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Hormone Therapy and Risk for Venous Thromboembolism: Comments and Correction

TO THE EDITOR: Grady and colleagues (1) speculate that effects of oral estrogen on factor VII and protein C may be possible mechanisms for the prothrombotic effects of hormone replacement therapy (HRT) observed in the Heart and Estrogen/progestin Replacement Study (HERS). I am concerned that the specific points made by the authors about protein C and factor VII provide an oversimplistic and somewhat inaccurate interpretation of the available data.

First, Grady and colleagues postulated that the higher levels of protein C seen with the use of estrogen may be thrombogenic. However, protein C is a natural anticoagulant; it is actually reductions in protein C levels that are associated with an increased risk for thrombosis. Furthermore, the effects of combined HRT with estrogen and progestin on coagulation factors are most relevant to HERS. Of note, in the same study that found higher levels of protein C with the use of estrogen, no effect on protein C levels was evident in current users of estrogen and progestin (2).

Second, Grady and colleagues speculated that an effect of estrogen to increase factor VII levels may have thrombogenic effects. Indeed, evidence suggests that conjugated equine estrogen increases factor VII coagulation activity (3). However, once again it is the effect of combined HRT on factor VII that is more relevant. Most studies of conjugated equine estrogen and medroxyprogesterone acetate that have examined this question have found no change in factor VII coagulation activity (2–4). The above findings suggest that medroxyprogesterone acetate may suppress or negate the effect of conjugated equine estrogen on factor VII.

While the prothrombotic effects of combined HRT may not occur by way of factor VII or protein C, evidence indicates that combined HRT can activate coagulation processes, resulting in increased production of thrombin and fibrin (5). More study is required to determine the mechanisms underlying such increases.

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References

1. Grady D, Wenger NK, Herrington D, Khan S, Furberg C, Hunninghake D, et al. Postmenopausal hormone therapy increases risk for venous thromboembolic disease.

The Heart and Estrogen/progestin Replacement Study. *Ann Intern Med.* 2000;132:689-96. [PMID: 0010787361]

2. Nabulsi AA, Folsom AR, White A, Patsch W, Heiss G, Wu KK, et al. Association of hormone-replacement therapy with various cardiovascular risk factors in postmenopausal women. The Atherosclerosis Risk in Communities Study Investigators. *N Engl J Med.* 1993;328:1069-75. [PMID: 0008384316]

3. Lobo RA, Pickar JH, Wild RA, Walsh B, Hirvonen E. Metabolic impact of adding medroxyprogesterone acetate to conjugated estrogen therapy in postmenopausal women. The Menopause Study Group. *Obstet Gynecol.* 1994;84:987-95. [PMID: 0007970483]

4. Nozaki M, Ogata R, Koera K, Hashimoto K, Nakano H. Changes in coagulation factors and fibrinolytic components of postmenopausal women receiving continuous hormone replacement therapy. *Climacteric.* 1999;2:124-30.

5. Teede HJ, McGrath BP, Smolich JJ, Malan E, Kotsopoulos D, Liang YL, et al. Postmenopausal hormone replacement therapy increases coagulation activity and fibrinolysis. *Arterioscler Thromb Vasc Biol.* 2000;20:1404-9. [PMID: 0010807761]

TO THE EDITOR: Grady and colleagues (1) reported that in HERS, the increased risk for venous thrombosis and pulmonary embolism in women with coronary disease given postmenopausal estrogen/progestin HRT was substantially reduced by aspirin use. In this population, not surprisingly, the authors also noted that having cancer was independently associated with having a thromboembolic event.

Also recently, the Pulmonary Embolism Prevention trial, a meta-analysis of 17 444 patients undergoing orthopedic surgery who were randomly assigned to receive 160 mg of aspirin daily or placebo, reported that aspirin was associated with a 36% reduction in thromboembolic events but a 58% reduction in fatal pulmonary emboli (2).

In our experience, concerns about pulmonary embolism, venous thrombosis, and stroke are major reasons why women with breast cancer decline to receive tamoxifen therapy. The same concerns are voiced by clinicians and patients with regard to breast cancer chemoprevention with tamoxifen (3, 4) or enrollment in the Study of Tamoxifen and Raloxifene (STAR) for women at high risk for breast cancer.

There is an urgent need to know whether aspirin given with tamoxifen or raloxifene prevents thromboembolism. In the absence of a controlled study, many clinicians are recommending it, and many women are using it.

The participants in STAR are menopausal but otherwise are generally at low risk for thromboembolism. It would be helpful to factor in their aspirin use habits when assessing their outcome. A subset of women in STAR who are at higher risk for thromboembo-

lism (those who are >60 years of age, are black, have impaired mobility, or have coronary disease) might benefit from participating in a randomized trial of aspirin. Separately, a trial of aspirin could be offered to women with the above risk factors who have invasive breast cancer and require tamoxifen therapy.

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References

1. Grady D, Wenger NK, Herrington D, Khan S, Furberg C, Hunninghake D, et al. Postmenopausal hormone therapy increases risk for venous thromboembolic disease. The Heart and Estrogen/progestin Replacement Study. *Ann Intern Med.* 2000;132:689-96. [PMID: 0010787361]
2. Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial. *Lancet.* 2000;355:1295-302. [PMID: 0010776741]
3. Fisher B, Costantino JP, Wickerham DL, Redmond CK, Kavanah M, Cronin WM, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Natl Cancer Inst.* 1998;90:1371-88. [PMID: 0009747868]
4. Gail MH, Costantino JP, Bryant J, Croyle R, Freedman L, Helzlsouer K, et al. Weighing the risks and benefits of tamoxifen treatment for preventing breast cancer. *J Natl Cancer Inst.* 1999;91:1829-46. [PMID: 0010547390]

TO THE EDITOR: Grady and colleagues' interesting report (1) from HERS demonstrated that postmenopausal estrogen and progestin therapy increased the risk for venous thromboembolism nearly three-fold in women with established coronary heart disease. Unexpectedly, the risk for venous thromboembolism was decreased by half in the women who were taking statin drugs.

In the original HERS report (2), treatment with estrogen and progestin over a 4.1-year period did not reduce the overall rate of coronary heart disease events despite a favorable effect on lipoproteins. In fact, event rates were significantly higher during the first year in the estrogen-progestin group. This suggests an initial increase in the rate of arterial thromboembolism in that group.

Perhaps the authors have data on whether women taking statin drugs during HERS had a decrease in coronary heart disease events over the 4.1 years. Did statins prevent the increase in coronary heart disease events during the first year of the trial in women taking estrogens and progestins? It is plausible that statins decreased both arterial and venous thromboembolic events in HERS because of their pleiotropic effects on platelet function (3). If so, the combination of statins and estrogens in postmenopausal women with coronary heart

disease may be particularly beneficial in decreasing subsequent coronary events. However, this remains to be proven by prospective trials.

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References

1. Grady D, Wenger NK, Herrington D, Khan S, Furberg C, Hunninghake D, et al. Postmenopausal hormone therapy increases risk for venous thromboembolic disease. The Heart and Estrogen/progestin Replacement Study. *Ann Intern Med.* 2000;132:689-96. [PMID: 0010787361]
2. Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. *JAMA.* 1998;280:605-13. [PMID: 0009718051]
3. Rosenson RS, Tangney CC. Antiatherothrombotic properties of statins: implications for cardiovascular event reduction. *JAMA.* 1998;279:1643-50. [PMID: 0009613915]

IN RESPONSE: We thank Drs. Peverill, Waitkevicz and Axelrod, and Goldstein for their comments on our manuscript.

We found an error in the manuscript after publication. Rates of venous thromboembolic events in the first 90 days after lower-extremity fracture and myocardial infarction were mislabeled as numbers of events per 100 women. In fact, the cited values were rates per 100 woman-years. Since the at-risk period was only 90 days or 0.25 year, the number of events per 100 women in the first 90 days after lower-extremity fracture is 23 (the rate per 100 woman-years cited in our paper) \times 0.25 = 5.8 venous thromboembolic events per 100 women in the first 90 days after fracture. A similar mistake was made in reporting the number of events per 100 women in the first 90 days after myocardial infarction; the correct number is 2.5 venous thromboembolic events per 100 women. We regret our error.

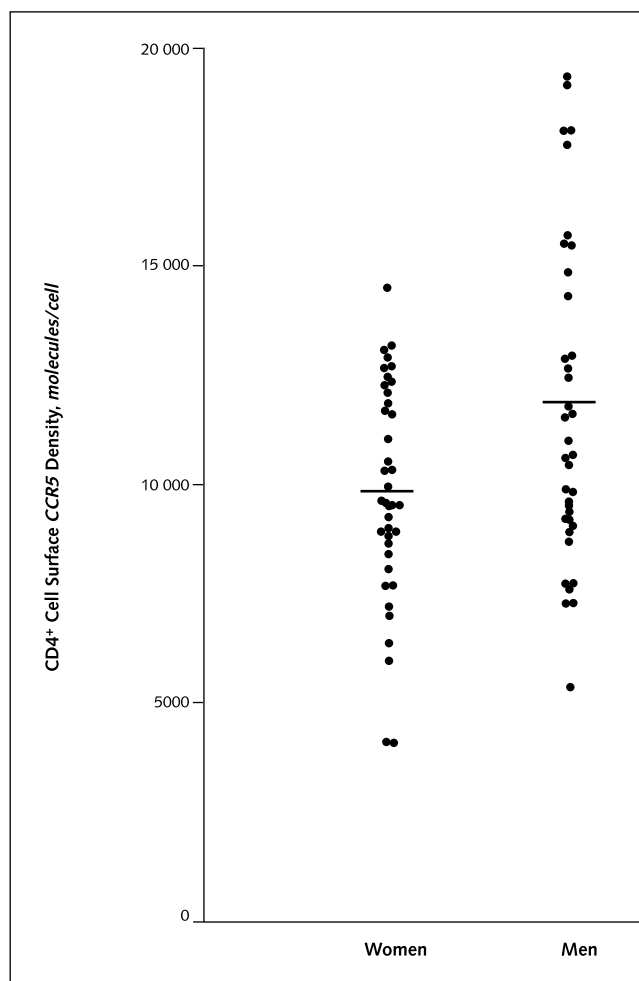
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Sex Differences in HIV-1 Viral Load Due to Sex Difference in CCR5 Expression

TO THE EDITOR: Farzadegan and colleagues recently reported a sex difference in serum HIV-1 RNA levels (1). Their results corroborate previous studies showing that mean viral loads are about 50% lower in women than in men. The reason for this difference remains unclear.

Membrane density in the main co-receptor CCR5 determines the in vitro infectability of a target cell by an HIV-1 R5 strain (2).

Figure. *CCR5* density in peripheral blood CD4⁺ cells from age-matched (19 to 49 years of age) healthy women (*n* = 39) and men (*n* = 37).



CCR5 density was calculated by converting fluorescein isothiocyanate mean fluorescence intensity (measured by flow cytometry) at the surface of CD4⁺ cells that had been indirectly labeled with the anti-*CCR5* monoclonal antibody 2D7 (PharMingen, San Diego, California) and fluorescein isothiocyanate-conjugated anti-immunoglobulin into antibody-binding capacity using standard microbeads (Dako QIFIKIT, Glostrup, Denmark), as described elsewhere (3). Horizontal lines represent geometric means.

Accordingly, we recently showed that CD4⁺ cell surface *CCR5* density correlates with viral load in HIV-1-infected patients (3). In the same study, we also provided evidence that this density was unmodified by HIV-1 infection. Therefore, we looked for a sex difference in *CCR5* density at the surface of peripheral blood CD4⁺ cells of healthy adults that could account for the sex difference in HIV-1 viral load of infected persons.

The **Figure** shows that *CCR5* densities at the surface of CD4⁺ T cells are lower in women (geometric mean, 9981 molecules/cell [95% CI, 9141 to 10 820 molecules/cell]) than in men (geometric mean, 11 823 molecules/cell [CI, 10 587 to 13 059 molecules/cell]) (*P* = 0.01).

Low *CCR5* expression in women could be a consequence of the inhibitory effect of progesterone on *CCR5* expression (4). Knowing that the relationship between *CCR5* density and viral production is logarithmic (2, 3), the difference in *CCR5* density we observed here could account for the 1:2 ratio in viral load reported between men and women. We propose that women exhibit low HIV-1 expression because they exhibit low *CCR5* expression.

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References

1. Farzadegan H, Hoover DR, Astemborski J, Lyles CM, Margolick JB, Markham RB, et al. Sex differences in HIV-1 viral load and progression to AIDS. *Lancet*. 1998;352:1510-4. [PMID: 9820299]
2. Platt EJ, Wehrly K, Kuhmann SE, Chesebro B, Kabat D. Effects of *CCR5* and CD4 cell surface concentrations on infections by macrophagetropic isolates of human immunodeficiency virus type 1. *J Virol*. 1998;72:2855-64. [PMID: 9525605]
3. Reynes J, Portales P, Segondy M, Baillat V, Andre P, Reant B, et al. CD4⁺T cell surface *CCR5* density as a determining factor of virus load in persons infected with human immunodeficiency virus type 1. *J Infect Dis*. 2000;181:927-32. [PMID: 10720514]
4. Vassiliadou N, Tucker L, Anderson DJ. Progesterone-induced inhibition of chemokine receptor expression on peripheral blood mononuclear cells correlates with reduced HIV-1 infectability in vitro. *J Immunol*. 1999;162:7510-8. [PMID: 10358206]