## Estrogen Plus Progestin and Risk of Venous Thrombosis

To the Editor: Dr Cushman and colleagues¹ presented data from the Women's Health Initiative (WHI) Estrogen Plus Progestin (E + P) trial and concluded that this combination was associated with increased risk for venous thromboembolism. The authors note that these results apply to the combination of oral conjugated equine estrogen (CEE) with medroxyprogesterone acetate (MPA) and are not necessarily relevant to other types of hormone therapy; they describe the association with transdermal estrogen therapy as controversial.

The Estrogen and Thromboembolism Risk (ESTHER) study showed that oral but not transdermal estrogen was associated with venous thromboembolism risk.2 Three other studies reported estimates of venous thromboembolism risk among users of transdermal estrogen,<sup>3</sup> but the results were based on few cases with transdermal estrogen use, and each study was inconclusive. Biological data support the difference in venous thromboembolism risk between oral and transdermal estrogen because randomized short-term trials have shown that oral but not transdermal estrogen enhanced invivo thrombin generation and induced an acquired resistance to protein C.4 Current available data suggest that transdermal estrogen has little or no effect on venous thromboembolism risk. Because pulmonary embolism accounted for about one third of the excess incidence of potentially fatal events with hormone therapy in the study by Cushman et al, evaluation of the long-term effects of transdermal estrogen in ongoing randomized trials is a research priority.

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To The Editor: The study by Dr Cushman and colleagues<sup>1</sup> is based on data from the WHI and details of the methods are reported in an earlier *JAMA* publication.<sup>2</sup> The prior study notes that of the 8506 participants in the CEE + MPA group,

3444 (40.5%) were unblinded for control of vaginal bleeding. Further, CEE and/or MPA doses could have been altered for treatment of this condition, yet no published data from this trial have indicated the effect that this treatment had on the study outcomes. It seems inaccurate to label this a blinded controlled trial of placebo against CEE + MPA.

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In Reply: Dr Scarabin and colleagues raise the possibility that transdermal and oral estrogens differ in their association with venous thrombosis. In their case-control study of venous thromboembolism, 30 cases and 93 controls used transdermal estrogen, and no association of transdermal therapy with thrombosis was found. This study, as well as all others addressing this question, included only hospitalized women with idiopathic thrombosis and without a history of coronary heart disease and other illnesses. The 3 other published studies had small numbers of users, but all suggested a 2-fold increased thrombosis risk with transdermal estrogen. <sup>2-4</sup>

We maintain that the data on transdermal estrogen and thrombosis risk are inconclusive. Given that millions of women might want to use transdermal therapy for treatment of menopausal symptoms, data from large studies on the safety of transdermal therapy are indeed needed. At present, we lack sufficient evidence that transdermal estrogen is a safe alternative to oral estrogen for women at risk of venous thrombosis.

Dr Blackwell asks about unblinding procedures and use of open-label CEE + MPA in the WHI E + P trial. During 5.6 years of follow-up, the consulting gynecologist at the clinical

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Letters Section Editor: Robert M. Golub, MD, Senior Editor.

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**1322** JAMA, March 16, 2005—Vol 293, No. 11 (Reprinted)

center was unblinded for 40.5% of the CEE + MPA participants, primarily for menopausal symptom management or vaginal bleeding. Randomization is intended to ensure equal risk profiles in treated and placebo groups, which is not altered by unblinding. Unblinding of adjudicators could lead to bias in outcome counts, but neither they nor study staff were unblinded during WHI, and objective internationally accepted criteria for venous thrombosis diagnosis were applied. Participating women remained blinded to the extent possible. The study protocol allowed dosage alteration to treat vaginal bleeding, using an algorithm based on bleeding severity, time since randomization, randomization group, and endometrial histology. A total of 21% of the women in the CEE + MPA group ever received open-label hormones. Typical treatment was an additional 0.3 mg/d of CEE for up to 3 months, but longer-term use and possibly higher dosing was used to manage persistent problems. Only 7.6% of the CEE + MPA participants used openlabel hormones for as long as 2 years. It is therefore unlikely that these estrogen dose modifications for vaginal bleeding would greatly alter the overall thrombosis rate in the trial.

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## **Pegylated Interferon vs Standard Interferon** for Chronic Hepatitis C

To the Editor: Dr Carrat and colleagues<sup>1</sup> compared ribavirin combined with either pegylated interferon or standard interferon for treatment of hepatitis C in patients infected with hepatitis C virus (HCV) and human immunodeficiency virus (HIV). Their results are consistent with previous studies in HIV-seronegative persons, which showed that viral load reduction correlates with improvement in hepatic function.<sup>2</sup> However, there are 2 issues I would like to address.

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First, the correlation of viral load reduction with a reduction in extrahepatic manifestations of HCV infection has not been well studied. Symptoms of neurological dysfunction are thought to arise as a parainfectious immune response to HCV mediated by cryoglobulins and rheumatoid factor.3 While interferons are often administered, their efficacy for these symptoms has not been definitely proven. Do the authors have data on cryoglobulin levels, rheumatoid factor titers, or the prevalence of neurological disease manifestations for their study participants?

Second, this study demonstrated a significant difference in response rates between the 2 interferon treatment regimens only for those patients infected by HCV genotypes 1 and 4. The clinical implications are uncertain, as the only statistically significant benefit in the pegylated interferon treatment group was an improvement in the Metavir subscore; no such benefit was noted in either the Ishak grade or the degree of hepatic fibrosis between these 2 groups. While steatosis improved in all treatment responders infected with the HCV genotype 3, this occurred irrespective of the type of interferon administered. Therefore, it seems that response to either form of interferon therapy will not necessarily result in a reversal of the underlying hepatopathy, but may merely slow the rate of progression.

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In Reply: Dr Menkes raises 2 issues not addressed in our study. The first concerns the correlation between the decrease in viral load and an attenuation of extrahepatic manifestations of HCV infection. This issue was beyond the scope of our trial, and the patients were not screened for cryoglobulinemia or rheumatoid factor. However, it is noteworthy that clinical extrahepatic manifestations of HCV infection were rare in our study participants (one patient had vasculitis and another had polyneuritis). This was probably due to the exclusion of patients with antinuclear antibodies at baseline. In previous studies of HIV-seronegative populations, we found that an HCV virological response was associated with a reduction in cryoglobulin levels and with an improvement in clinical extrahepatic manifestations.<sup>1-4</sup> The question of such an association remains open in the HIV-coinfected population.

The second point focuses on the small difference in histological responses between the 2 treatment groups. While we believe that our results indicate that a treatment response is associated with a halting rather than a slowing of fibrosis pro-

(Reprinted) JAMA, March 16, 2005—Vol 293, No. 11 1323