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INSIDE

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Results of Raloxifene RUTH and STAR Trials

ABSTRACT & COMMENTARY

By Leon Speroff, MD, Editor

Synopsis: *Clinical trial results indicate that raloxifene has no effect on the risk of coronary heart disease and is equivalent to tamoxifen in reducing the risk of invasive breast cancer.*

Sources: RUTH Trial, www.newsroom.lilly.com; STAR Trial; www.cancer.gov/newscenter.

THE ELI LILLY COMPANY AND THE NATIONAL CANCER INSTITUTE released preliminary results from two large clinical trials involving raloxifene. The Raloxifene Use for the Heart (RUTH) study included more than 10,000 women from 26 countries, either at high risk for myocardial infarction or with known coronary heart disease. The participants were randomized to placebo or raloxifene, 60 mg daily, and followed for up to 7 years. There was no effect of raloxifene treatment on coronary heart disease events; however, there was a small increase in stroke mortality. Invasive breast cancer was a secondary end point, and there were fewer cases in the treated group compared to placebo. The women taking raloxifene had an increase in venous thromboembolic events. The numbers for breast cancer and venous thrombosis were not provided in the preliminary report.

The Study of Tamoxifen and Raloxifene (STAR) enrolled 19,747 women at increased risk of breast cancer who were randomized to treatment with either raloxifene, 60 mg daily, or tamoxifen, 20 mg daily, in more than 500 centers in the United States, Canada, and Puerto Rico. The reported results after an average treatment period of almost 4 years are listed in the Table on page 10.

The numbers of invasive breast cancers were identical in the 2 groups of women. It was estimated that these results were equivalent to about a 50% reduction (based on the previous results in the tamoxifen prevention trial),[1,2] but without a placebo arm, an accurate assessment was impossible. Raloxifene appears to achieve the same reduction as tamoxifen in invasive breast cancers with a lesser

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Table

STAR Results

	Raloxifene (9745 women)	Tamoxifen (9726 women)
Invasive breast cancer	67 cases	163 cases
Breast cancer-in-situ	81	57
Deep venous thrombosis	65	87
Pulmonary embolus	35	54
Strokes	51	53
Fractures	96	104
Cataracts	313	394
Uterine cancer	23	36

increase in venous thrombosis, and perhaps no increase in cataracts and uterine cancer. Fractures, as well as strokes and heart attacks, were equally prevalent in the two groups. "Quality of life" was said to be the same for both drugs.

COMMENTARY

The results of the RUTH trial are not surprising. The known favorable impact of raloxifene on the cholesterol-lipid profile was not robust enough to prevent coronary events. Tom Clarkson has been teaching for many years that based on his monkey model, prevention of coronary events requires a direct impact on coronary vascular endothelium, an effect that is greater than and independent of lipid effects. In a 2-year randomized trial in monkeys reported 8 years ago, raloxifene exerted no protection against coronary artery atherosclerosis despite changes in circulating lipids similar to those achieved in women.[3]

The day after the release of the preliminary data, an article highlighting the STAR results appeared on the first page of my morning paper. The newspaper article and the release from the National Cancer Institute emphasized the "superiority" of raloxifene over tamoxifen, pointing out a lesser rate of uterine cancers, cataracts, and venous thromboembolic events with raloxifene. A National Cancer Institute spokesperson said that the ability to strengthen bones is an added bonus. One of the study investigators said that raloxifene will be the new yardstick for measuring other cancer-fighting drugs.

But wait a minute, there are some problems:

1. Tamoxifen has been demonstrated to reduce the incidence of both lobular carcinoma-in-situ and ductal carcinoma-in-situ.[1,2] In the 7-year follow-up report of the tamoxifen for prevention study, the risk for breast cancer was 0.57 (CI = 0.46-0.79), a 43% reduction, not the 50% cited in the results above, and the risk for in-situ disease was 0.63 (CI = 0.45-0.89), a 37% reduction.[1] Not only did raloxifene not yield a reduction, the number of in-situ cancers with raloxifene was greater. What does this mean? If raloxifene is truly preventing breast cancer, this should produce a reduction in in-situ disease; the greater increase with raloxifene is inexplicable and disturbing.
2. The fracture rates in the hip, wrist, and spine in the STAR trial were similar in the two groups. In the 7-year follow-up report of the US breast cancer prevention trial with tamoxifen, osteoporotic fractures were reduced by 32%; compared with placebo, there were 11 fewer hip fractures, 13 fewer spinal fractures, and 9 fewer fractures of the radius.[1] However, even after 8 years of follow-up, no effect of raloxifene has been evident on non-vertebral fractures.[4] A similar fracture rate in the STAR trial with the 2 treatments must reflect the incidence of spinal fractures. Neither tamoxifen nor raloxifene can achieve the efficacy in preventing all fractures well-proven with both hor-

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Questions & Comments

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mone therapy and bisphosphonate treatment. Raloxifene's lack of effect on the risk of hip fractures makes it less advantageous than even tamoxifen for bone protection.

3. The rate of strokes was equivalent in the 2 treatment arms; the rate of stroke was increased by 42% in the tamoxifen prevention trial (coming close, but not achieving statistical significance.[1] A small increase in stroke mortality was reported in the RUTH trial. This is a serious risk for both drugs.

And there is a new player in this field, the class of drugs known as aromatase inhibitors. Aromatase inhibitors nearly completely inhibit total body production of estrogen in postmenopausal women. In clinical trials, aromatase inhibitors have been more effective and safer than tamoxifen for the treatment of estrogen-sensitive breast cancers in postmenopausal women, either for early disease or for metastatic breast cancer. The American Society of Clinical Oncology[5] and the National Comprehensive Cancer Network (www.nccn.org), based on the results of clinical trials, now make the following recommendations:

- Postmenopausal women with hormone-positive breast cancers should be treated with an aromatase inhibitor.
- Treatment options include 5 years of aromatase inhibitor treatment alone or sequential therapy with 2-3 years of tamoxifen followed by aromatase inhibitor treatment for 2-5 years.
- The optimal timing and duration of treatment have not been established.
- Aromatase inhibitors are appropriate as initial treatment for women with contraindications to tamoxifen.
- Aromatase inhibitor treatment has been associated with better response rates compared with tamoxifen in postmenopausal women with tumors overexpressing HER-2. This evidence is not strong, but should be considered.
- Women finishing 5 years of treatment with tamoxifen should consider treatment with an aromatase inhibitor (for a minimum of 2.5 years).
- There is insufficient evidence available to support the use of tamoxifen after treatment with an aromatase inhibitor.

The major problem with aromatase inhibitors has been an increase in fractures due to the profoundly low estrogen levels (nearly a 99% decrease) and the subsequent loss of bone, a risk that can probably be prevented with bisphosphonate treatment. Besides hot flushing, other side effects are arthritic complaints, reduced sexual function, and myalgia.[6] Compared with tamoxifen, there is less, if any, endometrial stimulation, less venous thromboembolism, and slightly less hot flushing.

On-going trials are comparing one aromatase inhibitor with another (with and without an inhibitor of the cyclooxygenase system), 5 years of tamoxifen alone to 5 years of aromatase inhibitors, and sequential regimens comparing tamoxifen followed by an aromatase inhibitor and vice-versa. Large trials are also assessing the value of combining aromatase inhibitor treatment with ovarian suppression in premenopausal women with breast cancer. And appropriately, trials are testing the efficacy for prevention of breast cancer.

Given the greater efficacy and safety associated with aromatase inhibitors, one can safely predict that this class of drugs will perform better in the prevention trials as well. The problem of increased fractures can be prevented with adequate calcium and vitamin D supplementation and treatment with a bisphosphonate, once a month, once every 6 months, or even only once a year.[7] It's too soon to jump on the raloxifene bandwagon. ■

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Calorie Restriction on Biomarkers of Longevity, Metabolic Adaptation, and Oxidative Stress in Overweight Individuals

ABSTRACT & COMMENTARY

By Sarah L. Berga, MD

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Dr. Berga is a consultant for Pfizer, Organon, and is involved in research for Berlex and Health Decisions, Inc.

Synopsis: *Calorie restriction in overweight humans induces metabolic changes that are associated with increased longevity in some animal models.*

Source: Heilbronn LK, et al. Effect of 6-month calorie restriction on biomarkers of longevity, metabolic adaptation, and oxidative stress in overweight individuals: a randomized controlled trial. *JAMA*. 2006;295:1539-1548.

THE AIM OF THE PRESENT STUDY WAS TO DETERMINE IF prolonged calorie restriction in humans would impact biomarkers of aging and oxidative stress. 48 men and women with a BMI between 25 and 30 kg/m2 were randomized to one of 4 arms for 6 months: control (weight maintenance diet); calorie restriction (25% calorie restriction from measured baseline energy requirements); 12.5% calorie restriction + 12.5% increase in energy expenditure by exercise); and very low-calorie diet until 15% weight reduction followed by a weight maintenance diet. Outcome variables were measured before and at 3 and 6 months into the interventions and included body composition, dehydroepiandrosterone sulfate (DHEAS), glucose, insulin, protein carbonyls, DNA damage, 24-h energy expenditure, and core body temperature. Because subjects were highly selected and well paid, adherence was high.

Associated weight changes were: controls -1.0%, calorie restriction -10.4%; calorie restriction + exercise -10.0%; and very low calorie diet -13.9%. Fasting insulin was reduced in all intervention groups while DHEAS and glucose levels were unchanged. Core body temperature was reduced in the calorie and calorie + exercise groups but not in the very low-calorie diet. The reduction in 24-h energy expenditure was greater than expected on the basis of weight loss alone. DNA damage also was reduced.

The authors conclude that calorie restriction induces metabolic changes that in animals are associated with increased longevity.

COMMENTARY

Prolonged calorie restriction increases life span in rodents and other species with shorter life spans, presumably by reducing metabolism. The very act of metabolizing food creates radical oxygen species (ROS) that are then hypothesized to wreck havoc on the intracellular environment, including DNA, leading to cell death and disease states. In this study, the investigators clearly demonstrate what has been known for some time, namely that low calorie diets induce metabolic adaptations, including reduced metabolism. Whether these metabolic changes actually confer longevity in humans is another matter and one that cannot be easily addressed using customary and conventional study designs.

Although the present study was assiduously designed and conducted, this alone does not mitigate the trouble inherent in the slippery slope of interpreting the outcome data. In this study, the induction of energy deficits and weight loss reduced insulin levels. However, in other contexts associated with increased longevity, insulin resistance is associated with lower metabolism. Thus, a simple story seems elusive. Further, in humans, long-term dietary restriction carries many potential risks, including nutrient imbalance, increased cortisol secretion, and stress reactivity. Perhaps the reconciliation rests with whether the dietary restriction results in a BMI that is lower than ideal or a reduction in BMI toward ideal. Indeed, calorie restriction that results in a BMI of less than 20 has been associated with increased mortality and morbidity, especially in women.

Long story short is that calorie restriction might well be a good thing in humans with a BMI greater than ideal. The ideal for women is a BMI between 21 and 23. The ideal for men is between 20 and 22. Once ideal weight is achieved and maintained, then further reductions have the potential to cause more harm than good. This is especially true if the goal is to preserve reproductive potential, as reproductive drive is extremely sensitive to weight reductions below ideal and to nutrient imbalance. A limitation of the present study is that stress and reproductive hormones were not assessed, but based on other studies in humans, the same dictum is likely to hold. Weight reduction below the ideal may compromise fertility and reproductive outcomes in both men and women while weight reduction toward the ideal may enhance fertility and reproductive outcomes. ■

Membrane Sweeping at Initiation of Labor Induction

ABSTRACT & COMMENTARY

By John C. Hobbins, MD

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Dr. Hobbins reports no financial relationship to this field of study.

Synopsis: *Membrane sweeping at initiation of labor induction increased the spontaneous vaginal delivery rate, reduced oxytocic drug use, shortened induction to delivery interval, and improved patient satisfaction.*

Source: Tan PC, et al. Membrane sweeping at initiation of formal labor induction: a randomized controlled trial. *Obstet Gynecol*. 2006;107:569-577.

THE MARCH ISSUE OF OBSTETRICS AND GYNECOLOGY contained an article which may have a rejuvenating effect on the sometimes controversial practice of membrane sweeping.

Tan et al randomized 264 women scheduled for induction to either have membrane swept (136) or to not have this done (128) prior to induction. If the cervix allowed the introduction of a finger, the membranes were swept once clockwise and once counter clockwise as high as possible. If the endocervix could not be entered then the cervical canal was swept. All patients were then immediately followed by induction by progesterone pessaries or amniotomy, in the latter case, if the cervix were dilated to equal or greater than 3 centimeters.

Among many end points the authors scored the patients' satisfaction with the labor process by a simple analogue system.

With sweeping, there was an impressive difference in spontaneous vaginal delivery (69 % vs 56%), shorter labors (14 vs 19 hours), need for oxytocin augmentation (46% vs 59%), and less time of oxytocin infusion (2.6 vs 4.3 hours).

Interestingly some of the above variables translated into less total pain during labor (out of a scale of 1-10, 4.0 vs 4.7). Those swept had more discomfort during (obviously) and after the sweep (4.7 vs 3.5). No statistical differences were noted in the neonatal outcomes.

COMMENTARY

Sweeping has been shown to cause release of phospholipase A and prostaglandins for as much as 6 hours. These, in turn, are instrumental in the initiation of labor, and if there is such a thing as Ferguson's reflex, the sweep may cause an endogenous release of oxytocin.[1-4]

So—why not do this on everyone? First, this study required that the patients proceeded immediately to induction after the sweep. The common practice in the United States is to send the patients home after a sweep to await initiation of spontaneous labor. Second, the study did not address maternal or neonatal sepsis, and probably would have been underpowered to evaluate neonatal infection in any case.

I bring this up because the sweep will be guaranteed to drag bacteria up into the lower uterine segment, where they can initiate their own cascade of events leading not only to labor but the consequences of their presence.

A few years back we attempted to document the accent of bacteria into the cervix during labor to validate the "insuck theory." This required putting an ultrasound opaque medium into the vagina, after which we traced the material with vaginal ultrasound. One patient was a nurse midwife who was scheduled to have her membranes swept to initiate labor. We invited her to have this done at the end of the study period so that we could see what happened to the ultrasound medium. Surprisingly, it lit up the entire lower third of the uterine cavity—far higher than the sweeping finger could be advanced. This medium could easily have represented bacterial.

I rest my case. ■

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Special Feature

Angiogenesis and the Strategic Target for Ovarian Cancer Therapy

By Robert L. Coleman, MD

Associate Professor, University of Texas; M.D. Anderson Cancer Center, Houston

Dr. Coleman is on the speaker's bureau for GlaxoSmithKline, Bristol-Myers Squibb, and Ortho Biotech.

ANGIOGENESIS IS A NECESSARY AND CRUCIAL ASPECT of physiologic homeostasis. Under normal circumstances the processes and factors regulating new blood vessel formation are tightly controlled. Activated in response to injury, ovulation, inflammation, among other stressors, the intricate balance between pro- and anti-angiogenic factors favors development of new vasculature. In the malignant state, however, angiogenesis is functionally "switched on" under the influence of specific mitogens produced by tumor cells. This becomes a key step for tumor sustenance, growth and progression. The concept has been considered for more than a century, however, the mechanisms promulgating this paradigm in cancer were only first described about 35 years ago.[1] Today, in response to ameliorate the consequences of aberrant and uncontrolled angiogenesis, a virtual explosion of new agents have been developed which are beginning to show promise particularly in the management of solid tumors.

Studies have well documented that tumor cell populations growing beyond 1-2 mm^3 in size require new blood vessel formation to enlarge and metastasize.[2] The factors initiating this process can occur as a result of genetic changes and/or tumor microenvironment perturbations such as hypoxia, stress and starvation. While mediating factors are primarily produced by cancer cells, recent discoveries have documented that stromal components also contribute to cancer growth and progression. Several mechanisms for establishment of a vascular platform have been documented including ingrowth of new vessels from established vasculature (also referred to as "sprouting"), vessel cooption (growth of tumor around established vasculature), vascular mimicry (the ability of tumors cells to form vascular-like channels) and a peripheral mechanism stemming from the recruitment of bone marrow-derived endothelial cell precursors. Each of these mechanisms fulfill the tumor's request for vital nutrients to continue growth; they also provide a pathway for metastases, as the vasculature being developed is unlike that of established vessels and is characterized by loosely fitted and arranged endothelial cells. Collectively, these new vessels are leaky and exist in tangled networks. The crowded nature of these vessels leads to the increased interstitial pressure, which can limit conventional drug delivery and distribution.

The primary trafficking agent guiding this process is vascular endothelial growth factor (VEGF), which is also known as vascular permeability factor. Practically, tumor and its associated vasculature form a "functional unit" by which VEGF and other secreted mediators of angiogenesis such as epidermal growth factor (EGF) promote growth and survival of both elements. In this manner, VEGF and EGF function in a paracrine and autocrine fashion to propagate the cancerous milieu. Recent studies have documented both cancer cells and the new vasculature, express a number of targetable antigens and receptors, which, along with the growth factors themselves, have become the recent focus of intense clinical investigation.

Ovarian cancer growth and metastases, like many other solid tumors, appear to be dependent in part on this process. Studies evaluating both tissue expression and circulating levels of VEGF in ovarian cancer patients, for example, have demonstrated this growth factor to be prognostic to overall survival.[3] This observation along with the ability to selectively target VEGF (and EGF) and their receptors has recently ushered in an era of novel therapeutics and innovative therapeutic strategies. The first specific anti-angiogenesis agent to receive FDA-approval for cancer therapy was bevacizumab—a humanized monoclonal antibody which recognizes VEGF-A isoforms. Successful registration of this agent came from the documentation of a statistically significant improvement in overall survival in colon cancer patients who received bevacizumab in combination with chemotherapy compared to those receiving chemotherapy alone.[4] This observation has also been seen in patients with lung, renal, and breast cancer with similar randomized trials now started and planned for untreated and previously treated epithelial ovarian cancer patients. However, interest in this agent for ovarian cancer management was heightened following the recent presentations of 2 open-label trials of bevacizumab in recurrent ovarian cancer patients. The first study, conducted by the Gynecologic Oncology Group, evaluated single-agent bevacizumab in women who had received up to

2 prior regimens for their disease prior to entry.[5] Among the 62 enrollees, 11 (18%) achieved a clinical response with nearly 40% being disease-free at 6 months. No severe hematologic toxicity was observed and severe non-hematologic toxicity was limited. In the second, bevacizumab was administered with very low dose (metronomic) cyclophosphamide to 29 patients with recurrent ovarian cancer.[6] Responses were observed in 8 (28%) with nearly 60% being disease free at 6 months. Hematologic and non-hematologic toxicity were similarly limited. The data from these biological therapies are impressive given the absence of cytotoxic therapy. In addition, the biological effect of these agents makes combination chemotherapy clinical trials a robust new avenue for ovarian cancer treatment.

While clinical improvement in disease burden is a recognizable reflection of efficacy, does the absence of tumor resolution imply inefficacy? This is an important outcome question to answer as many of the novel biologic therapeutics, targeting specific cellular pathways or growth factors incur cytostatic effects. Their efficacy, however, may be measured in perfusion alterations not readily discernible by conventional imaging. The concern with relying on conventional technology for establishing clinical activity is making a decision to discard a potentially important agent, which may affecting a specific target but not one critical for cancer growth. Such has been the recent focus of creative imaging and biomarker discovery specifically focused on mechanisms altered by biological therapy. For instance, as previously mentioned, the systemic secretion of VEGF will lead to recruitment of peripherally derived (bone marrow) endothelial cell precursors cells. These can be phenotypically identified in the peripheral circulation through specific cellular markers. Therapy targeted to VEGF whether it be to the molecule itself or to its receptor, can affect the peripheral conscription of these cells. In this manner, the level of the endothelial cell precursors can be a "biomarker" of local effect. The proof of principle has been reported in the preclinical and clinical setting including ovarian cancer models.[7,8] Future studies are looking at these and other tests (such as circulating cell free nucleic acids) to determine dose and target modulation in cancer treatment.

Finally, evaluating the promise of new angiogenic agents, like cytotoxic (chemotherapy) agents requires systematic clinical study. However, like the issue of imaging, "response" determination needs to be more creative and adaptive to what the agent is targeting. Traditional clinical study designs are clearly not robust enough to provide a clear signal of potential efficacy. For instance, new statistical designs incorporating simultaneous evaluation of agents with similar but different profiles that are matched to the tumor profiles in specific patients are being initiated to allow for the recruitment of more patients who will receive agents that are most likely to work for them. In addition, new adaptive designs allow for real time adjustments in randomization based on the performance of previous patients increasing the likelihood of reaching a statistical end point in the most expeditious fashion.

These are exciting times in the world of cancer therapeutics as the potential for new agents and strategies in ovarian cancer management has never been more promising. Advances in imaging, biomarker development, and statistical design are needed to keep pace with drug discovery to efficiently determine which agent or agents should be elevated to the next "standard of care." ■

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CME Questions

11. In the present study, the effects of prolonged calorie restriction include all of the following *except*:

a. reduced body temperature.
b. reduced insulin.
c. reduced DNA damage.
d. reduced longevity.
e. reduced weight.

12. The following statements are true regarding tamoxifen and raloxifene *except*:

a. both drugs have a modest favorable effect on lipids.
b. both drugs have no important clinical effects on the risk of coronary heart disease.
c. neither drug increases the risk of strokes.
d. both drugs apparently reduce the risk of invasive breast cancer.

Answers: 11 (d); 12 (c)

Readers are Invited. . .

Readers are invited to submit questions or comments on material seen in or relevant to *OB/GYN Clinical Alert*. Send your questions to: Robert Kimball, *OB/GYN Clinical Alert*, c/o American Health Consultants, P.O. Box 740059, Atlanta, GA 30374. For subscription information, you can reach the editors and customer service personnel for *OB/GYN Clinical Alert* via the internet by sending e-mail to robert.kimball@thomson.com. ■

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The objectives of *OB/GYN Clinical Alert* are:

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- To present new data concerning prenatal care and complications, as well as neonatal health; and
- To discuss the pros, cons, and cost-effectiveness of new testing procedures.

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Gastric Acid Secretion and the Absorption of Thyroxine

The absorption of thyroxine is strongly influenced by stomach acidity, according to new study. Researchers from Italy looked at 248 patients with multinodular goiter who were treated with thyroxine with a goal thyrotropin (TSH) level of 0.05 to 0.20 mU/L. Of these patients, 53 had *Helicobacter pylori* related gastritis and 60 had atrophic gastritis of the stomach. The reference group comprised 135 patients with multinodular goiter and no gastric disorders. The study also included 11 patients who were infected with *H. pylori* during the study and 10 patients who were treated with omeprazole and had no gastroesophageal reflux. Patients with *H. pylori*-related gastritis, atrophic gastritis, or both had a daily requirement of thyroxine that was 22-34% higher than the reference group. In the 11 patients who became infected with age by lower *H. pylori* during the study, thyrotropin levels increased significantly (P = 0 .002), an effect that was nearly reversed with eradication of *H. pylori*. Treatment with omeprazole also increased serum thyrotropin levels (median 1.70mU/L increase in thyrotropin; P = 0.002), requiring a 37% increase in thyroxine dose.

The authors conclude that normal gastric acid secretion is necessary for effective absorption of thyroxine, and factors that impair acid secretion including atrophic gastritis, *H. pylori* gastritis, and treatment with omeprazole require increased doses of thyroxine (*N Engl J Med*. 2006;354:1787-1795). This study has important implications, given millions of patients who take thyroxine, the frequency of *H. pylori* infections in this country, and frequency of use of OTC and prescription proton pump inhibitors.

Can Plavix Add to the Efficacy of Aspirin?

Does clopidogrel (Plavix) add to the efficacy of low aspirin in patients with vascular disease? No, according to new study published in the April 20th *New England Journal of Medicine*. CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) is a multinational study which randomized 15,603 patients with either clinically evident cardiovascular disease or multiple risk factors to receive clopidogrel (75 mg/d) plus low-dose aspirin (75-162 mg/d) or placebo plus low-dose aspirin for median of 28 months. The efficacy primary end point was a composite of myocardial infarction, stroke, or death from cardiovascular causes. The rate of this end point was 6.8% with the combined drug treatment versus 7.3% with aspirin plus placebo (P = 0.22) for the subgroup of patients with multiple risk factors, the rate of the primary end point was lower for aspirin plus placebo (5.5% aspirin plus placebo versus 6.6% aspirin plus clopidogrel; P = 0.20) and the rate of death from cardiovascular causes was also higher with clopidogrel plus aspirin vs aspirin plus placebo (3.9% versus 2.2%; P = 0.01).

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5416. E-mail: leslie.hamlin@thomson.com.

In the subgroup with clinically evident atherothrombosis, there was a slight benefit for aspirin plus clopidogrel (6.9% versus 7.9%, P = 0.46).

The authors conclude that overall, clopidogrel plus aspirin was not significantly more effective than aspirin alone in reducing the rate of myocardial infarction, stroke, or death from cardiovascular disease (*N Engl J Med*. 2006;354:1706-1717). An accompanying editorial acknowledges that there were many subgroups within CHARISMA that showed varying outcomes with clopidogrel plus aspirin, but cautions against differentiating patients along the lines used in the study. The editorialists find that "these data showed no significant benefit associated with long-term clopidogrel therapy in addition to aspirin." (*N Engl J Med*. 2006;354:1744-1746).

Prevention of Hypertension?

Prehypertension is defined as blood pressure in the range of 120 to 139 mm Hg systolic or 80 to 89 mm Hg diastolic. Since JNC-VII, there has been increased interest in prehypertension since it has been associated with excess morbidity and deaths from cardiovascular causes. A new study suggests that pharmacologic intervention in patients with prehypertension may help prevent progression to hypertension. The Trial of Preventing Hypertension (TROPHY) looked at 809 patients with prehypertension. A total of 409 patients were randomly assigned to candesartan or placebo for 2 years, followed by 2 years of placebo for both groups. When a study participant reached the study end point of stage I hypertension, they were treated with antihypertensive agents.

Both treatment and placebo groups were instructed in lifestyle changes to reduce blood pressure throughout the trial. During the first 2 years, hypertension developed in 154 participants in the placebo group and 53 in a candesartan group ($P < 0.001$). After 4 years, hypertension had developed in 240 participants in the placebo group and 208 in the candesartan group (relative risk reduction 15.6%; $P < 0.007$). Serious adverse events were slightly higher in the placebo group.

The authors conclude that treatment of prehypertension with candesartan was well-tolerated and reduced the risk of incident hypertension during the study period (*N Engl J Med*. 2006;354:1685-1697). In an accompanying editorial, it is pointed out the prehypertension is present in the about 70 million Americans, and is estimated to decrease average life expectancy by as much as 5 years. Despite this, the author urges caution in recommending wholesale treatment of all patients with prehypertension until more information is available on which drugs are most effective and the best duration of therapy. In the meantime, lifestyle changes, which benefit all risk factors, should be recommended for all patients with prehypertension (*N Engl J Med*. 2006;354:1742-1744).

Estrogen Alternatives

Since publication of the Women's Health Initiative (WHI), many postmenopausal women have discontinued estrogen, and most newly menopausal women are considering alternatives. A recently published paper systematically reviews clinical trials of nonhormonal treatments for hot flashes. More than 4000 studies were considered. Forty-three trials met inclusion criteria, including 10 trials of antidepressants, 10 trials of clonidine, 6 trials of other medications, and 17 trials of isoflavone extracts. In the antidepressant group, both selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) were effective in decreasing the daily number of hot flashes compared to placebo (mean difference -1.13; 95% CI, -1.70 to -0.57). Clonidine was also somewhat effective (-0.95; 95% CI, -1.44 to - 0.47), as was gabapentin (-2.05; 95% CI, -2.80 to -1.30). Red clover isoflavone extracts were not effective, and mixed soy isoflavones had mixed results. The authors conclude that SSRIs, SNRIs, clonidine, and gabapentin provide evidence for some efficacy; however, none are as effective as estrogen (*JAMA*. 2006;295:2057-2071).

FDA Actions

In April, the FDA issued a statement rejecting the medical use of marijuana, citing past evaluations by several US government agencies that showed that "no animal or human data supported the safety or efficacy of marijuana for general medical use." The statement supports the Drug Enforcement Agency's approach to treating all use of marijuana as a criminal act.

Zanamivir (Relenza), GlaxoSmithKline's inhaled anti-influenza drug has received a new indication for prophylaxis of influenza in patients age 5 years and older. The approval was based on 4 large-scale, placebo-controlled trials which showed that the drug was effective in reducing spread of influenza among household members and in community outbreaks. ■