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Hormone Replacement Therapy, Deep Vein Thrombosis, and Pulmonary Embolism Statement from the Women's Health Initiative Project Office

The October 12, 1996, issue of the *Lancet* contains three articles and a letter reporting that current users of postmenopausal hormone replacement therapy (HRT) may have a twofold or higher increased risk of venous thromboembolism (VTE). VTE starts as deep vein thrombosis in the legs and may lead to pulmonary embolism (a blood clot that passes from the legs to the lungs). The increased risk of VTE for HRT users is similar to that previously found for oral contraceptives (OCs) in premenopausal women. However, because the dose of estrogen in HRT is much lower than that in OCs, up to now it has been assumed that HRT regimens probably do not confer an increased risk of deep vein thrombosis or pulmonary embolism. It is difficult to know whether the new findings are sufficient to cause a reconsideration of this assumption for women with no previous history of blood clots.

The importance of these findings is uncertain. All of the reports stress that VTE is not common. The four *Lancet* studies combined report on a total of only 231 cases of VTE in postmenopausal women. In the large Nurses' Health Study there was about 1 case of pulmonary embolism per year for every 10,000 women followed, and taking HRT may have increased the risk by about half a case per 10,000 women per year. As noted by the Nurses' Health Study investigators, "The many other substantial risks and benefits of hormone use observed in epidemiological studies, including possible increases in endometrial and breast cancer and decreases in the rate of heart disease and osteoporosis, are more important factors to be considered by women choosing whether to use hormones after menopause."

The findings must be regarded as very preliminary, and need to be confirmed with definitive studies. All of the *Lancet* reports are of observational studies rather than clinical trials. VTE is not easy to diagnose unless specific tests are done. Doctors treating women on HRT may be more likely to test for (and find) VTE because of heightened awareness caused by the experience with OCs. In an observational study this will lead to a falsely low estimate of VTE in women not on HRT, which will create an impression that HRT elevates the risk of VTE. On the other hand, in a

clinical trial such as the Women's Health Initiative the diagnosis is made in the absence of knowledge of whether a patient is on HRT or an inactive placebo, and therefore this ascertainment bias is eliminated.

In the Women's Health Initiative trial of HRT 27,500 women will be randomly assigned to either HRT or placebo, and they will be followed for an average of 9 years. From the beginning the Women's Health Initiative has taken steps to safeguard the health of women who participate in the study. An independent Data and Safety Monitoring Board regularly reviews the study data and information from other studies, including data on VTE, and can recommend any changes needed to protect the safety of participants. Women with previous primary VTE (those with no antecedent cause such as trauma) and women with recent active VTE for any reason are excluded from the trial, and study drug is withdrawn in women who develop VTE during the trial.

Even the large Women's Health Initiative trial may not have sufficient numbers of VTE to examine the effect of HRT on VTE; however when combined with two other trials being done in the U.S. and Britain the numbers should be sufficient to provide a confident estimate. The Women's Health Initiative will look very carefully at VTE in conjunction with all the other possible conditions that may be influenced by HRT. When the results are published in 10 years' time, doctors will for the first time have definitive answers on heart disease, fractures, breast cancer, and many other conditions. More importantly, women will know whether the overall benefits of HRT outweigh the risks. Women who wish to join the trial can call 1-800-54WOMEN.