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INSIDE

Financial Disclosure: *OB/GYN Clinical Alert*'s editor, Leon Speroff, MD, is a consultant for Warner-Chilcott; peer reviewer Catherine LeClair, MD, reports no financial relationship to this field of study.

WHI Analyzes Cardiovascular Risk by Age and Years Since Menopause

ABSTRACT & COMMENTARY

By Leon Speroff, MD, Editor

Synopsis: *The risk of cardiovascular disease associated with post-menopausal hormone therapy is found only in older women.*

Source: Rossouw JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA.* 2007;297:1465-1477.

The Women's Health Initiative (WHI) investigators conducted a secondary analysis of the two canceled clinical trial arms.[1] The results in the estrogen-only arm, the combined estrogen-progestin arm, and with the participants combined were separated into age groups at randomization (50-59, 60-69, and 70-79) and according to years since menopause (< 10, 10-19, and 20 or more). An increased risk for coronary heart disease (CHD) was present only in the oldest women in the trials. The only statistically significant reduced risk was for total mortality in women age 50-59.

Statistically Significant Increased Risks

All subjects combined:
- CHD HR=1.28 (CI=1.03-1.58) in women 20+ years since menopause
- Stroke HR=1.50 (CI=1.17-1.92) in women ages 60-69
  HR=1.77 (CI=1.05-2.98) in women < 10 years since menopause

Estrogen-only:
- Stroke HR=1.62 (CI=1.15-2.27) in women ages 60-69

Estrogen-progestin:
- CHD HR=1.48 (CI=1.04-2.11) in women ages 70-79
  HR=1.66 CI=1.14-2.41) in women 20+ years since menopause

Table Adapted by L. Speroff

The authors calculated absolute risks and found no increases for CHD, stroke, or total mortality in women ages 50-59. In fact, only the increase in CHD events in women 20+ years since menopause reached statistical significance. The authors conclud-

VOLUME 24 • NUMBER 1 • MAY 2007 • PAGES 1-8

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ed that there was no apparent increase in cardiovascular disease risk in treated women close to their menopause.

COMMENTARY

The data in this WHI report are not new. A careful reading of the original adjudicated reports reveals that the risk of CHD was present only in the oldest women in the trials.[2, 3] What is new is that the WHI finally emphasizes this finding to the public, almost 5 years since the first dramatic report in July, 2002, that we remember so well.[4]

This report from the WHI is a complicated statistical exercise involving 137 calculations of risk and 182 analyses of subgroups. I cannot authoritatively assess the validity of these tests; however, some things do attract this clinician's eyes. First is pooling of the two canceled trials in order to achieve greater numbers a reliable and valid exercise? The women in the two trials differed considerably. The women in the estrogen-only arm had a higher prevalence of obesity, abnormal EKGs, hypertension, diabetes, hypercholesterolemia, and a previous history of cardiovascular disease. More women in the estrogen-only arm used hormone therapy previously, and for longer durations. Although I am not convinced it is appropriate to combine the subjects of the two arms; nevertheless, the combined results are not markedly different compared with the results in the two arms analyzed separately. However, because of the marked differences in patient characteristics comparing the two arms, I do not believe it is appropriate for the WHI authors to imply that a difference that is clinically important can be derived from comparing estrogen-only treatment with combined estrogen-progestin treatment.

The authors emphasize that, overall, hormone therapy increased the risk of stroke (HR = 1.32; CI = 1.12-1.56 in the combined analysis of the two arms). However, in the subgroup analyses, the only significant increase in stroke occurred in the estrogen-only arm in women ages 60-69. The only significant increase in CHD occurred in those women in their 70s. The important point to be emphasized can be found in the authors' discussion: When women with prior cardiovascular disease or those older than 60 years were excluded, the risk of stroke in women less than 10 years since their menopause was not significantly increased.

There is a statement in the methods section that drew my attention: "Due to the compressed timeline for the initial publications, 13 additional adjudicated cases each of CHD and stroke form the CEE + MPA trial were available for this analysis." Why in the world didn't the WHI investigators wait for their full results, finish their full analysis, and provide the public with accurate information? The initial public impression, reinforced by the early publications, was that the risk of cardiovascular disease was robust, and that it applied to all postmenopausal women using hormone therapy. What is the opposite of robust? Pick your word and apply it to the analyses in this current report. Even the WHI authors recognize this by calculating estimates of absolute risk and stating that there is no increase in absolute risks due to hormone therapy in women ages 50-59.

Do these results rule out the possibility that hormone therapy given to young postmenopausal women may prevent CHD? I think not. In the WHI, the number of women in this young age group was small, the duration of hormone exposure relatively short, and long-term follow-up is yet to be reported. The number of women ages 50-54 or less than 5 years since menopause was too small to allow analysis. A meta-analysis of 23 randomized hormone therapy trials concluded that treatment reduced the risk of coronary heart disease events in younger women (OD = 0.68; CI = 0.48-0.96) compared with older women (10 or more years since menopause or greater than 60 years of age).[5] This is a conclusion that is less firm than at first apparent, because most of these trials were not designed to measure an endpoint of cardiovascular disease. However, another meta-analysis by the same authors concluded that hormone therapy reduced overall mortality in women with an average age less than 60.[6]

OB/GYN Clinical Alert, ISSN 0743-8354, is published monthly by AHC Media LLC, 3525 Piedmont Road., NE, Building. 6, Suite 400, Atlanta, GA 30305.

SENIOR VICE PRESIDENT/GROUP PUBLISHER: Brenda Mooney.
ASSOCIATE PUBLISHER: Lee Landenberger.
MANAGING EDITOR: Iris Williamson Young.
MARKETING PRODUCT MANAGER: Shawn DeMario.
Registration Number: R128870672.
Periodicals postage paid at Atlanta, GA.

POSTMASTER: Send address changes to **OB/GYN Clinical Alert**, P.O. Box 740059, Atlanta, GA 30374.

Back issues: $42.

Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

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Questions & Comments

Please call **Iris Young**, Managing Editor at (404) 262-5413 between 8:00 a.m. and 4:30 p.m. ET, Monday-Friday.

There is a growing story that adequate estrogen exposure prior to the onset of clinical events provides protection against cardiovascular disease. ■

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Extracting Information About the Fetal Chromosomal Status from Maternal Blood Samples

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: *Use of free fetal DNA to diagnose fetal chromosomal abnormalities has been hindered by the inability to distinguish fetal DNA from maternal DNA. The researchers here aim to establish whether single nucleotide polymorphisms (SNPs) can be used to distinguish fetal DNA from maternal DNA—and to determine the number of fetal chromosomes—in maternal blood samples.*

Source: Dhallan R, et al. A noninvasive test for prenatal diagnosis based on fetal DNA present in maternal blood: a preliminary study. *Lancet.* 2007;369:474-481.

HAS THERE BEEN ANY PROGRESS IN EXTRACTING information about the fetal chromosomes status from maternal blood samples?

For the last 15 years, investigators have been attempting to isolate fetal cells from the maternal circulation to screen for aneuploidy. Since the techniques to accomplish this feat have been cumbersome, expensive, and not consistently reliable, there has been a strong movement to work with fetal DNA in the maternal circulation as an alternative, because this fetal material has a short half-life in this environment (and, therefore, does not represent the last pregnancy's fetal information), and it does not require prohibitively expensive cell sorting equipment.

In a recent article in *The Lancet*, a technique has been described which puts into play single nucleotide polymorphisms (SNPs). The concept is that one can identify fetal DNA by noting paternal signals at various SNP sites. Then, by comparing the amount of these signals with the amount of separate SNP signals which are specific to the mother, one can indirectly quantify the amount of fetal DNA in the sample (by assuming that fetal DNA contains one half maternal DNA). Step 2 involved looking specifically at chromosomes 21 and 13 in the maternal blood sample. In normal fetuses, one copy of chromosome 21 comes from the mother and one from the father. In trisomy 21, the fetus has two copies from his/her mother and one copy from the father. Therefore, with this technique in normal pregnancies one would expect 1 paternal signal for every 3 maternal signals, resulting in a ratio of the amount of paternal signal to combined (maternal and fetal) SNP signals of about 0.33. In trisomy 21 pregnancies, the addition of an extra maternal chromosome would result in a ratio that would be closer to 0.25. The authors used chromosome 13 as a control (to make sure that the normal ratio was maintained for this chromosome in the same maternal sample).

The investigative group analyzed 57 maternal and paternal bloods from normal pregnancies and 3 sets of samples from pregnancies complicated by fetal Down syndrome. As expected, the amount of free fetal DNA in the samples varied appreciably, but averaged 34%, with generally smaller yields in the first trimester. Regarding the trisomy cases, the technique identified 2 out of 3 cases. Therefore, this translated into 1 false-negative and 1 false-positive, giving a sensitivity and positive predictive value of 66 percent, and a negative predictive value of 98.2%.

■ COMMENTARY

The total numbers of Down syndrome fetuses in this study were very small, and spiking the deck with more cases of trisomy 21 might show different results, therefore negating the enthusiasm that is being generated by this report. Hopefully, this will not be the case, as it seems to have taken so long for anything new and exciting to occur in this field after the initial hype generated by the early reports of the ability to isolate fetal red blood cells and DNA in the maternal circulation.

It is cautioned that this is simply another form of non-invasive screening that could either replace, or be

used in conjunction with, other prenatal diagnostic methods such as first and second trimester biochemistry, nuchal translucency screening, and the genetic sonogram. Nevertheless, the possibility of finally separating out specific fetal information from simple maternal and paternal blood sample sets is very exciting. ■

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Postmenopausal Hormone Therapy and Breast Cancer—The French E3N Cohort Study

ABSTRACT & COMMENTARY

By Leon Speroff, MD, Editor

Synopsis: *French cohort study finds an increased risk of breast cancer associated with synthetic progestins.*

Source: Fournier A, et al. Unequal risks for breast cancer associated with different hormone replacement therapies: results form E3N cohort study. *Breast Cancer Res Treat.* February 27, 2007;Epub.

E3N is a French prospective cohort study initiated in 1990.[1] The participants are members of an insurance plan that covers mostly teachers. The results are obtained by self-administered questionnaires, and this report represents 12 years of follow-up of 80,377 postmenopausal women available for analysis (88.7% completed the last questionnaire in 2002). A remarkable 70% of the women had used hormone therapy for an average of 7 years. The relative risks for invasive breast cancer were as follows:

(table adapted by L. Speroff)

	Oral Estrogen		Transdermal Estrogen	
	Cases	*Relative Risk*	*Cases*	*Relative Risk*
Estrogen alone	13	1.32 (0.76-2.29	56	1.28 (0.98-1.69)
E plus				
Progesterone			121	1.08 (0.89-1.31)
Dydrogesterone	7	0.77 (0.36-1.62)	90	1.18 (0.95-1.48)
Medrogestone	9	2.74 (1.42-5.29)	28	2.03 (1.39-2.97)
Chlormadinone	8	2.02 (1.00-4.06)	35	1.48 (1.05-2.09)
Promegestone	13	1.62 (0.94-2.82)	-	
Nomegestrol	46	2.11 (1.56-2.86)	91	1.60 (1.28-2.01)
Medroxyprog.	29	1.48 (1.02-2.16)	-	

The authors concluded that it would be preferable to use progesterone or dydrogesterone because estrogen used with these two progestins was not associated with an increase in the relative risk of invasive breast cancer. For any given progestin, the route of administration of estrogen (oral or transdermal) had no effect on relative risk. The authors then grouped all other progestins together, and grouped oral and transdermal estrogen alone together. They reported a statistically significant increase in relative risk with estrogen alone, RR = 1.29 (1.02-1.65) and with other progestins, RR = 1.69 (1.50-1.91). The increased relative risks seemed to rapidly dissipate after discontinuation of treatment; however, this analysis was limited by small numbers.

■ COMMENTARY

Hormone users are known to differ in their personal characteristics when compared with non-users. However, in this instance, the entire cohort, users and nonusers, was very homogenous (mostly teachers and all in the same insurance company), and the authors argue that for that reason it is unlikely that the results are affected by confounders. Nevertheless, in their earlier report, data were provided revealing that the hormone users did differ considerably compared with the nonusers (earlier menarche, earlier menopause, less nulliparity, more children born before age 30, more benign breast disease, less obesity, and more education).[2] This leaves readers uncertain regarding the impact of confounding differences. One problem that was not assessed is the prevalence of mammography. Hormone users have a greater prevalence of mammography, and an important criticism of the study is the lack of assessment for mammography frequency.

The authors of this study argue that their results indicate that the "natural" progestins are safer than "synthetic" progestins. But to accurately differentiate among various agents one would have to be certain that the doses administered represented bioequivalent doses in terms of target tissue impact, something that would be difficult to do. Let's focus on the rapidity at which cases of breast cancer were identified. In the current report, the use of estrogen combined with "other progestins" had an increased relative risk even with less than 2 years of exposure, RR = 1.376 (1.07-1.72). In their previous report, an increased relative risk was even apparent with less than one year of exposure of estrogen combined with synthetic progestins.[2]

In both of the French reports from this study, the

results could be due to earlier detection of pre-existing tumors, an effect accelerated by specific progestins with greater potency. At this point in time we don't know whether there is a small increase in the risk of breast cancer with postmenopausal hormone therapy or whether the epidemiologic data reflect an impact on preexisting tumors. These French data are consistent with an effect on preexisting tumors, and that, contrary to the prevailing belief, estrogen-progestin exposure causes greater differentiation and earlier detection of preexisting tumors, resulting in better outcomes. ■

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New Examination of HPV Prevalence in US Women

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: *Vigorously conducted study of HPV infection demonstrates prevalence is higher than previously estimated.*

Source: Dunne ER, et al. Prevalence of HPV infection among females in the United States. *JAMA.* 2007;297:813-819.

Human papilloma virus (HPV) infection is the most common sexually transmitted disease in US women. Its prevalence rises sharply after sexual debut and peaks between ages 20 and 29; prevalence is lower in older women. Since more than 99% of cervix cancer patients have evidence of HPV infection, clear understanding of the health care burden is necessary, particularly in light of the recent availability of the HPV vaccine. Using data obtained from a recent survey of women participating in the National Health and Nutrition Examination Survey (NHANES), Dunne and her colleagues examined the prevalence of HPV infection in this large cohort. Participants were women who were surveyed in 2003 and 2004 and had their HPV infection status determined by standard methodology from self-collected vaginal swabs. Both high- and low-risk HPV subtypes were evaluated (n = 38 total) in the study cohort of 1921 evaluable women aged 14-59. Over all age cohorts, HPV was identified in 26.8% of women. This corresponds to an estimated 24.9 million women in this age group in the US population. Prevalence was highest in women aged 20-24 years (44.8% or 7.5 million individuals). There was a significant trend in prevalence with each year from 14 to 24 years of age followed by a gradual decline in prevalence through age 59. HPV 6, 11 and 16, 18 (targets of the current quadravalent HPV vaccine) was detected in 3.4% of the participants. Overall, 40% of women had more than one HPV type infection. The authors conclude HPV prevalence is high in the US population, particularly in women aged 20-24. However, the prevalence of HPV subtypes included in the current HPV vaccine is low.

COMMENTARY

It has been widely known that HPV is prevalent in the US population. Fortunately, despite this finding, the incidence of cervix cancer is low owing to broad acceptance of Pap smear testing and effective treatment of slow growing preinvasive lesions. However, the impact of HPV infection in the setting of underdeveloped preventative care is prominently represented; worldwide, cervix cancer is among the most frequent causes of cancer death in women. These observations are driving impetus for both prevention and screening programs throughout the world for this largely preventable killer. In the US, a quadravalent HPV vaccine (HPV types 6, 11, 16, 18) is approved and has been demonstrated to be nearly 100% effective in preventing infection and disease associated with these subtypes and is currently approved for routine use. Two interesting facts are highlighted in the current study: first, the prevalence of infection is much higher than previously documented. In this cross-sectional determination, over one quarter of the participants tested positive and the prevalence among 20-24 year olds has increased over serial studies. However, the prevalence in 14-19 year olds was also nearly 25%, suggesting effective intervention strategies have to start in younger girls. In fact, only this age group was associated with a

significantly increased ratio of high risk to low risk HPV subtype infection. The second important observation in the trial was the high prevalence of HPV types, which are not currently a target of the HPV vaccine. Just 3% of infected individuals had these subtypes. Other studies, predominantly from clinic-based populations, have demonstrated a much higher contribution of these serotypes and their high frequency in cancer specimens has directed the current vaccine portfolio. It is possible that these more prevalent serotypes have shorter infection cycles and less significant clinical implications. It is also possible that certain HPV types have a tropism for the vagina, as opposed to the cervix. However, a concern of vaccination programs is that over time there could be a "serotype-shift" or selection to other cancer-inducing HPV serotypes. Indeed, the most prevalent high-risk HPV serotype identified in this study was HPV-53; this serotype is identified in less than 1% of cancer currently. The impact of these observations will likely direct future vaccine development as the portfolio expands. ■

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The French ESTHER Study of VTE

ABSTRACT & COMMENTARY

By Leon Speroff, MD, Editor

Synopsis: *A French case-control study reported an increased risk of venous thromboembolism (VTE) with oral postmenopausal estrogen therapy, but no increase with transdermal treatment. In addition, results suggested an increase with estrogen combined with norpregnane progestins.*

Source: Canonico M, et al. Hormone therapy and venous thromboembolism among postmenopausal women. Impact of the route of estrogen administration and progestogens: the ESTHER study. *Circulation.* 2007;115:840-845.

The ESTROGEN AND THROMBOEMBOLISM RISK (ESTHER) study is a case-control study performed with cases from 8 French hospitals and controls from the general population.[1] The results were as follows:

	Cases	Controls	Adjusted Odds Ratio
Oral estrogen	4	39	4.2 (1.5-11.6)
Transdermal estrogen	67	180	0.9 (0.4-2.1)
With micronized progesterone	9	63	0.7 (0.3-1.9)
With pregnane progestins	39	79	0.9 (0.4-2.3)
With norpregnane progestins	40	37	3.9 (1.5-10.0)

(table adapted by L. Speroff)

The authors concluded that transdermal estrogen is not associated with an increased risk of VTE, and that norpregnane progestins may be thrombogenic.

■ COMMENTARY

This current report is an update of a previous report from the ESTHER study in which no increase in VTE risk was found with transdermal estrogen therapy.[2] In addition, this study has reported that oral estrogen treatment adds to the risk of VTE associated with obesity, but transdermal estrogen does not.[3] They have also reported (although limited by small numbers) that transdermal treatment, in contrast to oral estrogen, does not further increase the risk of VTE associated with Leiden or prothrombin mutations.[4]

France is unique in that transdermal estrogen therapy is very popular, providing sufficient numbers to perform a case-control study of a relatively infrequent event. In addition, a wide variety of progestational agents is in use in Europe, allowing subgroup analyses of different progestins.

But there are some problems with this French case-control study. First, look at the wide confidence interval for the significant odds ratio associated with oral estrogen treatment. Usually this reflects small numbers, but the number of cases and controls in this study should allow greater precision. It is possible that this imprecise conclusion is influenced by the fact that the cases and controls differed significantly in several characteristics that influence the risk of VTE, specifically greater body weight and a positive family history of VTE. Nevertheless, we know that an increased risk of VTE is uniformly reported, includ-

ing the data from the Women's Health Initiative (WHI).[5, 6] It is very likely that the French estimate is higher compared with the usual 2-fold increased risk because of the confounding differences between their cases and controls. It is worth noting that in the WHI, the cases of venous thrombosis were concentrated in the first year of exposure, in the oldest women in the study, and in the heaviest women in the study. It makes you wonder how large the risk is, if any, in younger, normal weight postmenopausal women.

The French case-control study found no increase in VTE risk associated with estrogen combined with progesterone or pregnane derivatives, and an increase with norpregnane derivatives. The pregnane group includes synthetic progestins familiar to us such as medroxyprogesterone acetate, chlormadinone, and cyproterone. The norpregnanes (progesterone without the 19-carbon) included two progestins, nomegestrol acetate and promegestone, which are not used in the US (Nomegestrol acetate is the progestin in Uniplant, a single rod implant contraceptive). But can we make the conclusion that the norpregnanes are thrombogenic? The confidence interval in the norpregnane group is very wide, again apparently not due to small numbers, but this makes this conclusion shaky and suspect.

In this study, oral hormone users used almost exclusively estradiol in doses that averaged 1.5 mg per day. Transdermal users most commonly used an estradiol dose of 50 µg or less daily. There is another problem here. To legitimately compare oral and transdermal methods, one would have to be sure the two groups had similar blood levels, to account for the wide variation in metabolism and clearance among individuals. It is possible that the difference between the oral and transdermal groups represent differences in estrogen doses.

A greater safety with transdermal administration of estrogen in regards to VTE makes some sense because of the known lesser impact on clotting proteins when the first-pass liver effect is avoided. This is supported by transdermal's almost negligible effect on activated protein C resistance when compared with oral therapy.[7, 8] Therefore, the ESTHER study supports the clinical choice of a transdermal method for women who are at higher risk for VTE. The data are too weak to make any statements with confidence regarding the effect of various progestins. ■

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CME / CNE Questions

1. The following statements are true regarding postmenopausal hormone therapy and the risk of cardiovascular disease except:

a. Hormone therapy should not be given to elderly women in the expectation that it will prevent heart disease.
b. Stroke and heart disease are not increased by hormone therapy given to women in their 50s.
c. The WHI was adequately powered to measure the effect of hormone therapy on women in their 50s.
d. Available evidence does not indicate that progestins exert an adverse effect on the cardiovascular system.

2. In this study by identifying specific maternal and paternal SNP sites the authors found that maternal samples yielded an average of:

a. 35% fetal DNA
b. 10% fetal DNA
c. 60% fetal DNA
d. 100% fetal DNA

3. **In this study by identifying specific maternal and paternal SNP sites the authors found that maternal samples yielded an average of:**
   a. 35% fetal DNA
   b. 10% fetal DNA
   c. 60% fetal DNA
   d. 100% fetal DNA

4. **The following statements are true regarding postmenopausal estrogen-progestin therapy and breast cancer except:**
   a. An apparent increase in breast cancer risk is limited to current and recent users.
   b. The French study found no difference comparing oral vs transdermal administration of estrogen.
   c. All progestins affect breast tissue in a similar fashion.
   d. Estrogen-progestin treatment may lead to earlier detection of breast cancers.

5. **In the current study, marital status was evaluated for prevalence. Which of the following was associated with the highest prevalence?**
   a. married
   b. widowed, divorced or separated
   c. never married
   d. living with a partner

6. **The following statements are true regarding postmenopausal hormone therapy and the risk of VTE except:**
   a. Obesity is an insignificant risk factor for VTE.
   b. Oral treatment with both conjugated estrogens and micronized estradiol has been reported to increase the risk of VTE.
   c. Transdermal estrogen is the best choice for women at increased risk of VTE.
   d. There is no firm evidence that progestins contribute to the risk of VTE.

Answers: 1(c); 2(a); 3(a); 4(c); 5(d); 6(a)

CME Objectives

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

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Long-Awaited Torcetrapib Will Not Be Released, Too Risky

Torcetrapib, a cholesteryl ester transfer protein (CETP) inhibitor, has been in development by Pfizer for nearly 15 years. The drug has been shown to elevate HDL levels while reducing LDL levels, prompting hopes that torcetrapib would be the first in a new class of important cholesterol medications. In December, Pfizer abruptly pulled the plug on further development of torcetrapib when the Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events trial showed an increase in death from all causes associated with the drug, including an increased rate of cardiovascular events and hypertension. A new study points out a possible mechanism for the lack of cardiovascular benefit. In the international study, 1,188 patients with cardiovascular disease underwent intravascular ultrasonography. They then received atorvastatin and were randomized to receive 60 mg of torcetrapib daily or placebo along with atorvastatin for 24 months. Atorva/torcetrapib resulted in a 61% relative increase in HDL and a 20% further reduction in LDL, resulting in an average HDL higher than LDL. But the drug combination was also associated with an increase in systolic hypertension of 4.6mm Hg, and more importantly an increase in atheroma volume of 0.12%, compared to an increase of 0.19% in the atorvastatin alone group (P = 0.72). The authors conclude that treatment with the CETP torcetrapib was associated with improved lipid endpoints, but was also associated with an increase in blood pressure and no significant decline in coronary atherosclerosis (*N Engl J Med.* 2007;356:1304-1316.). In an accompanying editorial, Dr Alan Tall holds out hope that other CETP inhibitors may not show the same adverse effects but suggests that further development of this class of drugs needs to proceed with caution (*N Engl J Med*. 2007;356:1364-1366). ■

IBS-Drug Treatment Pulled, CV Side Effects

Tegaserod (Zelnorm), Novartis Pharmaceutical's drug for irritable bowel syndrome has been removed from the market by the FDA based on recent findings of increased risk of serious cardiovascular events associated with use of the drug. Tegaserod was approved in 2002 for women with irritable bowel syndrome whose primary symptom was constipation. It was given the additional indication in August 2004 for chronic constipation in men and women under the age of 65. Withdrawal was based on analysis of 29 studies involving more than 18,000 patients that showed a small, but statistically significant increase in the risk of cardiovascular side effects (0.1% serious adverse effects with tegaserod vs 0.01% with placebo). The FDA may allow continued use of the drug in a limited number patients for whom no other treatment options are available and the benefits of tegaserod outweigh the chance of serious side effects. The FDA may consider limited reintroduction of the drug at a later date if the population patients can be identified in whom the benefit of the drug outweighs the risk. ■

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Drug Combo Better for Migraine Treatment

Naprosyn plus sumatriptan is better than either drug alone for the treatment of acute migraine according to a new report. In 2 studies, nearly 3,000 patients with a history of migraine were randomized to sumatriptan 85 mg plus naproxen sodium 500 mg, both drugs alone, or placebo to be used after the onset of a migraine with moderate to severe pain. The primary outcome was headache relief at 2 hours, absence of photophobia, absence of phonophobia, absence of nausea, and sustained pain-free response. Sumatriptan plus naproxen was superior to placebo in all measures and was superior to either drug alone in sustained pain-free response. The incidence of adverse effects was the same for the combination as for the individual medications. The authors conclude that sumatriptan 85 mg plus naproxen 500 mg as a single pill for acute treatment of migraine is more effective than either drug as monotherapy (*JAMA*.2007; 297:1443-1454.). Pozen Pharmaceuticals/ GlaxoSmithKline is developing the combination pill, which is expected to be approved later this year under the trade name Trexima. ■

Pergolide Off the Market, Heart Disease Risk

Pergolide (Permax) is being withdrawn from the market after reports of serious valvular heart disease associated with the drug. Pergolide is a dopamine agonist used for the treatment of Parkinson's disease, hyperprolactinemia and pituitary tumor (?). The action was prompted by 2 reports in the January 4, 2007, *New England Journal of Medicine* that showed increased rates of valvular dysfunction in Parkinson's patients who were taking the drug. These findings coupled with the availability of other dopamine agonists prompted the FDA's action. Valeant Pharmaceuticals is removing Permax brand pergolide as are all generic manufacturers. ■

Hormone Treatment, Does Timing Matter?

Further analysis of the Women's Health Initiative suggests that the timing of the initiation of hormone therapy may have an effect on the risk of cardiovascular disease. The analysis looked at postmenopausal women who had undergone a hysterectomy and were randomized to conjugated estrogen or placebo and women who had not had a hysterectomy who were randomized to conjugated estrogen plus medroxyprogesterone or placebo. The main outcomes were coronary heart disease (CHD) and stroke. Women who initiated hormone therapy within 10 years of menopause had a lower incidence of CHD (HR 0.76 [95% CI, 0.50-1.16]), which equates to 6 fewer events per 10,000 person-years. For women who initiated therapy 10-19 years after menopause the hazard ratio was 1.10 (95% CI, 0.84-1.45), and for women who initiated therapy 20 years after menopause the hazard ration was 1.28 (95% CI, 1.03-1.58) or 12 excess events per 10,000 person years. CHD risk increased when patients were stratified by age as well. Hormone therapy increased the risk of stroke with no significant difference based on time since menopause or age. There was a non-significant trend for improved overall mortality in younger women. The authors conclude that women who initiated hormone therapy closer to menopause had a reduced risk of CHD, with an increase risk among women more distant from menopause although the trends did not meet their criteria for statistical significance (*JAMA*. 2007:297;1465-1477.). ■

FDA Actions

The FDA has approved Cangene's immune globulin to prevent reinfection with the hepatitis B virus in certain liver transplant patients. The product was previously approved for preventing hepatitis B infection after exposure in 2006. It is marketed as HepaGam B.

The FDA has banned rectal suppositories that contain trimethobenzamide due to lack of efficacy in preventing nausea and vomiting. The popular suppositories have been marketed under various trade names including Tigan, Tebamide, T-Gen and others. The drug will still be available as oral and injectable preparations. The evaluation which eventually led to the withdrawal is part of the FDA's ongoing Drug Efficacy Study Implementation (DESI) which evaluates older drugs previously approved based on safety data to make sure that they are also effective.

The FDA has approved Merck's combination diabetes drug Janumet, which combines sitagliptin with metformin. Sitagliptin, which is a dipeptidyl peptidase-4 inhibitor, has been marketed by Merck since last October under the trade name "Januvia." The combination is approved for the treatment of patients with type 2 diabetes; it should be dosed twice daily with meals with gradual dose escalation. ■