

Smeeth L, Cook C, Thomas S, Hall AJ, Hubbard R, Vallance P. Risk of deep vein thrombosis and pulmonary embolism after acute infection in a community setting. *Lancet*. **APRIL 1-7 2006**;367:1075-1079.

## Q Does acute infection raise the risk of venous thromboembolism?

**A** Yes. Acute urinary or respiratory tract infection is linked to a substantial but reversible increase in the risk of venous thromboembolism. The risk increased significantly in the first 2 weeks after acute infection and gradually returned to baseline over 12 months.

In this study, the incidence ratio for deep venous thrombosis (DVT) following urinary tract infection was 2.10 (95% confidence interval [CI] 1.56-2.82), and for respiratory tract infection, it was 2.86 (95% CI 2.05-3.97).

The incidence ratio for pulmonary embolism (PE) following urinary tract infection was 2.11 (95% CI 1.38-3.23). Although the risk of PE following respiratory tract infection was 11-fold higher, possible misdiagnosis of PE as a respiratory infection precluded reliable estimates of the precise risk.

### Details of the study

The study assessed the risk of a first-ever DVT or PE after acute urinary tract infection or acute systemic respiratory infection, excluding pharyngitis and coryza.

Data were from the United Kingdom's Health Improvement Network, which has complete diagnostic and prescribing information, and covered the years 1987 to 2004, or approximately 20 million person-years.

One strength was use of a self-controlled case series method, which allowed patients to serve as their own controls, thus eliminating variation among individuals in risk factors for venous thromboembolism.

Patients were observed for 12 months after an acute urinary or respiratory tract infection to determine whether a thromboembolic event had occurred. Incidence ratios and confidence intervals were calculated, and the study had adequate power at 5% significance to detect a 4-fold difference during the first 2 weeks after acute infections.

### EXPERT COMMENTARY

**G. Rodney Meeks, MD**, Winfred L. Wiser Professor of Gynecologic Surgery; Professor of Obstetrics and Gynecology; and Director of Gynecology; University of Mississippi Medical Center, Jackson

The exact mechanism of thrombosis is still unknown, and the possibility of a common pathway not linked to a specific infection is intriguing. Uncovering the mechanism could help us direct therapy to a particular biochemical process.

Virchow proposed his triad of precipitating factors 150 years ago: venous stasis, increased coagulability of the blood, and vessel wall damage.<sup>1</sup> It now seems entirely plausible that damage to the vessel wall need not be physical damage, but could include factors, such as inflammation, that affect endothelial function. As the authors noted, "Inflammation is a key determinant of endothelial function in both arteries and veins, and a link between infection and venous thrombosis via endothelial activation has been suggested." In fact, earlier studies already identified infection as a potential risk factor for venous thromboembolism.<sup>2,3</sup>

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### FAST TRACK

**Anticoagulation is most beneficial during the first 8 weeks after infection, when risk is greatest**

Thromboembolic events occur at a rate of about 0.5 cases per 1,000 person-years and cause considerable morbidity and mortality.

### How long to continue prophylaxis?

The study by Smeeth and colleagues should help ObGyns determine the level of prophylaxis appropriate for hospitalized patients. Less clear is whether thromboprophylaxis should be offered to women who have acute infections in an ambulatory setting. Although earlier studies suggested that thromboprophylaxis may be appropriate, I believe the question of whether every patient should receive preventive therapy remains unanswered.

Another unresolved issue: If prophylaxis is initiated, how long should it continue? Because the risk of a thromboembolic event does not return to baseline levels for 1 year, the duration of therapy

could be lengthy. At the same time, the risks of anticoagulation are not inconsequential and may increase with extended therapy. As the greatest risk occurs during the first 8 weeks after infection, prophylaxis is most beneficial during this time.

### Routine prophylaxis?

Given the data thus far, I do not believe therapy is warranted for every patient with an acute infection. Selective therapy may be justified.

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Stefanick ML, Anderson GL, Margolis KL, et al, for the WHI Investigators. Effects of conjugated equine estrogens on breast cancer and mammography screening in postmenopausal women with hysterectomy. *JAMA*. **APRIL 12 2006**;295:1647–1657.

Chen WY, Manson JE, Hankinson SE, et al. Unopposed estrogen therapy and the risk of invasive breast cancer. *Arch Intern Med*. **MAY 8 2006**;166:1027–1032.

## Q Does unopposed estrogen increase the risk of breast cancer?

**A** Not over the short term. Postmenopausal, hysterectomized women who use estrogen for less than 5 years do not appear to increase their risk of breast cancer—and may actually reduce it. The precise level of risk associated with longer periods of use remains unclear, but appears to be elevated.

### EXPERT COMMENTARY

**Anne McTiernan, MD, PhD**, Director of the Prevention Center, Fred Hutchinson Cancer Research Center, and Professor of Epidemiology and Medicine, University of Washington, Seattle

Although the US Food and Drug Administration requires drug treatment trials to include evidence of both benefit and risk, most clinical trials study adverse effects only over the short term, typically less than 2 years, with notable exceptions such as breast cancer adjuvant treatment trials.<sup>1</sup> The assessment of long-term effects has largely fallen to the field of pharmacoepidemiology, and the most common research tool has been the observational cohort study.

#### Details of the studies

The WHI offered a unique opportunity to determine long-term benefits and risks from the 2 most commonly prescribed hormone regimens in the United States at the time the study began.<sup>2,3</sup> In the estrogen-only arm, hysterectomized women were randomized to 0.625 mg daily of conjugated equine estrogen (CEE) or placebo, and were to be followed for 8 to 12 years to observe any major diseases that occurred, including breast cancer.

In 2004, the trial was stopped early after a mean 6.8 years of follow-up, because of a persistent elevated risk for stroke and no evidence of protection against coronary disease in the women randomized to estrogen.

**Stefanick et al.** In their closer look at WHI breast cancer data for the estrogen-only arm, Stefanick and colleagues found that women taking CEE had a nonstatistically significant 20% reduced risk of developing invasive breast cancer after a mean 7.1 years of follow-up. Examination over time did not suggest an increasing risk of breast cancer with CEE for up to 9 years of follow-up; rather, risk in CEE-treated women remained diminished, compared with placebo, throughout follow-up. Among women who had used estrogen alone for 5 or more years prior to enrollment in the WHI trial, the risk of invasive breast cancer increased nonsignificantly by 28% in CEE-treated women compared with placebo.

**Chen et al.** In their reanalysis of Nurses' Health Study data from 28,835 postmenopausal women without a uterus, Chen et al observed comparable results after 5 to 9.9 years of CEE use—ie, a nonsignificant 13% reduced risk of breast cancer. However, among women who used CEE for 15 to 19.9 years, a nonstatistically significant 19% increase in the risk of invasive breast cancer was observed, and among women who used CEE for 20 or more years, a statistically significant 41% increased risk was seen.

#### Findings agree with earlier data

These 2 studies are in accord with previous observational studies of exogenous estrogen and the risk of breast cancer.<sup>4</sup> A combined dataset representing more than 52,000 breast cancer cases and more than twice as many controls found that current or recent (past 1–4 years) use of a daily dose of unopposed CEE of 0.625 mg or less, for less than 5 years, was associated with a 23% reduced risk of breast cancer, compared with nonusers.<sup>4</sup> Use of this formulation for 5 or more years was associated with a 64% increase in risk.

### FAST TRACK

**Use of unopposed estrogen for less than 5 years does not raise the risk of breast cancer in hysterectomized women**

Similarly, the UK-based Million Women Study found that use of unopposed estrogen for less than 1 year reduced the risk for breast cancer by 19%, compared with never-users, but longer use increased risk by 25% to 37%.<sup>5</sup>

**Bottom line:**

**No heightened risk in the short term**

Women choosing to take unopposed estrogen to control menopausal symptoms do not appear to face an increased risk of breast cancer if they use it for less than 5 years. Observational studies suggest they may increase their risk of breast cancer by using estrogen for 5 or more years, but no data from clinical trials are available past 7 years of follow-up.

The lower risk of breast cancer for women using unopposed estrogen for only short periods of time, seen in both the

WHI clinical trial and the large observational studies, remains unexplained. ■

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Dr. McTiernan is a consultant to Novartis Canada, Procter & Gamble, and Zygenetics.

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