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INSIDE

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USPSTF Mammography Recommendations: Seeing Through the Screen

ABSTRACT & COMMENTARY

By Jeffrey T. Jensen, MD, MPH, Editor

Synopsis: *U.S. Preventive Services Task Force (USPSTF) issued a revised statement recommending against routine screening mammograms in women 40-49 years of age and against teaching self-breast exam skills.*

Source: Screening for breast cancer: U.S. Preventive Services Task Force Recommendation Statement. *Ann Intern Med* 2009;151:716-726.

BASED ON RESULTS OF TWO SYSTEMATIC EVIDENCE REVIEWS, THE USPSTF issued a revised statement regarding recommendations for breast cancer screening. The USPSTF recommends against routine screening mammography in women age 40-49 years, concluding that the risk of harm attributable to screening exceeds the potential benefit for low-risk women. Mammography for women age 50-74 years is recommended, but only every 2 years, and the USPSTF concluded that the evidence of additional benefits and harms of screening mammography in women 75 years or older was inconclusive. The Task Force found the evidence insufficient to recommend clinical breast examination in women age 40 years and older that undergo mammography, and determined that teaching breast self-examination (SBE) was harmful.

COMMENTARY

The Nov. 17, 2009, release of the USPSTF revised recommendations on breast cancer screening made front page news, and left women's health professional groups and patient advocacy groups stunned. The most obvious departure from the group's last recommendations issued in 2002 was to advise against routine mammograms for women younger than age 50. Considering the massive efforts made to teach self-breast exam and encourage mammogram screening of women older than age 40, the recommendations were as surprising as those from the Women's Health Initiative (WHI)

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study. Like the WHI, the recommendations are based on the concept of balancing risk and benefit. Unlike the WHI, which presented new data from a large scale randomized controlled trial, the recommendations of the USPSTF represent a consensus report based upon a systematic review of the literature that sought to balance the potential benefits of screening mammography with risk and harm. The data showing that screening women younger than age 50 with mammograms, or of performing SBE at any age, was much more likely to result in additional testing and biopsy for benign disease than breast cancer led to the conclusion that women were more likely to be harmed than helped by screening. Interpretation of this information for patients requires a discussion of the consequences of under-diagnosis (death due to progression of a potentially treatable early cancer) and over-diagnosis (emotional, financial, and physical costs due to additional diagnostic procedures for benign breast changes or cancers that would never progress). Most of my patients accept the burden of screening to avoid this serious disease.

The absolute incidence rate of breast cancer climbs with age, rising from 58.8/100,000 in women age 35-39 years to 115.9/100,000 in women age 40-45 years, and 215.6/100,000 at age 50-55 years. To be effective, screening programs need to be targeted to a disease that is serious and prevalent, and the test must detect the presence of disease at an early stage that renders it treatable. Breast cancer is undeniably a serious and prevalent condition, and 95% of cases and 97% of deaths occur in women age 40 and older.[1] More than 10% of all breast cancer deaths occur in women in their 40s.[2]

An ideal screening test would capture all with disease but exclude all that are well. In practice, the price of increasing sensitivity (detecting all true-positives) is lack of specificity (more false-positives). The predictive power of a positive (or negative) test is influenced by the underlying prevalence of disease; as disease prevalence increases so does the predictive power of a positive (or negative) test. Since about 10% of mammograms require additional evaluation, a large number of biopsies must be done to detect a single case of cancer. While this involves costs to the health care system and stress and anxiety to the affected individual, the overall benefit of mammography is worthwhile, and compares favorably to the cost and benefits of Pap smear screening for cervical cancer. Fine needle aspiration can reduce the need for open biopsy.[3] Ultrasound,[4] digital mammography,[5] and MRI[6] increase the sensitivity of detection, but greatly increase the number of false-positive screens. Therefore, combination screening is only recommended for very high-risk women (defined as a combination of factors that produces a 3-fold increase in risk), especially those women with dense breasts.

Do women in their 40s benefit enough from mammography to justify screening? The American Breast Cancer Detection Demonstration Project demonstrated that screening was just as effective for women in their 40s as in women older than age 50.[7] Meta-analyses of randomized clinical trials concluded that in women age 40-49 offered mammography screening, there was about a 20% reduction in breast cancer mortality.[8-10] Once detected by mammography, the stage of disease and survival expectations are the same comparing women age 40-49 with women older than age 50.[11] However, breast cancer tends to grow faster in younger women, and cancers that are detected between screenings have lower survival rates (at all ages).[12] Because the randomized clinical trials have screened younger women at 2-year or longer intervals, it is not surprising that screening has been less effective for these faster growing tumors. Rather than concluding (as the USPSTF did) that routine screening in the 40s is not effective, the basic biology of breast cancer would provide a sound argument that women age 40-49 should have annual screening mammography. A randomized trial in the United Kingdom of annual mammographic screening beginning at age 40 indicated a 24% reduction in breast cancer mortality in the screened women.[13] As the proportion of women screened with mammography has increased,

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Questions & Comments
Call **Paula Cousins**, Senior Managing Editor, at (404) 262-5468.

Table

Comparison of different mammogram screening strategies[15]

	Average Screenings Per 1000 Women	Potential Benefits/Harms† (vs No Screening)		
		Cancer Deaths Averted Per 1000 Women	Life-Years Gained Per 1000 Women	Unnecessary Biopsies Per 1000 Women
Different starting ages				
Biennial screening				
40-69 years	13,865	6.1	120§	85
50-69 years	8944	5.4	99	55
Annual screening				
40-69 years	27,583	8.3	164§	158
50-69 years	17,759	7.3	132§	95
Different stopping ages				
Biennial screening				
50-74 years	11,109	7.5	121	66
50-84 years	13,836	9.6	138	79
Annual screening				
50-74 years	21,357	9.5	156§	110
50-84 years	26,913	12.2	178	132

Note: Results are from model S (Stanford University). Model S was chosen as an exemplar model to summarize the balance of benefits and harms associated with screening 1000 women under a particular screening strategy.

† Over-diagnosis is another significant harm associated with screening. However, given the uncertainty in the knowledge base about ductal carcinoma and small invasive tumors, absolute estimates were not felt to be reliable. In general, over-diagnosis increases with age across all age groups but increases more sharply for women who are screened in their 70s and 80s.

§ Strategy is dominated by other strategies; the strategy that dominates may not be in this table.

the death rate from breast cancer in the United States has declined 3.2% in women younger than age 50 compared with only 2% in women older than age 50.[2] This decline in breast cancer mortality has been attributed to both improvements in breast cancer treatment and early detection.

The USPSTF recommendation against both clinical and self-breast examinations stems from the large number of follow-up imaging procedures and biopsies that occur in response to palpated masses. As discussed above, since the prevalence of cancer is low in young low-risk women, the chance of a breast cancer diagnosis is low with a biopsy for a palpable mass. However, the recommendations against breast self-exam come from randomized studies from Russia and China in women not receiving mammography that showed an increase in breast cancer detection with the introduction of SBE, but no difference in overall mortality. I find it hard to draw conclusions from these studies about the role of SBE in our population.[14] While I agree that clinical breast exam is unlikely to provide the same level of benefit in mortality reduction as mammography (palpated lesions are more likely to have metastasized), SBE in women younger than age 40 represents the only strategy to pick up fast growing tumors.

The consensus panel recommendations are based in part upon a model of screening strategies performed by Mandelblatt et al and reported in the same issue of the *Annals of Internal Medicine*.[15] Summary information from this publication *(see Table, above)* provides data that you can use to discuss these findings with patients considering screening. For example, annual mammograms starting at age 40 instead of age 50 and continued to age 69 will prevent 1 additional cancer death (8.3 vs 7.3) for every 1000 women screened at the expense of 63 unnecessary biopsies. You and she can decide if 10 additional years of mammogram screening and a 6% chance of getting a biopsy are worth the 0.1% chance of avoiding cancer mortality. There will be 70 fewer biopsies in 1000 women age 40-69 that get mammograms every other year compared to annually, but 2 additional women will die from breast cancer. In contrast, continuing annual

mammograms until age 84 (compared to stopping screening at 74) will prevent 3 additional breast cancer deaths at the expense of only 22 unnecessary biopsies.[15]

The American Cancer Society and American College of Obstetricians and Gynecologists (ACOG) have not changed their recommendations for breast cancer screening in response to the USPSTF report. ACOG maintains its current advice that women in their 40s continue mammography screening every 1-2 years and women age 50 or older continue annual screening. In my practice, we recommend that women begin SBE monthly in the follicular phase (right after menstruation) and have annual clinical breast examination starting by age 35. Women with a first-degree relative with premenopausal breast cancer should begin annual mammography 5 years before the age of the relative when diagnosed. All other women should receive annual mammograms starting at age 40. Since the prevalence of breast cancer increases with age, the decision to stop routine mammogram screening should be based upon factors that include general health and life expectancy. Ultrasound should be added to screening for women with dense breasts, particularly those on HRT. Depending on local availability, MRI should be considered for evaluation of women at very high risk for breast cancer, especially younger women with dense breasts.

Are the risks and benefits of screening for breast cancer worth it? Ask your patients. ■

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Intravenous Nitroglycerin for External Cephalic Version

ABSTRACT & COMMENTARY

By John C. Hobbins, MD

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University of Colorado Health Sciences Center, Denver

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

Synopsis: *A study showing some benefit of uterine relaxation with IV nitroglycerin in external version exemplifies, along with other studies, how many patients with breech presentations today can avoid the need for Cesarean section.*

Source: Hilton J, et al. Intravenous nitroglycerin for an external cephalic version. *Obstet Gynecol* 2009;114:560-567.

THREE TO 5% OF PATIENTS AT TERM WILL HAVE BREECH presentations, and in most countries 90% of these patients will be delivered by Cesarean section. With a Cesarean section rate in the United States > 30%, there has been some effort to circumvent the need for Cesarean section in patients motivated to have a vaginal delivery by attempting, in a variety of ways, external version (EV).

Hilton et al conducted a randomized clinical trial in which IV nitroglycerin was used to relax the uterus during EV. One hundred twenty women with breech presentations were recruited for the study — 82 were nulliparas and 44 were multiparas. About half in each group received 100 µg of nitroglycerin in 10 mL of diluent. The other half received saline. If the version was unsuccessful due to inadequate relaxation, a second dose was administered after 30 minutes and the EV was reattempted.

In nulliparas, the success rate was 24% with nitroglycerin vs 8% in the placebo group ($P = 0.04$), and in the multiparas, the difference was not statistically significant between treated and control groups (44% vs 43%), but there was a reasonable success rate of version alone. Side effects were minimal and, surprisingly, hypotension occurred as frequently in the placebo group as in the treatment group. Nine patients in this study described pain during the procedure as being "intolerable," resulting in the procedure being abandoned.

■ COMMENTARY

In 2000, the Hannah et al randomized trial, suggesting a higher rate of perinatal morbidity and mortality in breech fetuses delivered vaginally compared with Cesarean section,[1] put a nail in the coffin of vaginal delivery for breeches. A cost-analysis from 1993 showed that breeches were responsible for 15% of our Cesarean sections and they ate up $1.4 billion annually in health care dollars (obviously an under-estimate when considering 2009 figures). Also, importantly, some patients today are highly motivated to try anything to avoid Cesarean section.

The literature is filled with small studies involving various methods to convert a breech to a vertex, and some are more elaborate than others. The above study seems to show that nitroglycerin works reasonably well as an adjunct in converting breeches in the most difficult patient category — nulliparas. However, it does not seem to add anything in multiparas, in whom EV worked in about half of patients without the need for other help. Although many clinicians use medications such as terbutaline, ritodrine, and nifedipine for the same effect, it does seem likely that nitroglycerin would provide the ultimate short-acting uterine relaxation (to which any clinician who has used it to deliver a second twin can attest). Nevertheless, there appears to be more to version than uterine relaxation, such as operator experience and lowering maternal pain and anxiety. Here the literature provides conflicting results regarding the use of epidural or spinal anesthesia. One study showed no benefit from spinal anesthesia (49% vs 51%),[2] while another study did show benefit (67% vs 32%),[3] compared with controls. In yet another interesting paper, Rozenberg et al first tried converting 169 breeches at 36-37 weeks using a beta-mimetic (salbutamol) as a uterine relaxant.[4] They were successful in 56.8%. They then enrolled 68 of the remaining 73 patients to have epidural anesthesia. Seventy-two percent of these patients were nulliparas. In 27 patients (39%) the investigators were successful, with a combined success rate of 68% in multiparas and 28.6% in nulliparas.

Finally, "alternative" methods have also yielded modest success with far less fanfare, risk, and cost. For example, there have been a few studies showing some success with acupuncture. One such study worth mentioning involved a randomized trial by Neri et al, billed as the first study of its kind in a "Western" pregnant population (Italy).[5] Two hundred twenty-six women with breeches between 33 and 35 weeks had a combination of acupuncture and moxibustion applied to a specific acupoint (BL67). At delivery, 53.6% of the treated group of 112 patients showed up with vertex presentations vs 36.7% of the 114 patient controls ($P = 0.01$).

So, today there are some options open to those patients with breeches wishing preemptive measures to avoid Cesarean section. The first would be the seemingly innocuous acupuncture approach at 33-35 weeks. The next would be to attempt a version with a uterine relaxant such as nitroglycerin at 37 weeks, and then, if unsuccessful, to try again using spinal or epidural anesthesia. Another last ditch idea (on which I could find little information) would be to try to convert breeches at term under epidural anesthesia (with the usual anesthetic level of T5) before doing a cesarean section, and to let the level drop if the version is successful, followed by induction. Although this would require some fine tuning in timing, it might be successful, and only one anesthesia would be needed.

As to the technique, the most important first step is to gently dislodge the breech from the pelvis and then to guide the head downward only after the first step has been accomplished. It does not seem to matter whether the pathway involves a forward roll or a backward roll.

Ultrasound should be used to track progress and to observe fetal heart rate changes. Also, versions probably should not be attempted if there is a cord around the neck. Anterior placentas are not a contraindication to EV, but in Rh-negative patients it would be useful to do a post-version Kleihauer-Betke calculation of fetal cells in the maternal circulation to determine if a larger dose of anti-immunoglobulin would be needed. ■

References

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Update on Adhesions and Gynecologic Surgery

ABSTRACT & COMMENTARY

By Frank W. Ling, MD

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

Synopsis: *Some surgical barriers have been shown to reduce adhesions, but there are not substantial data to say that they reduce pain, improve fertility, or reduce the incidence of subsequent bowel obstruction.*

Source: Practice Committee of American Society of Reproductive Medicine in association with the Society of Reproductive Surgeons. Pathogenesis, consequences, and control of peritoneal adhesions in gynecologic surgery *Fertil Steril* 2008;90(5 Suppl):S144-S149.

THIS STATEMENT FROM THE PRACTICE COMMITTEE OF the American Society for Reproductive Medicine provides an update to what is known about pelvic adhesions and gynecologic surgery. It goes on to say that the use of some barriers, while effective in reducing postoperative adhesions, has not been shown to improve patient outcomes as related to fertility, pain, or bowel obstruction. In a brief yet complete review of the subject, topics such as the epidemiology and impact of postoperative adhesions, pathogenesis, and consequences are examined. Reduction of adhesion formation is also completely explored, covering surgical technique, anti-inflammatory agents, peritoneal instillates, and surgical barriers. The final summary and recommendations include:

1. Postoperative adhesions occur as a natural process after surgical trauma and healing;
2. Adhesions may result in infertility, pain, and bowel obstruction;
3. Reduction in adhesions may be achieved with microsurgical principles, minimally invasive surgery, and some peritoneal instillates;
4. There are no data to support the use of anti-inflammatory agents:
5. Surgical barriers may reduce adhesions, but that doesn't necessarily translate into better fertility, less pain, or less risk of obstruction.

■ COMMENTARY

This should be required reading for all practitioners of gynecologic surgery, including all residents in training. It provides a very digestible overview of what is known about adhesions and, more importantly, provides clinicians with what they need to know, i.e., the bottom line. The collaboration between the ASRM Practice Committee and the Society of Reproductive Surgeons is the appropriate group to know the breadth of the literature while culling out what is and isn't relevant to the practice of gynecologic surgery.

The implications for patient care are obvious. For example, the preoperative counseling and surgical approach must bear in mind that approximately one-third of patients who undergo open or pelvic surgery are readmitted on average twice during the 10 years following surgery for problems directly related or potentially related to adhesions. More than 1 of 5 admissions occurs within the first year following surgery. Not surprisingly, ovarian surgery had the highest incidence of readmission. These sobering data will hopefully create an air of caution when a patient is given informed consent about major gynecologic surgery, i.e., the first surgical procedure may well lead to others. Reading this article can

also help the surgeon inform the patient in a more complete fashion regarding the benefit, or lack thereof, of surgery when lysis of adhesions is being considered.

Similarly, the surgeon and patient should review the possible surgical approaches since minimally invasive procedures may well provide better long-term outcomes. Of note, it is not the surgical approach that is the key, but the extent of tissue damage at the time of surgery. If the surgeon is rough with tissue at the time of laparoscopy, it may well be that adhesions are as bad or even worse than those resulting from an open procedure if the surgeon handles tissue gently. Intra-operative surgical decision making is a major focus of the findings reported here. Listed under "microsurgical principles" are techniques that we all do or do not adhere to as part of our macroscopic surgery. These include gentle tissue handling, removal of necrotic tissue, strict hemostasis, reduction of ischemia and desiccation, prevention of foreign body reaction, reduction of infection, and use of nonreactive suture material. Hopefully we all think about each of these with every procedure we perform.

The report's recommendations also provide guidance regarding steroids and promethazine (no help), antibiotic solutions (don't help and may hurt), dextran and crystalloid solutions (don't help), Adept Adhesion Reduction Solution (FDA-approved to reduce adhesions in conjunction with good surgical technique), heparin (no help), Seprafilm (reduces midline adhesions, but little effect for myomectomy or bowel resection), and Interceed (helps reduce new and recurrent adhesions after laparoscopy and open procedures, but no effect on fertility). Gore-Tex Surgical Membrane reduces adhesions but requires suturing then reoperation for removal. Sepracoat and Spraygel were not approved by the FDA at the time of publication and Tissel VH is approved for cardiothoracic surgery, splenic surgery, and colostomies.

The teaching point of this Committee Opinion focuses on how we factor adhesions into our practice, both in the office as well as in the operating room. First, let's all recognize that minor surgery and good surgical technique don't totally eliminate the potential formation of adhesions. Second, knowing that adhesions are the natural result of the body healing after trauma, we must be mindful that every step we perform while the patient is under anesthesia may affect how she feels and what the course of her health may be after she leaves the operating room.

Please read the entire document. Hopefully, your response afterwards will be similar to mine. Perhaps you, too, will say to yourself, "Hmmmm, that's both interesting and helpful." ■

Anti-angiogenesis Targeting Agents in Recurrent Ovarian Cancer: Now There Are Two?

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

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Dr. Coleman is a consultant to GlaxoSmithKline, Eli Lilly Co., Abbott Laboratories, Sanofi-Aventis, and Pfizer; and serves on the speakers bureaus for GlaxoSmithKline, Eli Lilly Co., and OrthoBiotech.

Synopsis: *While true efficacy was not demonstrated, cediranib warrants further study in combination with chemotherapy due to its demonstrated response rate, shorter half-life, and toxicity profile.*

Source: Matulonis U, et al. Cediranib, an oral inhibitor of vascular endothelial growth factor receptor kinases, is an active drug in recurrent epithelial ovarian, fallopian tube, and peritoneal cancer. *J Clin Oncol* 2009;27:5601-5606.

ANGIOGENESIS IS AN IMPORTANT PROCESS, WHICH SUSTAINS ovarian cancer growth. Cediranib, a potent, oral tyrosine kinase inhibitor (TKI) of vascular endothelial growth factor receptor (VEGFR) 1, 2, and 3, and c-kit, has shown promise in other solid tumors, including non-small cell lung cancer. The current study aimed to define the response characteristics, survival, and toxicity of cediranib administered as a single agent to women with recurrent ovarian, fallopian tube, and primary peritoneal cancer. Patients eligible for this phase II open-label study included those with measurable disease and up to two prior courses of chemotherapy, although this was a modification of initial eligibility limited to elevated CA-125 and no measurable disease (n = 10 patients). Patients with prior exposure to vascular endothelial growth factor (VEGF)-targeted agents and those with uncontrolled hypertension or proteinuria were excluded from the trial. The primary endpoint was response (RECIST and GCIG criteria) and was conducted in a two-stage process with decision rules for platinum-sensitive (treatment-free interval > 6 months) and platinum-resistant disease cohorts. In all, 46 patients were enrolled. The overall response rate was 17%, with a median progression-free survival of 5.2 months. At 6 months, 17% of patients were progression-free. Mean overall survival was 16.3 months. Eleven patients were

removed from the study due to toxicity without assessment of response. This prompted a dose reduction of 33% for subsequent enrollees. Grade 3 toxicities observed were: hypertension (46%), fatigue (24%), and diarrhea (13%). Grade 2 hypothyroidism was seen in 43% of patients and one patient had a CNS hemorrhage. There were no bowel perforations. Based on the response characteristics, cediranib has significant activity in ovarian cancer and merits the planned investigation in combination with chemotherapy.

COMMENTARY

VEGF and VEGFRs are important to the growth and proliferation of many solid tumors including ovarian cancer. The first compound to demonstrate substantial single-agent activity in this disease was bevacizumab, and this observation has prompted an explosion of clinical trials of other VEGF/VEGFR-targeted agents, both alone and in combination with chemotherapy. To date, ligand (VEGF)-targeted strategies have produced higher response rates than oral TKIs to VEGFRs, but the shorter half-life of these agents and their oral administration have distinct clinical advantages. The current report brings a new agent to the clinical domain, which is a viable competitor to the VEGF-ligand-based strategies, such as bevacizumab and aflibercept. It is impressive that objective responses were observed; however, true efficacy should also consider the propensity to delay progression. In this regard, the agent appears on par with bevacizumab. The toxicity portfolio for cediranib is less well developed but appears to share a spectrum observed with other anti-VEGF agents, with the exception of hypothyroidism and bowel perforation. Nevertheless, the clinical activity of cediranib is sufficient to warrant further investigation. This is currently underway in the European Union in a phase III study of paclitaxel and carboplatin, with and without cediranib, and followed by maintenance cediranib or placebo (ICON-6). ■

CME Objectives

Upon completion of this educational activity, participants should be able to:

- Explain the latest data regarding diagnosis and treatment of various diseases affecting women;
- Discuss new data concerning prenatal care, neonatal health, and complications arising in pregnancy and the perinatal period; and
- Discuss the advantages, disadvantages, and cost-effectiveness of new testing procedures in women's health.

Additional Reading

1. Burger RA, et al. Phase II trial of bevacizumab in persistent or recurrent epithelial ovarian cancer or primary peritoneal cancer: A Gynecologic Oncology Group Study. *J Clin Oncol* 2007;25:5165-5171.
2. Cannistra SA, et al. Phase II study of bevacizumab in patients with platinum-resistant ovarian cancer or peritoneal serous cancer. *J Clin Oncol* 2007;25: 5180-5186.
3. Hennessy BT, et al. Ovarian cancer. *Lancet* 2009; 374:1371-1382.

CME Questions

36. Which of the following statements is *true* regarding EV?

a. It works best in multiparas.
b. It does not reduce health care costs.
c. It is contraindicated when anterior placentas are encountered.
d. Success can sometimes be achieved by a re-try with regional anesthesia.

37. Which of the following toxicities observed in this trial is considered unique relative to other anti-VEGF ligand agents studied in ovarian cancer?

a. Hypertension
b. Hypothyroidism
c. Fatigue
d. Proteinuria

Answers: 36. d, 37. b.

PHARMACOLOGY WATCH

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Niacin Beats Ezetimibe Head to Head

In this issue: *Statin and niacin increase HDL-C, omeprazole reduces effectiveness of clopidogrel, darbepoetin increases risk of stroke, statins decrease risk of gallstone disease, FDA Actions.*

Statin plus niacin or ezetimibe?

Raising HDL-cholesterol (HDL-C) with niacin plus a statin is superior to lowering LDL-cholesterol (LDL-C) with ezetimibe plus statin in reversing atherosclerosis according to the widely reported ARBITER trial published on-line in the *New England Journal of Medicine* in November and simultaneously reported at the American Heart Association meeting in Orlando, FL. The trial enrolled more than 200 patients with coronary heart disease or a coronary heart disease equivalent who were receiving long-term statin therapy with an LDL-C < 100 mg/dL along with an HDL-C < 50 mg/dL for men or 55 mg/dL for women. The patients were randomly assigned to receive extended-release niacin (target is 2000 mg/day) or ezetimibe (10 mg/day). The primary endpoint was the difference in change from baseline in mean and maximal carotid intima-media thickness after 14 months. The trial was terminated early in July of 2009. Both drugs were effective in their roles — the mean HDL-C in the niacin group increased by 18.4% over the 14-month study period ($P < 0.001$) and the mean LDL-C level in the ezetimibe group decreased by 19.2% ($P < 0.001$). Niacin significantly reduced LDL-C and triglycerides as well, while ezetimibe lead to a reduction in HDL-C and triglycerides. Niacin was superior to ezetimibe in reducing the primary endpoint, leading to a reduction of both mean ($P = 0.001$) and maximal carotid intima-media thickness ($P \leq 0.001$ for all comparisons). Paradoxically, greater reductions in LDL-C seen with ezetimibe were significantly associated with increases in the carotid intima-media thickness. The incidence of major cardiovascular events was also lower in the niacin group than in the ezetimibe group (1% vs 5%; $P = 0.04$ by the chi square test) (published on-line at: www.nejm.org; Nov. 15, 2009).

The study has received enormous attention not only because of the primary endpoint, but also because of the significant reduction in major adverse cardiac events in the niacin group, even though the numbers were quite small. At least one editorialist laments the early termination of the study and feels that it is impossible to make recommendations regarding the "adjuvant agent of choice" based on the small numbers (The HALTS Trial — Halting Atherosclerosis or Halted Too Early; published on-line at: www.nejm.org; Nov. 15, 2009). Still, this study provides enough evidence to consider adding niacin to a statin in patients who are at risk of or have low HDL-C. It also deals another blow to ezetimibe (Zetia®) and its partner drug ezetimibe/simvastatin (Vytorin®).

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Omeprazole's effect on clopidogrel

The FDA has issued a warning regarding the combination of clopidogrel (Plavix®) with omeprazole (Prilosec®) citing new data that suggest that the combination reduces clopidogrel's effectiveness by about half. Studies reported in 2009 suggested that omeprazole may block clopidogrel's conversion to its active metabolite via CYP2C19, an enzyme that is inhibited by omeprazole. New studies requested by the FDA from the manufacturers confirm a significant interaction between the two drugs, which can significantly hinder clopidogrel's ability to prevent platelet aggregation in patients at risk for heart disease. Omeprazole and clopidogrel are commonly prescribed together to prevent GI bleeding. At this time it is unclear whether this interaction extends to other proton pump inhibitors, although physicians are encouraged to avoid a combination of clopidogrel with esomeprazole (Nexium®, cimetidine (Tagamet®), and other drugs known to inhibit CYP2C19. The FDA is recommending that patients who need GI protection in conjunction with clopidogrel may safely use ranitidine (Zantac®), famotidine (Pepcid®), nizatidine (Axid®), or oral antacids.

Darbepoetin and risk of stroke

Darbepoetin alfa (Aranesp®) is commonly used in patients with chronic kidney disease and diabetes for the treatment of anemia. A new study suggests that the drug may be associated with increased risk of stroke in this patient population. More than 4000 patients with diabetes, chronic kidney disease, and anemia were randomly assigned to darbepoetin alfa to achieve a hemoglobin level of 13 g/dL or placebo with rescue darbepoetin alfa if hemoglobin levels dropped < 9 g/dL. The primary endpoints were the composite outcomes of death or cardiovascular event, and death or end-stage renal disease. After a follow up of 2.5 years, darbepoetin alfa was ineffective at preventing either primary outcome, and, more importantly, the rate of fatal or nonfatal stroke occurred almost twice as often in the treatment group (101 patients assigned to darbepoetin alfa vs 53 patients assigned to placebo; HR, 1.92; 95% confidence interval, 1.38-2.68; $P < 0.001$). The authors conclude that the use of darbepoetin alfa in patients with diabetes, chronic kidney disease, and moderate anemia who are not undergoing dialysis did not reduce the outcome of death, cardiovascular events, or renal events, but was associated with increased risk of stroke. For many "this risk will outweigh the potential benefits" of the drug (*N Engl J Med* 2009;361:2019-2032). Erythropoiesis-stimulating agents have come under fire in the treatment of cancer-associated anemia, and now in renal patients as well. As pointed out in an accompanying editorial, the risks and benefits of these agents must be weighed, namely an increased risk of stroke vs a perceived improvement in quality of life (*N Engl J Med* 2009; 361:2089-2090).

Statins and gallstone disease

Statins have been shown to reduce the risk of cardiovascular disease and death from all causes. Now another potential benefit is being reported: Statins may reduce gallstone disease. Utilizing a large patient database from the United Kingdom, researchers looked at the risk of developing gallstones followed by cholecystectomy in relation to exposure to lipid-lowering agents. The longer patients took statins, the lower the risk for gallstone disease, with patients who had filled 20 or more prescriptions noticing 36% reduction in risk (AOR, 0.64; 95% confidence interval, 0.59-0.70). The authors conclude that long-term use of statins is associated with a decrease risk of gallstones followed by cholecystectomy (*JAMA* 2009;302:2001-2007).

FDA Actions

The FDA has approved a new topical treatment for the treatment of post-herpetic neuralgia (PHN). The capsaicin 8% patch must be applied to the skin by a health care professional since placement may be quite painful, requiring the use of a local topical anesthetic. The patch is applied for one hour during which patients must be monitored, including observation for increases in blood pressure. The patches may be cut to conform to the area of pain and up to 4 patches may be used. The one-hour application is reported to provide up to 12 weeks of reduced pain from PHN. The capsaicin 8% patch will be manufactured by Lohmann Therapie-Systems and distributed by NeurogesX as Qutenza™.

The FDA has approved romidepsin for the treatment of cutaneous T-cell lymphoma in patients who received at least one prior systemic therapy. The drug is a histone deacetylase inhibitor, the first of a new class of antineoplastics. Romidepsin will be marketed as Istodax® by Gloucester Pharmaceuticals. ■

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