Tips from Other Journals

Tips from Other Journals are written by the medical editors of *American Family Physician.*

The trade names of drugs listed in Tips from Other Journals are based on what is currently available and not necessarily the brand of drug that was used in the study being discussed.

Cardiac Resynchronization Therapy Reduces Mortality in Patients with Heart Failure

Background: The number of patients with congestive heart failure is growing. Cardiac resynchronization therapy has been the focus of multiple studies. It involves pacing the right and left ventricles simultaneously to improve myocardial efficiency, and it has been shown to decrease morbidity and mortality compared with medical therapy alone. Until the Resynchronization/Defibrillation for Ambulatory Heart Failure Trial, studies had not shown improved mortality rates in patients with mild to moderate heart failure treated with cardiac resynchronization therapy and an implantable defibrillator. Wells and colleagues investigated the effect of cardiac resynchronization therapy combined with optimal medical therapy or with an implantable defibrillator in patients with symptomatic heart failure or arrhythmia.

The Study: Eligible trials evaluated the effects of cardiac resynchronization therapy compared with control therapy in patients who had arrhythmia or symptomatic heart failure with a QRS interval greater than 120 milliseconds. Comparisons were made between cardiac resynchronization therapy with optimal medical therapy versus optimal medical therapy alone, and between cardiac resynchronization therapy with an implantable defibrillator versus a standard implantable defibrillator alone. Optimal medical therapy included angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta blockers, diuretics, and spironolactone (Aldactone), if indicated. The primary outcome was all-cause mortality.

The authors searched Medline, EMBASE, and the Cochrane library for randomized controlled trials from the past 30 years. The Cochrane Risk of Bias Tool was applied to screen for biases. For statistical analysis, the data were combined using the random-effects model, and treatment effect was conveyed as a relative risk. Additional analysis was performed for each New York Heart Association (NYHA) subgroup.

Results: The search results were narrowed from 3,071 studies to 12, which were the focus of the meta-analysis. Cardiac resynchronization therapy with optimal medical therapy significantly reduced mortality compared with optimal medical therapy alone (relative risk [RR] = 0.73; 95% confidence interval [CI], 0.62 to 0.85). Cardiac resynchronization therapy plus an implantable defibrillator also significantly reduced mortality when compared with an implantable defibrillator alone (RR = 0.83; 95% CI, 0.72 to 0.96). Improved mortality with the combination of cardiac resynchronization therapy and an implantable defibrillator was significant only in patients with NYHA class I or II heart failure (RR = 0.80; 95% CI, 0.67 to 0.96) and not NYHA class III or IV. The authors note that there were fewer patients with class III heart failure in the studies reviewed, which may have affected the outcomes.

Conclusion: Cardiac resynchronization therapy in combination with optimal medical therapy significantly reduced mortality in patients with heart failure, including advanced heart failure (NYHA class III and IV), which supports the 2008 guidelines from the American College of Cardiology, the American Heart Association, and the Heart Rhythm Society. Cardiac resynchronization therapy in combination with an implantable defibrillator significantly reduced mortality in patients with mildly symptomatic heart failure (NYHA class I or II).

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Source: Wells G, et al. Cardiac resynchronization therapy: a meta-analysis of randomized controlled trials. *CMAJ.* March 8, 2011;183(4):421-429.

Long-term Follow-up After the Women's Health Initiative Study

Background: The estrogen-only arm of the Women's Health Initiative study was a double-blind, placebo-controlled randomized clinical trial that tested the

preventive effects of estrogen on chronic disease states in women who had undergone hysterectomy. The study, which randomized 10,739 women to daily therapy with 0.625 mg of conjugated equine estrogen (Premarin) or placebo, was stopped one year early because of an increased risk of stroke. During the intervention phase, women in the intervention group took estrogen for a median of 5.9 years. In this planned postintervention analysis, LaCroix and colleagues followed the participants for an additional mean of 47.2 months to see if short- and long-term risks and benefits persisted after discontinuing estrogen use.

The Study: Of the surviving estrogen-only participants, 77.9 percent (n = 3,778) of the estrogen group and 78.4 percent (n = 3,867) of the placebo group consented to continue in the observation portion. Participants were encouraged to get annual mammograms, and the results were tracked. Between 3.6 and 4.7 percent of women in the estrogen group and 2.7 to 3.0 percent of the placebo group reported using estrogen during the postintervention period. The estrogen and placebo group participants were analyzed on an intention-to-treat basis, and the baseline characteristics of women who gave consent for the continued study period were similar to those of women who declined to continue participation. Main outcome measures included annualized rates of coronary heart disease (CHD), invasive breast cancer, stroke, venous thrombotic event, colorectal cancer, hip fracture, and death.

Results: The hazard ratios (HRs) for CHD, venous thrombotic events, stroke, hip fracture, and invasive breast cancer were compared between the intervention phase and the postintervention phase. The risk of overall CHD was not significantly increased for estrogen users during the intervention phase; that risk did not change in the postintervention phase (HR = 0.95 versus 0.97). The increased risk of stroke in estrogen users during the intervention disappeared in the postintervention phase (HR = 1.36 versus 0.89; $P = .05$ for the difference). Similarly, the increased risk of deep venous thrombosis or pulmonary embolism found in estrogen users was not sustained when the medication was stopped (HR = 1.32 versus 0.72; $P = .01$ for the difference).

Approximately 81 percent of women in both groups had at least one mammogram during the postintervention phase. The reduced risk of breast cancer in the estrogen group during the intervention phase (0.28 percent for estrogen group versus 0.35 percent for placebo group) was maintained in the postintervention phase (HR = 0.79 versus 0.75, respectively). A reduced risk of hip fracture in the estrogen group was not maintained in the postintervention phase (HR = 0.67 versus 1.27; $P = .01$).

When the women were stratified by age (i.e., 50 to 59, 60 to 69, and 70 to 79 years), the risk of CHD was significantly lower in women 50 to 59 years of age who received estrogen compared with placebo; however, there was no difference in the older age groups. There were no age-related risk differences for venous thrombotic events, breast cancer, or stroke. The absolute rates of events per 10,000 women over the 10.7-year follow-up showed a benefit for women 50 to 59 years of age who took estrogen. Conversely, women 70 to 79 years of age who took estrogen had worse outcomes.

Conclusion: The increased risks of stroke and venous thrombotic events among estrogen users in the Women's Health Initiative dissipated after they stopped taking estrogen. The decreased risk of breast cancer persisted.

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Source: LaCroix AZ, et al. Health outcomes after stopping conjugated equine estrogens among postmenopausal women with prior hysterectomy: a randomized controlled trial. *JAMA*. April 6, 2011;305(13):1305-1314.

EDITOR'S NOTE: This study implies that the increased risk of stroke, for which the Women's Health Initiative study was stopped prematurely, decreases quickly after discontinuing estrogen use. Similar results were found for venous thrombotic events, but the benefit of hip fracture reduction disappeared. The decreased risk of breast cancer persisted in this study. In an accompanying editorial, Jungheim and Colditz caution about balancing short-term benefits with long-term risks.[1] Although hormone therapy is no longer used to prevent chronic disease, it remains the mainstay of treatment for menopausal symptoms, especially in women who have had hysterectomy with bilateral salpingo-oophorectomy. This study helps clarify risks and benefits after stopping estrogen therapy, but the safe duration of use remains unknown. It should be noted that 68 percent of women enrolled in the Women's Health Initiative were older than 60 years, which may decrease the significance of the age-specific benefits found in women 50 to 59 years of age.

The reduced risk of breast cancer among previous hormone users in this study conflicts with results from other studies that report increased breast cancer rates among estrogen users. Although some women and physicians will decide to use estrogen despite the possible risks, the authors of this editorial encourage them to take all data into account when choosing to use short-term estrogen for menopausal symptom relief.—A.C.F.

REFERENCE

1. Jungheim ES, Colditz GA. Short-term use of unopposed estrogen: a balance of inferred risks and benefits [published correction appears in *JAMA*. 2011;305(23):2418]. *JAMA*. 2011;305(13):1354-1355. ■