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INSIDE

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The Effect of Prior Use of Hormone Therapy on Breast Cancer Survival

ABSTRACT & COMMENTARY

By Leon Speroff, MD, Editor

Synopsis: *Current users of estrogen-progestin hormone therapy at the time of breast cancer diagnosis have a reduced risk of breast cancer mortality.*

Source: Newcomb PA, et al. Prediagnostic use of hormone therapy and mortality after breast cancer. *Cancer Epidemiol Biomarkers Prev* 2008;17:864-871.

Newcomb and colleagues reported breast cancer mortality in the Collaborative Breast Cancer Study Cohort, a prospective cohort of 12,269 postmenopausal women from Wisconsin, Massachusetts, or New Hampshire. Women were followed for an average of 10.3 years after breast cancer diagnosis. Observed ratio rates for breast cancer after adjusting for BMI, smoking, and history of mammography screening are listed in Table 1, below.

Compared with non-users, mortality from breast cancer was lower among current users of estrogen-progestin, and even greater with 5 or more years of use.

Table 1

Observed rate ratios for women using hormone therapy before diagnosis of breast cancer

Therapy/Use	Rate Ratio	Confidence Interval
Estrogen only	0.89	0.78-1.02
Estrogen-progestin	0.73	0.59-0.91
Current use, estrogen only	0.91	0.77-1.09
Current use, estrogen-progestin	0.69	0.55-0.88
Use of estrogen-progestin ≥ 5 years	0.60	0.43-0.84

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■ COMMENTARY

These are striking data. They support an argument I have been making in recent months, that, in terms of breast cancer, the use of estrogen and progestin may not be more harmful, but more beneficial. This idea is derived from the possibility that hormone therapy affects pre-existing tumors, and that estrogen-progestin produces a beneficial differentiation of the tumor that leads to earlier diagnosis.[1]

The evidence that favors an effect of hormone therapy on pre-existing tumors is as follows:

1. Epidemiologic studies find an increased risk within a few years of hormonal exposure.
2. Breast cancer associated with estrogen-progestin therapy is estrogen-receptor-positive, lower-grade, lower-stage disease with better survival rates.
3. Epidemiologic studies find an increased risk only in current users; 5 years after discontinuation the risk returns to baseline.
4. A recent rapid decrease in breast cancer prevalence coincides with a decrease in the use of postmenopausal estrogen-progestin therapy.

Let me summarize the evidence that supports a beneficial impact of progestins on pre-existing tumors:

1. An increase in estrogen-receptor-positive tumors is seen sooner with estrogen-progestin treatment, and greater risk is observed with continuous, daily estrogen-progestin use.
2. Genes up-regulated by estrogen are down-regulated by estrogen-progestin therapy.
3. Genes that are activated by estrogen-progestin are involved in DNA repair and cell cycle regulation.
4. Progestins decrease breast tissue levels of PR-A, causing a beneficial change in the PR-A:PR-B ratio that is associated with better differentiation and outcome.
5. A reduction in breast cancer case mortality has been reported with estrogen-progestin use, and not with estrogen alone.

Table 2

Reduced risks of cardiovascular disease in hormone therapy users

Therapy	Relative Risk	Confidence Interval
Estrogen only	0.62	0.48-0.60
Estrogen-progestin	0.27	0.12-0.57

The strength of the above study is the large size of the cohort. Indeed, this is the strongest evidence thus far published that the use of estrogen-progestin is associated with the development of less aggressive breast cancers. Even in studies that adjusted for the prevalence of mammography screening, breast cancers in hormone users are smaller, have fewer positive axillary lymph nodes, and are of lower-grade disease.

It is also important to note that this prospective cohort reports reduced risks from cardiovascular disease in hormone users, statistically significant for both treatments, estrogen-only and combined estrogen-progestin *(see Table 2, above)*.

This is consistent with other observational studies, and with the analyses of the Women's Health Initiative that revealed an increase in coronary heart disease only in women 70 years of age and older when they started hormone therapy.

At this point in time it is impossible to answer the question whether the epidemiologic data indicate a small increase in breast cancer risk associated with hormone therapy or whether we are seeing an effect on pre-existing tumors. But I believe the evidence is sufficient to share with patients the important possibility that hormone therapy affects pre-existing tumors, and that this leads to earlier diagnosis with better outcomes. ■

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Questions & Comments

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Bone Loss Is Reversible in Women of All Ages After Discontinuation of Depot Medroxyprogesterone Acetate Injectable Contraception

ABSTRACT & COMMENTARY

By Bliss Kaneshiro, MD, MPH, and Alison Edelman, MD, MPH

Dr. Kaneshiro is Assistant Professor, University of Hawaii, Honolulu. Dr. Edelman is Assistant Professor, Assistant Director of the Family Planning Fellowship, Department of Obstetrics & Gynecology, Oregon Health & Science University, Portland.

Dr. Kaneshiro receives research support from Wyeth Pharmaceuticals and the Society of Family Planning. Dr. Edelman reports no financial relationship to this field of study.

Synopsis: *Although data on fracture risk in depot medroxyprogesterone acetate (DMPA) users are lacking, the bone loss that occurs with DMPA use is reversible in women of all ages and is not likely to be a risk factor for low bone density in older women.*

Source: Kaunitz AM, et al. Bone density recovery after depot medroxyprogesterone acetate injectable contraception use. *Contraception* 2008;77:67-76.

OF NOTE, THIS PUBLICATION IS A REVIEW ARTICLE AND not original science. Because of its efficacy and convenience, DMPA has been used by millions of women in the United States and around the world.[1] Indeed, contraceptives like DMPA have been credited with decreasing rates of unintended pregnancy in this country, particularly in teens.[2]

There's no doubt about it, DMPA is an effective birth control method. However, questions have been raised recently about the effects of DMPA on bone mineral density (BMD) and the risk of osteopenia and osteoporosis in older age. To address this issue, the authors conducted a systematic review of the published literature between 1996 and 2006 to evaluate what happens to bone mineral density after DMPA is discontinued. The result is a comprehensive, understandable argument that the bone loss that accompanies DMPA use is reversible. More importantly, the authors demonstrate that DMPA use is not likely to be an important risk factor for low bone density in older women.

■ COMMENTARY

In November 2004, the FDA required that a "black box warning" be added to the DMPA package labeling. This warning stated that prolonged use of DMPA may result in significant loss of BMD, the loss is proportional to the amount of time on DMPA, and the decrease may not be completely reversible. The warning went on to state that women should use DMPA for more than 2 years only if other contraceptive methods are "inadequate."[3]

The suggested effect of DMPA on skeletal health is disturbing. Of particular concern are two groups, adolescents, who have not yet attained their peak bone mass, and perimenopausal women, who may be starting to lose bone mass.[4] On the other hand, many questioned whether the FDA's warning was based on the best available science. Regardless, there are anecdotal reports of clinicians changing their practice. Some clinicians no longer permitted their patients to use DMPA for more than 2 years. Others mandated that DMPA users (even healthy teenagers!) have dual X-ray absorptometry performed.

Kaunitz and colleagues sought to sort out these issues with this comprehensive review of the literature. In this review of 41 studies, Kaunitz outlined many of the controversies in the DMPA and bone mineral density debate and came to the following conclusions:

1. Studies examining the effect of DMPA use on bone mineral density in postmenopausal former users of DMPA are sparse and do not suggest an impact of DMPA on postmenopausal bone mineral density levels.
2. Bone mineral density returns to levels at or near baseline in premenopausal women who discontinue DMPA.
3. Bone mineral density loss is reversible after discontinuation of DMPA in adolescents.
4. Bone mineral density loss is reversible after treatment with DMPA for endometriosis.

Many, including these authors, have equated DMPA use to lactation. Lactating women demonstrate a decrease in bone mineral density of 4-6% over 6 months when compared to nonlactating women.[5,6] No one would ever dream of discouraging postpartum women from breastfeeding. For many women, preventing an unintended pregnancy is as important as breastfeeding. For some, it is more important. With seemingly equivalent risks, skeletal health concerns should not restrict initiation or continuation of DMPA.

However, it is important to talk to your patients about DMPA and bone mineral density. Anyone who cares for young women knows that shortly after receiving their

injection, they will look on-line at what the internet has to say about the medications they take. Anyone who checks on-line will see that the issue of bone mineral density in DMPA users has been raised and it is better to counsel patients before they call your office in a state of panic.

The authors were clear to outline that the most important question, the clinical significance of an apparent temporary decrease of bone mineral density in DMPA users is unknown. There are no published studies examining the risk of osteoporosis and the subsequent risk of fracture in DMPA users. Thus, as always, more studies are needed to ultimately find an answer, but this review provides a good indication that bone mineral density loss is reversible in DMPA users. ■

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Tibolone Fracture Trial

ABSTRACT & COMMENTARY

By Leon Speroff, MD, Editor

Synopsis: *A randomized clinical trial reported that tibolone reduced vertebral fractures by 45% and nonvertebral fractures by 26%.*

Source: Cummings SR, et al. The effects of tibolone in older postmenopausal women. *New Engl J Med* 2008;359:697-708.

THE LIFT STUDY (LONG-TERM INTERVENTION ON Fractures with Tibolone) was a randomized, placebo-controlled multicenter trial in 22 countries of tibolone, 1.25 mg, given daily over 3 years. The 4538 women who participated in the trial were age 60-85, all at high risk of fractures because of osteoporosis, and all treated with calcium and vitamin D supplementation. The study was stopped in February 2006 after a mean treatment of 34 months because of an increased risk of stroke. The risks of all events were assessed after 5 years of follow up. Major results are listed in the Table, below.

The reduction of fractures was about four times as great in women who already had a vertebral fracture upon entry to the study compared with women who had not had a fracture at baseline. It is noteworthy that the number of falls in the treated group was 25% less. The increase in stroke was greater in the oldest women (older than age 70).

■ COMMENTARY

Although tibolone is available in 90 countries, it is not an approved drug in the United States. Nevertheless

Table

Major results of the LIFT study

Event	Tibolone	Placebo	Relative Hazard	Confidence Interval
Vertebral fracture	70	126	0.55	0.41-0.74
Nonvertebral fracture	122	166	0.74	0.58-0.93
Breast cancer	6	19	0.32	0.13-0.80
Colon cancer	4	13	0.31	0.10-0.96
Stroke	28	13	2.19	1.14-4.23
CHD	27	20	1.37	0.77-2.45
VTE	5	9	0.57	0.19-1.69

it is obtainable over the internet, and it is important to be aware of the results from recent randomized trials. Based on previous bone density studies, the results of the LIFT trial on fracture reduction were not unexpected. The magnitude of the effect is roughly comparable to that with estrogen, bisphosphonates, and raloxifene (with the important exception being a lack of effect of raloxifene on hip fractures). The reduction of breast cancer was comparable to that reported with tamoxifen and raloxifene, but this was not a primary endpoint of the study. Although the difference was not statistically significant, there were 4 cases of endometrial cancer in the tibolone group and none in the placebo group.

The reported risk of stroke is similar to that observed with estrogen. In the Women's Health Initiative, no increase in stroke was observed in women younger than age 70 who had an absence of stroke risk factors. It seems prudent to avoid the use of tibolone in elderly women and in women who are at risk for stroke (specifically those with hypertension, diabetes, or atrial fibrillation, and those who smoke).

The OPAL study (Osteoporosis Prevention and Arterial effects of tiboLone) was a 3-year, randomized, double-blind trial in 6 U.S. centers and 5 European centers, treating 866 postmenopausal women with either 2.5 mg tibolone daily, 0.625/2.5 mg daily of conjugated estrogens/medroxyprogesterone acetate, or placebo.[1] Unfortunately, the OPAL trial did not achieve its goal of providing robust data on cardiovascular effects, due to the older age of the women and the notably different results in American and European women. There continues to be good reason to believe that tibolone will have a neutral effect in terms of coronary heart disease.

Tibolone treatment of postmenopausal women is as effective as estrogen therapy in relieving hot flushes, preventing bone loss, and increasing vaginal lubrication, but it stimulates libido to a greater degree than estrogen. There is less breast tenderness and mastalgia with tibolone. Endometrial safety has been reported to be comparable to that achieved with continuous combined estrogen-progestin regimens, and with a lower rate of breakthrough bleeding. The previously reported increased risks of breast cancer and endometrial cancer in observational studies very likely represent "preferential prescribing" of tibolone in Europe. Women prescribed tibolone in Europe more often had chronic breast disease, a personal history of breast cancer, previous dysfunctional uterine bleeding, hypertension, and previous uterine operations. Most importantly, more women prescribed tibolone had a history of treatment with unopposed estrogen. Thus, clinicians were more likely to prescribe tibolone to women they believed were at higher risks for these two cancers, and this would yield higher rates in treated groups compared with control groups. The standard dose of tibolone for many years was 2.5 mg daily, but the new studies support the use of the lower dose, 1.25 mg, with no apparent loss of efficacy. Tibolone continues to be an appropriate choice for hormonal therapy, suitable for many postmenopausal women. ■

Reference

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Müllerian Carcinosarcoma: Unique Neoplasm?

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

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

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

Synopsis: *The clinical behavior of uterine carcinosarcoma is more aggressive, stage for stage, than grade 3 uterine carcinoma.*

Source: Bansal N, et al. Uterine carcinosarcomas and grade 3 endometrioid cancers: Evidence for distinct tumor behavior. *Obstet Gynecol* 2008;112:64-70.

THE OBJECTIVE OF THIS STUDY WAS TO EXAMINE AND compare the clinical behavior and outcome of uterine carcinosarcoma relative to grade 3 endometrioid carcinoma. Demographic and pathology information and clinical outcomes were obtained over a 6-year period from the Surveillance, Epidemiology, and End Results (SEER) registry. Nearly 9000 patients were identified: 5024 (56%) grade 3 endometrioid cancers; 3962 (44%) carcinosarcomas. Patients with carcinosarcoma were older at diagnosis, more often non-Caucasian, and presented in more advanced disease stage relative to grade 3 endometrioid tumors. They were also less likely to undergo lymphadenectomy and receive adjuvant radiation. In a multivariate analysis of

factors predicting disease-specific mortality, carcinosarcoma histology, advanced age, non-Caucasian race, and advanced stage were all adversely independent. The 5-year disease specific mortality rates for each stage were lower for patients with carcinosarcoma — about 50% lower, even in stage I. The overall hazard ratio for survival was 0.55 (95% confidence interval, 0.5-0.6). Given these features and acknowledging the limitations of the SEER dataset, it appears that uterine carcinosarcoma is a distinct clinical entity from high-grade endometrioid cancer and associated with poor clinical outcome.

■ **COMMENTARY**

Uterine carcinosarcoma, also known as müllerian mixed mesodermal tumor (MMMT) is a rare uterine neoplasm, which consists, histologically, of epithelial and mesenchymal malignant elements. While the primary lesion may contain a large sarcomatous component, most metastatic and recurrent lesions are often characterized by pure epithelial carcinomas. In light of these observations, many clinicians have begun to consider the disease in the spectrum of endometrial cancer as opposed to sarcoma, such as leiomyosarcoma, where they have been traditionally studied.

The first step of investigation in sorting out this clinical question comes from data mining studies like the current. Carcinosarcomas are rare neoplasms, so while information may be gained from individual institutions, the data are limited in scope, highlighting the value of a registry like SEER. In this current report, nearly 4000 women with carcinosarcoma were investigated against a heterogenous cohort of grade 3 endometrioid tumors. Despite the limited number of variables upon which to interrogate, the authors were able to shed light on the clinical presentation of this tumor and its peripheral clinical behavior — all of which appear to be "worst case scenarios" for the histology. Age, non-Caucasian race, and stage are all relevant to poor endometrioid cancer survival — but all are worse in those with carcinosarcoma. Even in women with non-invasive, uterine-limited disease (Stage IA), those with carcinosarcoma had a 5-year survival of just 59% (compared to 78% in grade 3 endometrioid tumors). All of this points to a unique clinical scenario for this histology despite its appearance as an epithelial malignancy. Our contemporary, albeit crude, treatment studies are distinguishing these tumors in their eligibility.

As with all SEER-based studies, there are severe limitations that must be considered in interpreting the study's conclusion, not the least of which is lack of centralized pathological review. It is not uncommon that pathological dissent occurs in reviewing the rare histologies such as carcinosarcoma, and where the line is drawn distinguishing sarcomatoid carcinoma, adenosarcoma, and carcinosarcoma can be spurious and poorly reproducible. In addition, other uterine pathologies, such as clear cell and serous, have poor clinical scenarios relative to endometrioid carcinoma but are not distinguished in many research protocols. Ultimately, the lens through which we look at these unique tumors needs to be made molecular, particularly in light of the novel agents being developed targeting specific signaling pathways. It is this level of tumor biology enlightenment that needs to be developed to make meaningful strides in therapeutic strategies. ■

Suggested Reading

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A Comparison of Speculum and Non-speculum Collection Methods of Cervicovaginal Specimens for Fetal Fibronectin Testing

ABSTRACT & COMMENTARY

By John C. Hobbins, MD

Professor and Chief of Obstetrics, University of Colorado Health Sciences Center, Denver

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

Synopsis: *A simpler method to collect fetal fibronectin specimens is just as effective as the more elaborate standard method.*

Source: Stafford IP, et al. A comparison of speculum and nonspeculum of cervicovaginal specimens for fetal

fibronectin testing. *Am J Obstet Gynecol* 2008;199: 131.e1-131.e4.

FETAL FIBRONECTIN IS NOW BEING USED IN MANY HOSpitals to separate out those with preterm contractions (PTCs) who are in true labor from those with contractions who are not (and, therefore, not requiring tocolytics or hospitalization). However, the method to obtain a sample for analysis is somewhat cumbersome, requiring a speculum examination and careful placement of a cotton (or polyester) swab into the posterior fornix under direct visualization.

In this study, conducted in Mexico, two simpler methods of obtaining the specimen were tested against the above gold standard technique: 1) a single finger guided method to reach the posterior fornix, and 2) a blind insertion of the swab into the posterior fornix. Obviously, neither method requires insertion of a speculum or elaborate patient positioning.

In the first portion of the study, 169 paired samples were analyzed for fetal fibronectin (fFN) in women who were between 22 and 42 weeks gestation. All had samples obtained by the speculum method, as well as a non-speculum approach, in which a single finger was used to depress the perineum, and the swab was advanced over the finger, acting as an introducer. In the second part of the study, involving paired samples from an additional 35 patients, the swab was simply directed posteriorly through the introitus until resistance was encountered, where the sample was obtained. The specimens obtained in this manner were compared with those obtained with the speculum method. In part one of the study, the fFNs were analyzed via a standard rapid test, and in part two this was done by a batched ELISA assay.

In part one, 54 patients tested positive with both methods and 107 patients tested negative with both methods. There were discrepancies between the two methods in only 8 instances, giving a 95% agreement. In part two the authors were able to quantify the fFN results and there was discordance in only one case. The quantitative correlation between methods was excellent (0.97).

■ COMMENTARY

One might say that reviewing this paper represents wallowing in minutia. However, I would counter that this study provides very usable information that will not only save time in evaluating patients with questionable preterm labor, but also will diminish patient discomfort.

There are data now in the literature to validate the concept of using either fFN or cervical length (CL) to rule out preterm labor in patients with PTCs. For example, two studies have shown that if patients with this clinical backdrop had a CL by transvaginal sonography of >1.4 cm, they had only a 1%-2% chance of delivering within a week of the exam.[1,2] Another study showed that if the CL was >3 cm, 100% of these patients delivered after 34 weeks.[3] Fetal fibronectin seems to perform about as well as CL in some studies, but when the two are used together, the predictive ability to include or exclude patients destined to have preterm delivery (PTD) is improved even further. For example, in a collaborative study from Chile and Detroit, the investigators showed that CL was slightly better than fFN at predicting PTD at less than 35 weeks, occurring in 20% of the 215 patients studied with PTCs.[4] However, if both were positive, 81% delivered before 35 weeks, and if both were negative, only 2% delivered within a week of the exam, and none had a PTB <32 weeks. Most importantly, if the CL exceeded 2.9 cm, the fFN added no diagnostic value.

So, since the fFN adds extra cost to a workup that is already quite expensive, it seems from all the above information that a pragmatic approach to patients being evaluated for PTCs would be first to gently introduce the swab blindly into the patient's posterior fornix, and to set it aside, pending the results of a CL examination to follow (which might falsely affect the results of the fFN, if done first). If the CL is >2.9 cm, no further studies would be required, and the patient could be discharged. If the CL were between 1.5 cm and 3.0 cm, then the fFN specimen could be sent off for analysis, and if it is negative, the patient could be discharged. Also, if the cervix is <1.5 cm, the fFN would add little to the management, since these patients have a large enough chance of delivery that hospitalization would be warranted.

This simple approach would save precious time and money, and would diminish patient discomfort and anxiety. ■

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CME Questions

21. All of the following statements are true regarding hormone therapy and the risk of breast cancer *except*:
a. No increase in breast cancer risk has been reported with estrogen-only treatment.
b. An increase in breast cancer risk has been reported with long durations of estrogen-only treatment.
c. An increase in breast cancer risk has been reported with short durations of estrogen-progestin treatment.
d. Hormone therapy is associated with a greater prevalence of lower-grade and lower-stage tumors.

22. Bone mineral density loss is completely reversible *except* in teenagers.
a. True
b. False

23. The available data suggest a decrease in postmenopausal bone mineral density levels in previous DMPA users compared to non-users.
a. True
b. False

24. The following statements are true regarding tibolone *except*:
a. Tibolone is as effective as hormone therapy in preventing fractures.
b. A disadvantage of tibolone is the lack of a beneficial effect on the risk of CHD.
c. An advantage of tibolone is an increase in libido.
d. All postmenopausal women have a similar increase in stroke risk with tibolone.

25. Which of the following is *not* true regarding patients with müllerian carcinosarcoma in the Bansal et al study?
a. They were younger at diagnosis.
b. They were more often non-Caucasian.
c. They presented in more advanced disease stage relative to grade 3 endometrioid tumors.
d. They were less likely to undergo lymphadenectomy and receive adjuvant radiation.

CME Objectives

The objectives of *OB/GYN Clinical Alert* are:
- To present the latest data regarding diagnosis and treatment of various diseases affecting women, including cancer, sexually transmitted diseases, and osteoporosis;
- 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.

26. Which one of the following answers regarding methods for obtaining specimens for fFN is appropriate?
a. The speculum method was more accurate.
b. Agreement between the two methods was 85%.
c. Both methods performed equally well.
d. The "blind" technique was inferior to the "introducer finger" technique.

27. Studies show that fFN is better than CL in predicting PTB in patients with PTCs.
a. True
b. False

28. Which of the following answers does *not* fit?
a. Most patients with PTCs do not deliver preterm.
b. A CL <1.5 cm is associated with over a 90% chance of PTD in patients with PTCs.
c. In a patient with a CL >3.0 cm there is little reason to do a fFN.
d. If the CL is reassuring and the fFN is negative, there is little reason to keep patients presenting with PTCs in the hospital.

Answers: 21. (a); 22. (b), 23. (b); 24. (d), 25. (a), 26. (c), 27. (b), 28. (b).

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Gender Differences with Anticoagulation Discontinuation

In this issue: Some women with DVT may stop warfarin after six months; Vytorin and cancer; preventing recurrent stroke; and FDA news.

When is it safe to stop anticoagulation after an unprovoked venous thromboembolism? A new study suggests that women with minimal risk factors may safely stop anticoagulation after 6 months of therapy, although the same may not be true for men. Canadian researchers randomized 646 patients with a first, unprovoked major venous thromboembolism and followed them for 4 years. Data were collected for 69 potential predictors of recurrent venous thromboembolism while patients were taking oral anticoagulants and a multi-variable analysis of predictor variables was performed. Men had a 13.7% annual risk of recurrence after discontinuing oral anticoagulation and there was no combination of clinical predictors that could identify a low-risk subgroup of men. In women, 52% had zero or one of the following risk factors: hyperpigmentation, edema or redness of either leg, d-dimer ≥ 250 mcg/L while taking warfarin, body mass index ≥ 30 kg/m^2, or age ≥ 65 years. These women had an annual risk of recurrent thromboembolism of 1.6% (95% CI, 0.3% to 4.6%). Women who had two or more of these risk factors had an annual risk of 14.1%. The authors conclude that women with zero or one risk factor may safely discontinue oral anticoagulant therapy after 6 months of therapy following their first unprovoked venous thromboembolism; however, this conclusion does not apply to men (*CMAJ* 2008;179:417-426). An accompanying editorial points out that patients with the first episode of unprovoked venous thromboembolism have a high rate of recurrence if they stop anticoagulation therapy — about 10% in the first year. Current guidelines from the American College of Chest Physicians recommend lifetime therapy for patients with a first episode of proximal deep venous thrombosis or pulmonary embolism provided that good anticoagulant monitoring is achievable and indefinite treatment is consistent with patient preferences. This study identifies a large group of women who may safely stop anticoagulation after 6 months although the authors do recommend further validation (*CMAJ* 2008; 179:401-402).

FDA Announces Vytorin Investigation

The news keeps getting worse for Merck/Schering-Plough, the distributor of Vytorin®: The FDA has announced that it will investigate a report from the SEAS trial (Simvastatin and Ezetimibe in Aortic Stenosis) of the possible association between the use of Vytorin and increased incidence of cancer. The SEAS trial was designed to see if Vytorin, a combination of simvastatin and ezetimibe, would reduce cardiovascular events in patients with aortic stenosis. In a July press

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) 262-5468. E-mail: paula.cousins@ahcmedia.com.

release, the company reported on preliminary data which showed that the trial did not show benefit for the primary endpoint of aortic-valve related major cardiovascular events, but did show that a larger percent of subjects treated with Vytorin were diagnosed with, and died from, all types of cancer compared to placebo during the 5-year study. There was improvement in the secondary endpoint of ischemic events (15.7% vs 20%) but no benefit in other secondary endpoints. The number of cancers was 105 (11.1%) in the Vytorin group vs 70 (7.5%) in the control group (P = 0.01), and the number of cancer deaths was 39 (4.1%) in the Vytorin group vs 23 (2.5%) in the control group (HR 1.67; 95% CI, 1.00 to 2.79; P = 0.05). The FDA is also looking at interim data from two large ongoing trials of Vytorin, the Study of Heart and Renal Protection (SHARP) and the Improved Reduction in High-Risk Subjects Presenting with Acute Coronary Syndrome (IMPROVE-IT) which, so far, have not shown an increased risk of cancer associated with Vytorin. The SHARP trial should be completed in 2010, while the IMPROVE-IT trial should be finished in 2012. Initial data from the SEAS trial were presented in the recent news conference; full results were published at www.nejm.org (DOI: 10.1056/NEJMao0804602) on Sept. 2, 2008. The FDA says its investigation will take at least 6 months from the date of publication.

PRoFESS Trial Shows No Stroke Benefit

The recently published PRoFESS trial failed to show benefit of two strategies for preventing recurrent strokes. In the first arm of the study, the angiotensin-receptor blocker (ARB) telmisartan was compared to placebo in more than 20,000 patients with ischemic stroke. Patients were randomized to telmisartan 80 mg daily or placebo and followed for a mean follow-up of 2.5 years. Mean blood pressure was 3.8/2.0 mmHg lower in the telmisartan group; however, there was no difference in the rate of recurrent stroke (8.7% telmisartan vs 9.2% placebo [HR 0.95; 95% CI, 0.87 to 1.01; P = 0.11). The rate of new onset diabetes was 1.7% in the treatment group and 2.1% in the placebo group (P = 0.10). The authors conclude that therapy with telmisartan initiated soon after an ischemic stroke did not significantly lower the rate of recurrent stroke, diabetes, or major cardiovascular events. The second wing of the study compared aspirin plus 200 mg of extended release dipyridamole (Persantine®) twice daily vs clopidogrel (Plavix®) 75 mg daily in the same patient group. After a mean of 2.5 years of follow-up recurrent stroke occurred in 9% of patients receiving aspirin and dipyridamole and 8.8% of patients receiving clopidogrel (HR 1.01; 95% CI, 0.92 to 1.11). The secondary outcomes of stroke, myocardial infarction, or death from vascular causes occurred in 13.1% of both groups. The authors conclude that there is no evidence that either of the two treatments was superior to the other in the prevention of recurrent stroke (*N Engl J Med*, published on-line at www.NEJM.org, Aug. 27, 2008).

FDA Actions

The FDA has issued a warning regarding the use of simvastatin in patients who are taking amiodarone. More than 20 mg of simvastatin plus amiodarone puts patient at higher risk for rhabdomyolysis since amiodarone inhibits CYP 3A4, one of the enzymes that metabolizes simvastatin. The simvastatin labeling has contained a warning regarding concomitant use with amiodarone since 2002; however, the FDA continues to receive reports of rhabdomyolysis associated with use of the two drugs. Physicians are also urged to tell their patients to report any unexplained muscle pain, tenderness, or weakness while taking the drugs. Other risks for rhabdomyolysis associated with statins include advanced age, uncontrolled hypothyroidism, and renal impairment.

There should be plenty of flu vaccine this fall. The FDA has announced the approval of six manufactures including GlaxoSmithKline, ID Biomedical, MedImmune, Novartis, Sanofi Pasteur, and CSL Limited. The vaccine will again be a trivalent vaccine comprised of two influenza A viruses and one influenza B virus. All three strains are new this year, an unusual occurrence as usually only one or two strains are updated each year.

The FDA issued an alert in October 2007 regarding exenatide (Byetta®) and the risk of acute pancreatitis. Since then, 6 more cases of hemorrhagic or necrotizing pancreatitis have been reported to the FDA associated with use of the drug, including two deaths. Exenatide is an injectable incretin mimetic used to treat type 2 diabetes. The FDA is recommending that exenatide should be stopped immediately if pancreatitis is suspected. Currently there is no patient profile which would predict increased risk of pancreatitis. Amylin Pharmaceuticals, the manufacture of exenatide, is working with the FDA on new labeling regarding the risk of hemorrhagic or necrotizing pancreatitis. ■