When it was conceived and designed in the early 1990s, the Women's Health Initiative (WHI) trial was anticipated to confirm a suspected reduction in cardiovascular events associated with hormone therapy, as well as reductions in the risk of fractures and colorectal cancer. The specific aims of the WHI hormone replacement trial were the following:  
☐ to test whether estrogen plus progestin reduced the incidence of coronary heart disease;  
☐ to assess whether estrogen plus progestin increased the risk of breast cancer;  
☐ to assess the effect of estrogen plus progestin on the global index (a combined measure of risk and benefit); and  
☐ to assess the effect of estrogen plus progestin on the following secondary outcomes: cerebrovascular events, cardiovascular disease, endometrial cancer, colon cancer, other cancers, hip fracture, and other fractures.

In all, 16,608 healthy women who had an intact uterus were enrolled and randomly assigned to receive either conjugated equine estrogens (CEE), 0.625 mg/d plus medroxyprogesterone acetate (MPA), 2.5 mg/d, or placebo.1 A second group of 10,739 women who had undergone a hysterectomy were randomly assigned to receive either CEE, 0.625 mg/d, or placebo; this arm of the study continues to date. The investigators succeeded in enrolling a group representative of the US population of women aged 50 to 70 years.

The enrolled patient group was composed of 84% white women and 16% women of minority ethnicity, reflecting the 19% minority segment of the United States (Figure 1). On the whole, the group was also overweight, with an average body mass index of 28.5 (weight in kilograms divided by height in meters squared), also similar to that of a cross-section of female Americans. Prior hormone use was also representative, with 26.1% reporting current or former exposure to therapeutic hormones. The outcomes of the WHI hormone replacement trial included firm end points for the assessment of cardiovascular disease, fracture, cancer, and mortality1:

☐ coronary heart disease defined as acute myocardial infarction, silent myocardial infarction, or coronary death;  
☐ stroke, defined as rapid onset of a neurologic deficit lasting more than 24 hours and supported by imaging studies;  
☐ pulmonary embolism and deep vein thrombosis required clinical symptoms and verification by diagnostic studies;  
☐ cancer confirmed by pathology reports; and

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fractures verified by radiologic reports.

Summary of outcomes of the Women's Health Initiative hormone replacement trial

Intended to be completed in 2005, the estrogen plus progestin arm of the WHI hormone replacement trial was halted on July 9, 2002, because of concerns that the treatment with hormone replacement therapy (HRT) was increasing the risks for cardiovascular disease and breast cancer out of measure with reductions in colon cancer or fractures. Overall, the study showed an unexpected 29% increase in coronary heart disease (Figure 2) and a 41% increase in stroke over all study years (Figure 3). An expected risk for venous thromboembolism roughly doubled with estrogen plus progestin (hazard ratio [HR], 2.11); this relative increased venous risk with HRT was similar for both pulmonary embolism (HR, 2.07) and deep vein thrombosis (HR, 2.13).

Although total cancer rates were not substantially different between groups (HR, 1.03), the risk for colorectal cancer was reduced 37%, but breast cancer increased 26%. Women with previous exposure to HRT showed greater increases in risk of invasive breast cancer compared with women with no prior exposure, suggesting an additive effect over the duration of exposure to HRT.

These data were formulated using strict, intention-to-treat criteria. Reanalysis of the data, including only the data of those patients who were compliant with treatment, reveals even greater effects with estrogen plus progestin: coronary events were 51% higher; strokes, 67% higher, and breast cancer, 49% higher.

As expected, the risk for fractures was reduced. Overall, fracture risk was reduced 24%, with the greatest reductions (34% each) in hip and vertebral fractures.

Responses to the Women's Health Initiative trial

The American College of Osteopathic Obstetricians and Gynecologists (ACOOG), in response to the findings of the WHI hormone replacement trial first commended the WHI investigators for their diligence and integrity in bringing critical information to practicing physi-
The ACOG believes that hormone replacement therapy remains an important treatment modality for menopausal women. The role of hormone therapy needs to be redefined in regard to duration and indications. It is important that patients not unilaterally discontinue therapy, but rather contact their health-care provider to discuss the future course of their care.

Two criticisms of the WHI hormone replacement trial have been put forth. One concerns the overall dropout rate of 40%; the second, the average age of 63 years, which is older than most women initiating hormone therapy. The American College of Obstetricians and Gynecologists (ACOG) addressed criticisms of the WHI trial in a position statement. The dropout rate, the ACOG noted, was comparable in both the group receiving estrogen plus progesterin and the group receiving placebo, and reflects the true discontinuation rate with HRT in clinical practice. In addition, there were 5500 women aged 50 to 59 years enrolled in this arm of the WHI trial, a substantial number for statistical analysis and a fair proportion of the whole. The age range is reflective of women first entering menopause.

Comment
What do these hazard ratios mean for patients? Excess risk or benefit can be evaluated as events per person-years and estimated for each particular event (Figure 4). Added together, the additional estimated risk per 10,000 person-years with estrogen plus progesterin therapy is 31 events per year (ie, myocardial infarction, stroke, breast cancer), along with a reduction of 11 events per year (ie, fracture, colon cancer) per 10,000 person-years. The global index that was developed to capture the balance of risks and benefits yielded 20 additional events per 10,000 person-years. This is a small increase in overall risk for any individual patient.

Considering that roughly 6 million American women are currently receiving the estrogen plus progesterin combination treatment, however, yields a sum of nearly 12,000 additional events per year of CHD, stroke, pulmonary embolism, and breast cancer in this population, a significant problem. It is important to keep in mind that the participants of the WHI hormone replacement trial were healthy women and that the tolerance for harm due to treatment should be almost zero.

Because of concern about risks of using estrogen and progesterin combinations, the Food and Drug Administration approved new prescribing information and patient information leaflets as well as labeling revisions. New FDA labeling includes new boxed warnings to drug products that contain estrogen plus progesterin. Changes to approved indications of these products emphasize that decisions should be individualized to balance potential risks and benefits.

References
3. Response to the Women’s Health Initiative study results by the American College of Obstetricians and Gynecologists. Letter to ACOG members; July 9, 2002.