03) \) and between the oE2 and oE2+G group \( (P = 0.04) \).

Analyses of covariance of the nAPCsr was repeated with the addition of the absolute change between baseline and cycle 13 in either levels of total protein S, free protein S, protein C, or prothrombin as covariate. This did not materially change the results (data not shown). None of the changes in levels of the hemostatic variables were significantly related to changes in levels of estradiol or to changes in levels of C-reactive protein (data not shown).

At baseline, 13 women had serum estradiol concentrations higher than 150 pmol/L, which were divided as follows: 4 women in the placebo group (175, 246, 396, and 402 pmol/L), 4 women in the tE2 group (170, 207, 264, and 912 pmol/L), 1 woman in the oE2 group (192 pmol/L), and 4 women in the oE2+G group (153, 169, 173, and 333 pmol/L). Reanalyses of all variables were performed after excluding the women with high serum estradiol levels and for the nAPCsr data as well after excluding women who were heterozygous for the factor VLeiden mutation. The results were similar (data not shown).

### Discussion

In this randomized, double-blind, placebo-controlled trial, we observed a large increase in resistance to APC in healthy postmenopausal women using oral hormone replacement...
therapy consisting of 17β-estradiol either unopposed or combined with gestodene both after 4 and 13 cycles (1 year). Transdermal estradiol replacement also increased resistance to APC. However, the increase was much smaller than in the oral treatment groups and was significant only in cycle 13. Small but significant decreases were found in total protein S and free protein S in all active treatment groups, in protein C in the oE2+G group, and in prothrombin in the oE2 group. These changes, however, did not explain the changes in the nAPCsr.

The observed effects of transdermal estradiol administration on resistance to APC contrast with the results of other prospective studies. In 2 uncontrolled short-term studies, transdermal 17β-estradiol either unopposed or sequentially combined with an oral progestogen favorably reduced resistance to APC levels within 4 treatment cycles. These contrasting results might be the consequence of differences in study design (no placebo group or the addition of a progestogen) or differences in the determination of resistance to APC. In a cross-sectional study, no differences in resistance to APC were found between postmenopausal women using transdermal estrogens and women not using hormone replacement therapy. It is interesting that the observed increase in nAPCsr in the transdermal estradiol group in our study was overall much smaller than the changes in the groups in which estradiol was administered orally. This suggests a role of the first-pass hepatic pathway, which is largely avoided by transdermal administration of estrogens.

In an earlier study, we found a large and rapid increase in resistance to APC after 4 and 12 weeks of unopposed oral 17β-estradiol. The present trial extends these findings by showing that the early increase persists for at least 1 year of therapy and is not fully reversed within 4 cycles of discontinuation of unopposed oral estradiol. The clinical relevance of this persistent increase is unknown, as is its explanation, because the molecular mechanism of the estrogen-associated increase in nAPCsr remains, at present, unresolved.

This is the first randomized, placebo-controlled study to report an increase in resistance to APC during treatment with 17β-estradiol plus gestodene, a progestogen of the third generation. The observed increase was not significantly different from the increase found during unopposed oral estradiol. In other randomized, placebo-controlled trials in which the effect of oral combined hormone replacement therapy was studied, increases in resistance to APC were observed as well, irrespective of the progestogen used.

In the present study, resistance to APC was measured with an assay that is particularly sensitive to changes in the hormonal status of women, i.e., with a test that quantifies the effect of APC on thrombin generation initiated via the extrinsic coagulation pathway (endogenous thrombin potential-based test). nAPCsr determined with this test correlates remarkably well with the risk increase of venous thromboembolism reported in oral contraceptive users and in carriers of the factor VLeiden mutation.

The small changes in total and free protein S and in protein C are, in general, consistent with previous data. Estradiol levels differed between the unopposed oral estradiol group and the other active treatment groups. This may account for differences observed in variables among the groups. However, in additional analyses of covariance, none of the changes observed in the hemostatic variables were related to changes in estradiol levels. Furthermore, the increase in nAPCsr during the study was not related to changes in protein S, protein C, or prothrombin.

Hormone replacement therapy is known to increase the risk of venous thromboembolic disease. In only 2 case-control studies has the risk in users of transdermal therapy been assessed separately from the risk in users of oral therapy. The adjusted odds ratios of venous thromboembolism for current users of transdermal estrogen compared with nonusers were 2.0 (95% confidence interval [CI], 0.5 to 7.6) and 2.1 (95% CI, 0.9 to 4.6); and in the users of oral estrogens, 4.6 (95% CI, 2.1 to 10.1) and 2.1 (95% CI, 1.3 to 3.6). The risk in users of transdermal estrogen could not be shown to differ significantly from the risks in users of oral estrogen. A shortcoming of both studies is the very small number of cases during transdermal therapy (respectively, 5 and 7). Therefore, at present it remains unclear whether transdermal hormone replacement therapy confers a lower risk of venous thromboembolism compared with oral therapy, and, if so, whether differential effects of the route of hormone administration on, for example, resistance to APC play a role in this respect. The increased risk of developing venous thrombosis in postmenopausal women using oral hormone replacement therapy may in part be the result of the large increase in resistance to APC, because changes in other hemostatic parameters that are associated with the occurrence of venous thrombosis (protein S, protein C, and prothrombin) were much smaller. Our data, combined with the results from case-control studies on transdermal estrogen replacement therapy and venous thrombosis, suggest that in women with increased risk for venous thrombosis, transdermal administration of estradiol is preferred. However, it must be stressed that we only investigated the effect of unopposed transdermal estradiol. In women with a uterus, it is mandatory to add a progestogen to estrogen replacement to prevent the development of endometrial neoplasia. Furthermore, only data of 2 case-control studies are available, and our study was not powered to investigate whether the smaller increase in resistance to APC found in the transdermal estradiol group confers a lower venous thrombosis risk.

Because we wanted to study the effect of unopposed estradiol for 1 year, we included only hysterectomized women to prevent the development of endometrial neoplasia. Because a hysterectomy may hamper the diagnosis of the postmenopausal state, estradiol and follicle-stimulating hormone levels were measured twice during the screening period. Despite this, 13 women had estradiol levels above 150 pmol/L at baseline. Because reanalyses without these women did not affect the outcome of our study, we did not exclude these women from the analyses. Indications for hysterectomy were not related to risk of venous thromboembolic disease. There is no reason to believe that results would be different in women having a uterus.

C-reactive protein, a marker of inflammation, is associated with venous thrombosis and has been reported to be a strong predictor of cardiovascular events. Data on C-reactive protein obtained in this study have been reported earlier. The increase observed in C-reactive protein in the unopposed oral estradiol group, as for the nAPCsr, was significantly larger than the increase in the transdermal estradiol group. However, the in-
crease in C-reactive protein did not differ between the transdermal estradiol and the combined estradiol plus gestodene group and did not statistically explain the changes in any of the hemostatic variables.

In conclusion, in this randomized placebo-controlled study, a substantial increase in resistance to APC was found in healthy postmenopausal women using oral 17β-estradiol, either unopposed or opposed by gestodene, whereas a much smaller increase was observed in women using transdermal estradiol replacement.

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All women who participated in the study.

References


Effect of Oral and Transdermal Estrogen Replacement Therapy on Hemostatic Variables Associated With Venous Thrombosis: A Randomized, Placebo-Controlled Study in Postmenopausal Women
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