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INSIDE

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MRI for Diagnosis of Breast Ductal Carcinoma *In Situ*

ABSTRACT & COMMENTARY

By Leon Speroff, MD, Editor

Synopsis: *MRI is more sensitive than mammography for the diagnosis of breast cancer when it is in the stage of ductal carcinoma* in situ.

Source: Kuhl CK, et al. MRI for diagnosis of pure ductal carcinoma *in situ*: a prospective observational study. *Lancet.* 2007;370:485-492.

KUHL AND COLLEAGUES FROM THE UNIVERSITY OF BONN, Germany, compared the sensitivity of mammography and MRI for the diagnosis of breast ductal carcinoma *in situ* (DCIS).[1] Seven thousand three hundred and nineteen women received both screening tests. In 167 women with ductal carcinoma *in situ*, 93 (56%) were diagnosed by mammography and 153 (92%) by MRI. Eighty-nine high-grade ductal *in situ* cancers were all diagnosed by MRI, but 43 (48%) were missed by mammography. The authors concluded that MRI is more sensitive in diagnosing breast DCIS.

COMMENTARY

Ductal carcinoma *in situ* is a precursor of invasive breast cancer, with progression occurring more often and more rapidly with higher grade *in situ* lesions, and the subsequent invasive disease is of a higher grade with a poorer prognosis. Diagnosis of higher grade ductal carcinoma *in situ* is, therefore, highly desirable. Mammography has led to an increase in the diagnosis of DCIS from 2% of breast cancers in 1980 to 20% today.

Earlier studies concluded that MRI was no better, and even worse, than mammography in diagnosing DCIS, and thus, the results in the current report were unexpected. However, it has been learned that diagnostic criteria differ with the two techniques, incorporating not only morphology but enhancement kinetics with contrast during MRI. MRI does not just detect cases of DCIS at an earlier stage, but this method detects lesions without microcalcifications (a different group of tumors). Mammography detects cases of

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DCIS that have microcalcifications caused by necrosis.

One of the important messages of this report is that both film screen mammography and digital mammography have limited sensitivity for diagnosing DCIS (determined by the size of microcalcifications). Another important message is that MRI was better for the detection of the higher grade DCIS associated with worse prognosis. The reason for this is the contribution of contrast enhancement. Tissues with higher grade lesions will have greater capillary permeability and an increase in microvasculature, accounting for more contrast enhancement. It is also important to note that an analysis of risk factors (including breast density) in the current report could not differentiate those subjects where mammography would or would not detect DCIS.

The availability of MRI in general population screening is currently limited by an insufficient number of radiologists with the required level of expertise. Therefore the results in the current report are likely not achievable in many centers. Having said that, there are an increasing number of specialty centers with the expertise and technology to perform accurate MRIs. The full use of MRI to detect breast cancer at its earliest stage awaits the results of a large multicenter trial that is obviously now indicated. ■

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Reference

1. Kuhl CK, et al. *Lancet.* 2007;370:485-492.

Oral Contraceptives and Risk of Myocardial Infarction

ABSTRACT & COMMENTARY

By Leon Speroff, Editor

Synopsis: *A Swedish cohort study finds no increase in risk of myocardial infarction associated with low-dose oral contraceptives.*

Source: Margolis KL, et al. A prospective study of oral contraceptive use and risk of myocardial infarction among Swedish women. *Fertil Steril.* 2007;88:310-316.

MARGOLIS AND COLLEAGUES ANALYZED DATA from a large prospective study of a cohort of 48,321 Swedish women who are part of the Women's Lifestyle and Health Cohort Study.[1] Of the women who took part, 16.6% had never used oral contraceptives, 69.3% were former users, and 14.1% were current users (more than half were age 35 and older). There were 214 cases of myocardial infarction (24 fatal) during 11 years of follow-up.

Table 1

	Cases	Relative Risk Adjusted for Risk Factors
Former users	156	1.0 (0.7-1.4)
Current users	11	0.7 (0.4-1.4)
First use after age 30	10	1.0 (0.5-1.9)

The risk of myocardial infarction among current users was not elevated in smokers, but the conclusion was limited by small numbers. There was no trend for an increase in risk with duration of use. The authors concluded that low-dose (less than 50 µg ethinyl estradiol) oral contraceptives are not associated with an increased risk of myocardial infarction.

■ COMMENTARY

The Women's Lifestyle and Health Cohort Study is a prospective cohort study of 106,841 Norwegian and Swedish women, started in 1991, specifically designed to assess the long-term health effects of

hormonal contraceptives. All previous cohort studies date back to oral contraceptive use with higher doses of estrogen in the 1970s and 1980s. For example, in the report from the Nurses' Health Study in 1988, an increased risk of myocardial infarction was found in current users.[2]

Case-control studies of low-dose estrogen oral contraceptives have concluded that an increased risk of arterial disease occurs only in women who have hypertension or are smokers.[3-7] The cohort studies don't help us with this important issue because the numbers are too small for definitive analyses of subgroups. Nevertheless, British and Finnish cohorts were reported to have increased risks of developing myocardial infarction in oral contraceptive users who smoked.[8, 9]

This new study supports the conventional wisdom of the last decade that low-dose oral contraceptives do not increase risk of myocardial infarction or stroke in healthy, nonsmoking women, regardless of age. Screening for hypertension is especially important in that it is the major risk factor for stroke associated with oral contraceptive use. With no hypertension, the effect of smoking in women under age 35 is too small to be measured. It is currently believed that with medical control of blood pressure and close follow-up (blood pressure monitoring every 3 months), nonsmoking women under age 35 and otherwise healthy can use low-dose oral contraception. There is no reason to doubt that these conclusions apply as well to the transdermal and vaginal methods of steroid contraception. ■

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Increased Risk of Cognitive Impairment or Dementia in Women Who Underwent Oophorectomy before Menopause

ABSTRACT & COMMENTARY

By Sarah L. Berga, MD

James Robert McCord Professor and Chair, Department of Gynecology and Obstetrics, Emory University School of Medicine, Atlanta

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

Synopsis: *Both unilateral and bilateral oophorectomy preceding the onset of menopause increased the risk of cognitive impairment and dementia. Younger age at time of oophorectomy and lack of hormone use after premenopausal oophorectomy were associated with a greater risk of dementia.*

Source: Rocca WA, et al. *Neurology. [Epub ahead of print]* 2007;69:1074-1083.

THE PRESENT STUDY INDIRECTLY TESTED THE hypothesis that estrogen exposure is neuroprotective by studying the risk of dementia in women who underwent oophorectomy premenopausally. All women residing in Olmstead, MN, from 1950 to 1987 who underwent unilateral or bilateral oophorectomy were followed through death or end of study (staggered from 2001 to 2006). There were 813 women who had unilateral oophorectomy and 676 with bilateral oophorectomy. The referent group was 1472 women residing in the same county who were of comparable age. The RR for cognitive impairment or

dementia after premenopausal oophorectomy was 1.46 (confidence interval 1.13-1.90), $p < 0.0001$. The younger the age of the woman at the time of oophorectomy, the greater was the risk of cognitive impairment or dementia. However, use of hormones up to age 50 after the oophorectomy was associated with a risk of cognitive impairment or dementia comparable to that of the referent (intact) group.

COMMENTARY

The data come from the Mayo Clinic Cohort Study of Oophorectomy and Aging. Using this same cohort, the investigators previously reported that women who underwent prophylactic bilateral oophorectomy before age 45 years and who did not use replacement hormone therapy experienced an increased risk of all cause mortality. Other studies have shown that premenopausal oophorectomy increased the risk of osteoporosis and cardiovascular disease. The investigators interpreted the prior and current studies as evidence for a critical age window of exposure to gonadal steroids. Further, they suggest that the current study results help to reconcile the finding of the Women's Health Initiative Memory (WHIM) study, which showed an increased risk of mild cognitive impairment and dementia in women who took hormones after menopause. Indeed, several lines of evidence support the notion that estrogen is neuroprotective, including the findings that: (1) estrogen improves synapse formation in the hippocampus, a key memory center; (2) estrogen improves cerebral blood flow and glucose metabolism; (3) estrogen increases choline acetyltransferase activity in basal forebrain and hippocampus; (4) estrogen reduces the deposition of beta-amyloid in the brain; and (5) estrogen prevents beta-amyloid from causing mitochondrial damage. There are other data as well, including neuroimaging data in humans that show better reading performance and increased blood flow to regions activated during cognitive tasks in postmenopausal women taking hormones (Shaywitz S, et al. *Menopause.* 2003; 10:420). No one study alone is conclusive or convincing, but when considered in aggregate, it would appear that estrogen exposure is especially important for women who undergo oophorectomy before menopause. The WHIM trial could be interpreted as suggesting that estrogen loses its neuroprotective actions as women age. Alternatively, it could be that a hiatus in estrogen exposure is the critical insult from which complete recovery is not possible with subsequent estrogen use. Clearly it matters to understand which of these potential interpretations is most likely, as clinical intervention strategies would need to be revised if a hiatus were the factor most likely to accelerate brain aging. It may seem curious that both unilateral and bilateral oophorectomy done before menopause increase the risk of cognitive impairment and dementia. The authors suggest that unilateral oophorectomy or concurrent hysterectomy contribute to premature ovarian failure by interfering with blood supply to the remaining ovary.

Detailed Pathological Assessment of Fallopian Tube Paramount in Women Undergoing Prophylactic BSO for BRCA Mutation

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

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

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

Synopsis: *Adnexal tissues removed during surgery for risk-reduction in women with BRCA mutations should have thorough and directed evaluation of the ampulla and fimbrial sections for occult malignancy.*

Source: Callahan MJ, et al. *J Clin Oncol.* 2007;25:3985-3990.

The performance of risk-reducing surgery in women with BRCA mutation has a profound effect on the potential for subsequent cancer development. While gross tumor is occasionally identified in these specimens, it is more common that pathological processing identifies occult cancer. This has led to the recommendation of serial step sectioning of the ovaries and tubes in these cases. Callahan and colleagues sought to determine the frequency and location of malignancies detected after prophylactic salpingo-oophorectomy in women with BRCA mutations. Over an eight-year period, 122 women (median age 46.5 years) with BRCA mutations undergoing risk-reducing surgery were evaluated for cancer in the resected adnexa. The group used two techniques of serialized pathologic sectioning: a standard cross-sec-

tional method and a newer technique, which in addition to cross-sectional sectioning of the proximal tube, sagittally sectioned the amputated fimbrial portion. The majority of the procedures were done laparoscopically (70%) and included cytology in all but 3 cases. Concomitant hysterectomy was performed in 25%. In total, 7 cancers (5.7%) were identified; 6 were microscopic and discovered on pathological analysis. All patients were older than 44 years and all involved the fallopian tube. Two also had microscopic foci in the ovary and two were associated with malignant cytology. There was no difference in identification by technique; however, fewer rounds of sectioning were required to identify occult malignancies. The authors conclude that the distal fallopian tube appears to be the dominant site for early, occult malignancies identified in the adnexa of women undergoing prophylactic risk-reducing surgery. They implore aggressive sectioning to accurately identify these cases given their potential for metastatic spread.

COMMENTARY

Concomitant with an increased awareness of and sought-after professional counseling for women with potential genetic risk of gynecologic malignancy has been a wider acceptance of risk-reducing prophylactic surgery. The net impact of these procedures appears to have a beneficial effect on lifetime cancer risk. In addition, recognition of the potential for occult cancer has ushered in recommendations for a more careful inspection of the resected tissues. Reports to date have suggested that occult malignancy may be found in 2.3% to 17% of patients with BRCA mutation. What is being more clearly defined, and is one of the stated objectives of the current report, is that the fallopian tube is "ground zero" for these occult malignancies. Further, it appears that the ampulla and fimbrial sections of the distal tube are the most common sites for primary involvement. While the entire fallopian tube is still recommended to undergo serial sectioning, the authors recommend sagittal sectioning of this higher-risk locale in order to clearly find these tumors. This is being emphasized as many of the occult lesions represent tubal *in-situ* carcinomas, which have been additionally associated with malignant cytology despite the absence of an invasive component. While the impact of adjuvant chemotherapy is not known in these patients, recurrences have been documented. In addition, some patients develop cancer subsequently despite prophylactic surgery. It is not known if these cases are a result of sampling error or peritoneal transformation.

The Society of Gynecologic Oncologists has published guidelines in the care of these women including a recommendation to perform risk-reducing surgery at the completion of childbearing or by age 44. Given the age at diagnosis in the current and previous studies, this recommendation appears sound. Further follow-up and continued reporting of improved sectioning techniques will refine the care of these women. ■

Advancing the 'Comfort Zone' with Laparoscopic Gynecologic Oncology

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

Synopsis: *Laparoscopic radical hysterectomy appears to be a potentially viable alternative to open radical hysterectomy for women with early stage cervix cancer amenable to surgical therapy.*

Source: Frumovitz M, et al. Comparison of total laparoscopic and abdominal radical hysterectomy for patients with early-stage cervical cancer. *Obstet Gynecol.* 2007;110:96-102.

Advances in laparoscopic instrumentation and surgical skill have enabled the adoption of oncologic procedures traditionally approached via ceiliotomy to the minimally invasive modality. However, little comparative data are available on some of the most complex of these operations. Frumovitz and colleagues looked retrospectively, over a 3-year period, at patients undergoing radical hysterectomy and pelvic lymphadenectomy for invasive primary cervix cancer. Comparative groups were those patients undergoing laparotomy vs laparoscopy to complete the procedure. Physician preference dictated which patients received which approach; however, few surgeons at the primary center performed both approaches. This was highlighted by the tendency to more frequently offer open radical hysterectomy (n = 54) as compared to laparoscopic radical hysterectomy (n = 35). Both groups were comparable in patient (age, weight, BMI, race) and tumor (Stage, histology) characteristics. Surgical outcomes demonstrated while laparoscopy

was associated with longer OR times and higher rates of vascular injury (n = 3), it was associated with lower intraoperative blood loss and post-operatively with significantly lower infectious morbidity and hospitalization. Pathology specimens were equivalent relative to size of the parametrium, vaginal cuff length, negative margins, and nodal metastases. There was a significantly higher number of nodes (19 vs 14) in the open cohort. Equal rates of bladder atony, resolution of normal voiding function, and readmission to the hospital was observed between the two cohorts. Median follow-up was 13 months, during which 3 recurrences were documented (2 abdominal, 1 laparoscopic); survival was immature. The authors concluded the cohorts provided equivalent surgical specimens but that the laparoscopic approach, albeit longer in duration, was associated with more favorable operative morbidity.

COMMENTARY

Definitive operative management of most early stage cervix cancer consists of removal of the uterus with margins encompassing the parametrium, upper vaginal and utero-sacral ligaments along with a pelvic lymphadenectomy. In selected patients, the procedure has been associated with high cure rates but its complexity requires precise mobilization of the bladder and ureter as well as preservation of a portion of the pelvic nerves to reduce potential morbidity ranging from intraoperative blood loss to prolonged neurogenic bladder and bowel dysfunction. Recent adaptation of laparoscopic techniques and improvement in surgical instrumentation has enabled a spectrum of procedures to be approached with minimal access points. Although prophylactic oophorectomy and treatment reassessment procedures have been performed in patients at risk or diagnosed with gynecologic cancer for more than 40 years, extirpative surgery was only first explored less than 20 years ago. Both laparoscopic hysterectomy and radical hysterectomy were described in the early 1990s; the former has been validated as an alternative to open hysterectomy for endometrial cancer patients by phase III investigation. By contrast, laparoscopic radical hysterectomy is still largely performed in select centers. However, interest and expertise is rapidly increasing and plans are underway to perform a similar validation study for radical hysterectomy. This worldwide effort is necessary to clearly elucidate the safety of offering the procedure in the general community. Despite the obvious academic and practical impact of this trial, the greatest challenge may lie in getting the "believers" to commit to performing "standard" arm. ■

Special Feature

Is There Value in CA125 Distinguishing Benign from Malignant Ovarian Tumors?

By Robert L. Coleman, MD

CA-125 measurements alone or as part of a multimodal strategy are routinely used clinically to aid in developing a treatment plan for women with adnexal masses. Well-known limitations in CA-125 testing, particularly in premenopausal women, generally indicate additional measures—usually imaging, to most accurately describe the clinical state of affairs and to develop a therapeutic strategy. Timmerman and colleagues[1] reviewed the performance of CA-125 alone and in combination with a number of mathematical models to predict the histologic nature of persistent adnexal masses in 809 recruited women participating in the International Ovarian Tumor Analysis (IOTA) study. Prevalence of cancer in this study was 30%, with approximately two-thirds representing primary invasive ovarian cancers; 55% of the women participating were premenopausal. Test performance was measured by calculating the area under the receiver operator characteristics curve for each of the models. For menopausal and premenopausal cohorts, a training set and testing set were used. The prevalence of cancer in the prospective test set was 37%. Overall, CA-125 did not add to the testing performance of the ultrasound-dominant malignancy index model (M1). The original M1 was constructed from 12 independent variables including personal history parameters. When new models were constructed in the pre- (designated "M3") and menopausal (designated "M4") cohorts, CA-125, once again, did not improve the testing performance of the models; however, CA-125 as a single parameter performed well relative to the model in menopausal women. The authors conclude that adding CA-125 to clinical information and ultrasound information does not improve the discrimination of mathematical models between benign and malignant adnexal masses.

COMMENTARY

Over the more than two and a half decades since CA-125 was discovered, the biomarker has proved to be profoundly useful in a number of clinically important scenarios, including prognosticating outcomes to therapy, monitoring response to adjuvant treatment, surveillance, and defining progression of disease. Its reliability in these arenas has also led to the incorporation of CA-125 as a measure of disease progression in clinical studies and is being considered as a measure of response by the Food and Drug Administration. It is also being evaluated prospectively in serial measures as a determinant of ovarian cancer development (screening) and has served in a surveillance role in primary malignancies and diseases other than ovarian cancer. On the whole this single biomarker is incredibly useful. However, it is not perfect — and, as demonstrated in the current study, CA-125, as a one-time measure, may not be the most accurate way to discriminate malignancy in women with adnexal masses.

The authors of this report have championed the utility of clinical history, such as history of ovarian cancer, hormone use, and age combined with specific ultrasound characteristics as the most efficacious way to identify a probability estimate of malignancy. The impetus to develop and validate a model such as this is to help with the triage of patients to the appropriate specialists (gynecologic oncologists) should the index of suspicion for cancer be high. The study was well-conceived and conducted and used a prospective testing set with rigorous parameters to compare the various models. Although the sample is larger than most others reported to date, the number of cancers in the subgroups is still relatively small upon which to make inference. In addition, the prevalence of cancer among the cohorts by history was likely not equivalent nor large enough to evaluate a differential effect. For example, the probability of malignancy in a premenopausal woman with an adnexal mass in this study was much lower than the likelihood of malignancy in a woman with a history of ovarian cancer and an adnexal mass. Nonetheless, there are other considerations to note, which limit the "common" utility of the report's conclusions.

First, while the model is statistically derived, it has detailed information about the patient that is not always available to the sonographer. The regression formula contains 7 to 12 variables (depending on menopausal status) and cannot be practically calculated without a computer. Such a limitation can be overcome but it raises the next question: "what's a significant probability estimate in which to become concerned?" Is any number about 10% important enough for referral? For surgery? For repeat testing? In addition, highly trained sonographers retrieving specific information on the mass(es) led to the model's construction. Are such characteristics reproducible outside of a tertiary care referral center? Last, while CA-125 was dropped in these models as not adding significantly to the testing performance, several surrogates likely overshadowed its impact, such as ascites and mass size—particularly the solid component.

The clinical utility of biomarkers is immense and subject of intense investigation. The advantage a blood test as over operator-dependent testing is obvious in its generalization. However, the search for equally performing biomarkers has been problematic, though progress is being made. It is likely that future reports will include a panel "cocktail" in which to develop a risk index. However, decision algorithms based on these results will need validation for clinical practice.[2-3]

Any effort improving the precision of estimation is worthwhile. The trick will be in developing a clinically useful model that is applicable to the population in general. ■

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CME Questions

23. The following statements are true regarding screening for breast ductal carcinoma *in situ* (DCIS) except:

a. The sensitivity of screening for DCIS with mammography depends on the presence of microcalcifications.
b. The sensitivity of screening for DCIS with MRI depends on the presence of microcalcifications.
c. Acceptable sensitivity of MRI screening requires contrast enhancement.
d. MRI may detect DCIS of higher grade disease.

24. The following statements regarding oral contraceptives and arterial disease are true except:

a. Arterial disease is a dose-related side effect with

the estrogen component in oral contraceptives.
b. With low-dose oral contraceptives, arterial disease occurs only in association with recognized risk factors.
c. Hypertension and smoking are the two factors most influencing the risk of arterial disease in oral contraceptive users.
d. Aging by itself is a risk factor for arterial disease in oral contraceptive users.

25. Premenopausal oophorectomy has been shown to increase the risk of all of the following except:
a. cardiovascular disease
b. dementia
c. all-cause mortality
d. breast cancer
e. osteoporosis

26. Which of the following is true regarding the median age of those identified with cancer in the prophylactic specimens compared to those with benign lesions:
a. Patients with cancer were significantly younger than patients with benign disease
b. There was no difference in age between the cohorts
c. Patients with cancer were significantly older than those with benign disease

27. In this study (*Advancing the 'Comfort Zone' with Laparoscopic Gynecologic Oncology),* data was collected on both estimated blood loss and use of transfusion. Which of the following is true of these two factors in patients undergoing laparoscopic radical hysterectomy relative to laparotomy: Patients undergoing laparoscopic radical hysterectomy had:
a. lower EBL, similar transfusion rate
b. lower EBL, lower transfusion rate
c. equivalent EBL and transfusion rate
d. equivalent EBL and higher transfusion rate

28. In the subgroup evaluation, the authors developed a model (M4) in menopausal women which included CA-125 as one of the seven variables. Which of the following statement most accurately describes the performance of M4 relative to the original model M1 (which excludes CA-125):
a. M4 was significantly better than M1 in discriminating a malignant ovarian mass
b. M4 was similar to M1 in diagnostic accuracy
c. M4 was significantly inferior to M1 in this cohort
d. M4 was no better than CA-125 alone in menopausal women with adnexal masses

Answers: 23 (b); 24 (d); 25 (d); 26 (c); 27 (a); 28 (b)

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.

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Stopping Statins in At-Risk Patients — Just Too Risky

In this issue: *Make sure your patients don't stop statins after a stroke or surgery; MRSA is becoming more resistant to mupirocin; new asthma treatment guidelines; and FDA approvals and warnings.*

Stopping statins, even briefly, after stroke or cardiovascular surgery increases vascular complications according to 3 new studies. Spanish investigators looked at 89 patients who were on chronic statin therapy and were admitted with acute stroke. Half were randomized to statin withdrawal for the first 3 days after admission, while the other half immediately received atorvastatin 20 mg/day. After 4 days, the statin withdrawal group was also started on atorvastatin. The primary outcome was death or dependence after 3 months as defined by modified Rankin scale of 2 or more. After 3 months, 60% of those in the statin withdraw group were disabled to the point of dependence compared with 39% of those that continued statin therapy (P = 0.043). Early neurologic deterioration was also far greater in the statin withdrawal group (65.2% versus 20.9%; $P < 0.0001$). Statin withdrawal patients also had greater infarct volume (P = 0.002). The authors conclude that statin withdrawal in the first few days after stroke is associated with a markedly increased risk of death or dependency at 90 days; hence, treatment should continue the acute phase of an ischemic stroke (*Neurology* 2007; 69:904-910).

In another study, researchers in Italy looked at stroke patients who discontinued statins after discharge from the hospital. The study population included 631 stroke patients (322 men, 309 women) without evidence of heart disease. All patients were discharged on a statin, but 38.9% discontinued the drug within 12 months. In the 12 months of follow-up, 116 patients died. After adjustment for all confounders and interactions, the hazard ratio for mortality in patients who quit a statin was 2.78 (95%CI, 1.96-3.72; P = 0.003) or nearly 3 times higher risk of death (*Stroke* 2007, published online ahead of print 8/30/07).

Another study from the Netherlands looked at a brief interruption in statin therapy associated with major vascular surgery. Nearly 300 patients on statins underwent major vascular surgery, and statin therapy was interrupted in the perioperative period in 70 patients for mean duration of 3 days. An association was observed between statin discontinuation and an increase risk of postoperative troponin release (HR 4.6) and the combination of MI and cardiovascular death combined (HR 7.5). Because many surgical patients are NPO and unable to take oral statins, and there's no intravenous statin available, the only extended release statin was tried on a subset of patients preoperatively. Patients receiving extended-release fluvastatin had fewer perioperative cardiac events compared to other statins (*Am J Cardiol* 2007; 100:316-320). The message of these studies is that statin interruption, even for a brief period during hospitalization, may lead to serious adverse events in patients at risk.

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Mupirocin Less Effective Against MRSA

Mupirocin (Bactroban) is becoming less and less effective against MRSA, even in hospitals with low levels of mupirocin use. Researchers from Washington University in St. Louis performed nasal swab cultures for MRSA in all patients admitted to their surgical intensive care unit (SICU) on admission, weekly during hospitalization, and at discharge. Of the 302 positive MRSA isolates, 13.2% were resistant to mupirocin, with 8.6% having high-level resistance. Patients with mupirocin-resistant MRSA were more likely to be older, have a history of a previous admission in last year, and had higher in-hospital mortality. The authors conclude that patients carrying mupirocin-resistant MRSA acquired it through contact with the health-care system; the strains were probably not acquired in the SICU (*Clin Infect Dis* 2007; 45:541-547). Mupirocin is commonly used to decolonize patients who are *staph aureus* carriers or have nasal colonization with MRSA. With resistance patterns increasing nationwide, this strategy may need to change.

New Guideline for Asthma Diagnosis/Management

The National Asthma Education and Prevention Program has issued an update to their clinical practice guidelines for diagnosis and management of asthma (Expert Panel Report 3 [EPR-3]). The new guideline emphasizes the importance of asthma control and highlights 4 areas of emphasis including assessment and monitoring, patient education, control of environmental factors and other asthma triggers, and pharmacotherapy. The new guideline recommends continued use of a stepwise approach to asthma control in which medication doses or types are stepped up or down as needed based on asthma control. Recommendations now are based on 3 age groups, 0-4 years, 5-11 years (a new category), and 12 years and older.. The new age group was added because of evidence that children respond differently to medications than adults. The entire guideline can be found at: http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf .

FDA Actions

The FDA announced on August 14 that manufacturers of rosiglitazone (Avandia) pioglitazone (Actos), and other combination medications containing the 2 drugs will be required to add a "black box" warning to their labeling to reflect the risk of heart failure associated with the 2 drugs. Both drugs have been associated with reports of significant weight gain and edema, and some cases continuation of therapy has lead to poor outcomes including death. The black box warning advises health-care professionals to carefully observe patients taking these drugs for signs and symptoms of heart failure including rapid weight gain, shortness of breath, edema. The warning also recommends not starting either drug in patients with a history of congestive heart failure. The agency continues to review rosiglitazone for the possible increase risk of myocardial infarction associated with use of the drug.

The FDA has approved a new indication for zoledronic acid (Reclast) as a once-a-year treatment for postmenopausal osteoporosis. Reclast is administered as an annual 15-minute intravenous infusion. The drug is a bisphosphonate similar to oral bisphosphonates such as alendronate and risedronate.

Anesiva has received approval to market lidocaine topical powder intradermal injection system (Zingo) to provide local analgesic prior to venipuncture or peripheral intravenous cannulation in children ages 3-18. Zingo is a single-use helium powered system that is administered 1-3 minutes prior to needle insertion. The system is also being studied in trials of adults.

The FDA has approved a new combination of carbidopa, levodopa, entacapone (50 mg/200 mg/200 mg) for the treatment of Parkinson's disease. The new preparation helps reduce the pill burden for Parkinson's patients on multiple medications. Carbidopa/levodopa/entacapone will be marketed by Orion Corporation as Stalevo.

Omrix Biopharmaceuticals has received approval to market human thrombin (Evithrom) to promote blood clotting and control bleeding during surgery. Evithrom is the first human thrombin approved since 1954 and the only product currently available for this indication. It is applied to the surface of bleeding tissue during surgery and may be used in conjunction with absorbable gelatin sponge. Other thrombins currently on the market are derived from cattle plasma.

Nursing mothers who were taking codeine may put their babies at risk of morphine overdose if they are "ultra-rapid metabolizers of codeine," a condition that may affect up to 28% of the population. Codeine is generally recommended for nursing mothers as a cough suppressant and pain medication; however, ultra-rapid metabolizers quickly convert codeine to morphine and excrete it in breast milk. At least one infant death has been associated with this condition. The FDA has issued warning regarding codeine use by nursing mothers, recommending that mothers observe their infants closely while taking the medication for signs of morphine overdose including sleepiness, difficulty breast feeding, breathing difficulties or limpness. ■