**DMPA Use and Bone Fractures**

**ABSTRACT & COMMENTARY**

**By Rebecca H. Allen, MD, MPH**

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Dr. Allen reports no financial relationships relevant to this field of study.

**Synopsis:** Although users of depot medroxyprogesterone acetate (DMPA) experienced more bone fractures than users of other contraceptives, their risk of bone fractures was higher at baseline before initiating DMPA and did not change while on DMPA. This suggests that confounding, unknown factors led to the association between DMPA and fractures in previous studies.


**The authors performed a retrospective cohort study using data from the General Practice Research Database in the United Kingdom, which contains de-identified records from more than 350 general practices. The data are collected longitudinally and have been validated for drug safety studies. The study population included all women under the age of 50 who had at least one prescription contraceptive record between January 1987 and December 2005. Women were followed until December 31, 2005, or until a first recorded fracture or termination from the practice. DMPA users were compared to non-users, who included women using oral contraceptives, the intrauterine device, cervical cap, or diaphragm.

Using data from the full cohort of 312,395 women, the authors found that prior to starting contraception, the crude incidence rate ratio for fractures for women who later became DMPA users was 1.28 (95% confidence interval [CI], 1.07-1.53) compared with women who had never used DMPA. The rate in DMPA users before starting contraception was 8.4 per 1000 person-years and in DMPA never-users it was 6.6 per 1000 person-years. After starting contraceptives, DMPA users still had a higher risk of fracture than never-users; however, it did not increase from baseline (relative risk [RR], 1.23; 95% CI, 1.16-
Although studies have documented BMD recovery after DMPA use, no study has examined the incidence of actual fractures in DMPA users in the general population. Research instead has focused on the intermediate outcome, BMD, which may not be an appropriate marker for fractures in premenopausal women. Therefore, the authors of this study explored the association between DMPA use and fracture incidence using a validated research database from the United Kingdom that contained medical and prescription records. Their study is unique in that they were able to assess fracture risk both before and after initiating DMPA. After controlling for many risk factors associated with fracture, such as smoking and alcohol abuse, DMPA use was still associated with increased fracture risk. Thus, the authors concluded that there must be some unmeasurable confounder that led to this association. Likely, women who choose DMPA are more at risk for trauma-related fractures due to behavioral or lifestyle factors. Or perhaps, over-reporting occurred with DMPA users because they presented every 3 months for their injection. It is reassuring that DMPA use was not associated with fractures of the axial skeleton, typically associated with decreased BMD. In addition, longer DMPA use was no more associated with fractures than short-term use.

In sum, the unintended pregnancy rate in the United States stands at 49%.7 DMPA is one of the methods of contraception that users do not have to remember on a daily, weekly, or monthly basis. In addition, young women and adolescents are able to use DMPA as reliably as adults.1 DMPA is very forgiving, as well, given that users can be up to 4 weeks late for an injection and still be protected. Keeping DMPA available as an option for women is important, and this study should reassure providers that use of DMPA does not need to be limited out of concern for fractures. In our clinic, per ACOG recommendations, we do not limit DMPA use, nor assess BMD in DMPA users.

References
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1.30). Furthermore, longer use of DMPA did not increase fracture risk. Compared with nonusers, DMPA users had more codes for extremity and miscellaneous fractures but there was no excess risk for fractures typically associated with decreased bone mineral density (BMD) such as the hip, pelvis, and vertebrae.

**COMMENTARY**

DMPA is a highly effective, injectable contraceptive with a failure rate of 0.22 per 100 person-years when used correctly.1 DMPA does cause declines in BMD in adults, with mean loss of 5.4% (lumbar spine) and 5.2% (hip) after 5 years of use.2 In adolescents, there are mean decreases of 2.7% (spine), 4.1% (hip), and 3.9% (femoral neck) after 5 years.3 Given that decreased BMD in postmenopausal women is associated with fragility fractures, there was concern that decreased BMD in DMPA users could also lead to fractures. In 2004, the FDA placed a black box warning on DMPA, stating that it should not be used for longer than 2 years unless other birth control methods were inadequate and that evaluation of BMD was recommended for long-term use.4 In 2002, 5.3% of U.S. women on contraception used DMPA, declining to 3.2% as of 2008.5 Studies have shown, however, that the decreased BMD caused by DMPA is fully reversible on discontinuation.6 The American College of Obstetricians and Gynecologists (ACOG) does not place any limits on DMPA use and advises that BMD assessment in reproductive-aged women on DMPA is not useful. Despite reassurance from ACOG, the FDA warning caused physicians to limit patient use of DMPA.4

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**Questions & Comments**

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Ectopic Pregnancy and Subsequent Fertility

ABSTRACT & COMMENTARY

By Jeffrey T. Jensen, MD, MPH

Synopsis: In a large, multicenter, randomized study of women in Europe who presented with ectopic pregnancy, there was no significant difference in the rate of subsequent intrauterine pregnancy observed following early ectopic pregnancy managed with medical therapy or conservative (salpingostomy) surgery, or following acute ectopic pregnancy managed with radical (salpingectomy) or conservative surgery.


In the DEMETER trial, the authors designed a study to address whether treatment for ectopic pregnancy (EP) affects subsequent spontaneous fertility. This multicenter trial was conducted at 17 participating centers in France from 2005 to 2009. Eligible subjects were women with an ultrasound-confirmed EP. Key exclusions included EP as a result of contraceptive failure or in vitro fertilization (since these might confound the time to subsequent pregnancy) or a single fallopian tube (randomization to salpingectomy considered unethical). Women presenting with EP were divided into two arms depending on the activity of the EP. In Arm 1 (less active ectopic pregnancies considered hemodynamically stable), medical treatment was considered practical, and women were randomly allocated to conservative surgery (e.g., salpingostomy with postoperative methotrexate) or methotrexate injection alone. In Arm 2 (active ectopic pregnancies), medical treatment was not considered practical, and subjects were randomly allocated to undergo either a radical (e.g., salpingectomy) or conservative (plus postoperative methotrexate) tubal procedure. Sample sizes were computed to provide a statistical power of 80% to detect a 20% difference in subsequent cumulative fertility rates between treatments in each arm. Cumulative fertility curves were drawn with the Kaplan–Meier method and compared with the log-rank test. Hazard ratios (HRs) were computed with the Cox model. Analysis was performed according to the intention-to-treat principle.

Over 5 years, 207 women were randomized in Arm 1 and 199 in Arm 2. For early EP (Arm 1), the cumulative fertility curves were not significantly different between medical treatment and conservative surgery. The 2-year rates of intrauterine pregnancy were 67% after medical treatment and 71% after conservative surgery (HR, 0.85; 95% confidence interval [CI], 0.59–1.22) Findings were similar among those women presenting with advanced EP (Arm 2), with cumulative 2-year fertility curves not significantly different between conservative (70%) and radical (64%) surgery (HR, 1.06; CI, 0.69–1.63).

COMMENTARY

DEMETER was the Greek goddess of fertility. EP remains one of the most important surgical problems faced by gynecologists. In the United States, EP occurs in about 1 in 80 pregnancies.¹ Over the last 20 years, the surgical treatment of EP has become less needed as early diagnosis and highly effective medical management protocols using methotrexate have developed. Still, the question that occupies our mind as we counsel women with a first EP is “how will this treatment affect her subsequent fertility?” Our job requires us to balance all of the competing goods — lowest overall cost, need for follow-up, invasive nature of surgical procedures vs uncertainty of medical outcomes, risk of complications — and package this into something our patient (and her family) can digest during an acute health care event. The information in this study helps provide more clarity regarding how the treatment
decision may impact subsequent fertility.

To study this question, the authors created a protocol designed to look at the real-life treatment decisions involved in early (medical management or conservative surgery) and advanced (conservative or radical surgery) EP. They studied only those women with EP as a result of a spontaneous conception (not contraception failure or IVF), as the primary outcome was subsequent spontaneous intrauterine pregnancy and this group was felt most likely to attempt repeat pregnancy in the next 2 years. However, interest in subsequent fertility was not a requirement for participation. In fact, enrollment was slow in Arm 2, as many women refused participation, apparently out of concern for randomization to the salpingectomy arm. It may be that those women most concerned and motivated about subsequent pregnancy did not participate. Given that, the finding that the 2-year rate of pregnancy was only 64-71% is not bad and may not reflect the overall chance of subsequent fertility.

The noteworthy result is that outcomes are generally good and similar between all of the treatments. Although the two treatment arms represent different severity of disease, the 2-year rate of subsequent pregnancy was similar (71% Arm 1, 70% Arm 2) among women treated with conservative surgery. In Arm 1, the pregnancy rates with medical therapy (67%) were not statistically different from conservative surgery. Although pregnancy rates were slightly lower (64%) among women randomized to salpingectomy in Arm 2, this was not statistically significant.

All studies have limitations and caveats. One important consideration in this study is that all women managed with conservative surgery received routine postoperative methotrexate. In the United States, this practice is less common, with careful follow-up of postop hCG levels used to guide the need for methotrexate treatment at many centers. The DEMETER protocol was guided by evidence reported by Graczykowski and Mishell that the relative risk of developing persistent EP after prophylactic methotrexate was 0.13 (CI, 0.02-0.97) in a study of 129 women. Therefore, while the observed effect size of 4-6% noted between treatment groups was not statistically significant, it might be worth considering if this is real. Consider that a 4-6% difference in survival would generally be considered highly relevant in a cancer study. Thus, it is appropriate to reflect on whether the observed difference would affect clinical judgment if a larger study confirmed these results with statistical significance. For early EP (Arm 1), medical therapy was slightly inferior to conservative surgery. This margin is small (4%) and would not motivate me to suggest surgery as an option to women who were good candidates for methotrexate. However, subsequent fertility should not be a factor in recommending against surgery in women interested in that approach. For women with advanced EP, the larger (6%) difference in subsequent pregnancy still argues for a conservative approach with linear salpingostomy.

References

Reproductive and Sexual Function after Gastric Bypass Surgery

By Michael A. Thomas, MD

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Dr. Thomas reports no financial relationships relevant to this field of study.

Synopsis: In a prospective cohort of obese, reproductive-aged women, there were no changes in the number of ovulatory cycles, but there was a shortening of the follicular phase and an improvement in sexual function after gastric bypass surgery.

drugs, and had a medical condition that was thought to contribute to obesity (hypothyroidism, Cushing’s syndrome, or a genetic predisposition). Every woman who qualified underwent a Roux en Y gastric bypass. Forty-one women were consented and screened, but only 29 were enrolled. A preoperative study visit was performed, and visits were scheduled postoperatively at months 1, 3, 6, 12, and 24. Only nine subjects completed the entire 24 months of the study. Over the course of the study, urine was collected daily and measured for estrone 3-glucuronide and pregnanediol 3-glucuronide. Other assessments included fasting serum at each visit for estradiol, progesterone, testosterone, and SHBG; transvaginal ultrasound at months 6 and 12; bone and body composition by DEXA at each visit; Female Sexual Function Index (FSFI) questionnaire preoperatively and at month 12; and a diary of vaginal bleeding. Prior to surgery, 90% of the women had ovulatory cycles; this did not change postoperatively. However, the follicular phase of the menstrual cycle decreased by 6.5 days by month 3 and continued to show a decrease between 7.9-8.9 days in months 6-24. Sexual function improved, with a FSFI score improving from 21.2 ± 9.6 preoperatively to 27.1 ± 7.4 (P = 0.02). Body composition showed a significant decrease in absolute total, fat, and lean mass at months 12 and 24, but bone mineral density did not change. The authors concluded surgical weight loss had a modest effect on overall reproductive hormone function, but it did show an improvement in body composition and sexual function. Although the majority of cycles remained ovulatory, the follicular phase shortened, potentially making the ovulation date more predictable if pregnancy was a possible goal.

COMMENTARY

An increasing number of hospitals have started a gastric bypass program to meet the needs of obese individuals who have developed medical problems. These serious medical problems, for which a surgical intervention for obesity becomes an option, primarily include metabolic syndrome, sleep apnea, dyslipidemia, diabetes, and high blood pressure. The media has inundated us with the fact that there is an obesity epidemic in the United States with causes including genetics, a high-fat/high-caloric diet, and a lack of adequate physical activity. The authors of this study set out to observe changes in reproductive hormone concentrations, menstrual cyclicity, body composition, and sexual function in obese women who decided to undergo surgical gastric bypass as an alternative to medical therapies, diet, and/or exercise. Surprisingly, the vast majority of the study participants were already ovulatory (90%) and remained that way postoperatively. However, the follicular phase of their cycles shortened over 24 months; this would be helpful for those individuals who were attempting conception or practicing natural family planning. In fact, six of the 29 patients conceived during the first 12 months after surgery. This study as well as others demonstrated an improvement of sexual function by scores from a validated survey.

Overall, this study highlights the need for similar observations in anovulatory obese women with and without a diagnosis of polycystic ovary syndrome who are actively considering conception as a goal. Though weight loss was accomplished with an improvement in menstrual cyclicity, body composition, and sexual function, it is assumed that their medical issues also improved — a result that is not well outlined. Diet and exercise are thought to be first-line interventions for patients with obesity, but few are able to reduce and then maintain their weight with this approach exclusively over time. Whether other surgical gastric procedures, like gastric banding, biliopancreatic diversion, or sleeve gastrectomy, confer any better reproductive hormone, body composition, or sexual function outcomes remains to be seen in this patient population. The American College of Obstetricians and Gynecologists recommends that pregnancy be avoided for 12-18 months after bariatric surgery to minimize any nutritional deficiencies that may arise that potentially could affect the mother or fetus. Also, barrier or non-oral hormonal contraceptives should be considered because of the potential absorption concerns that can occur postoperatively.

References

Special Feature
Thyroid Disease in Pregnancy

By John C. Hobbins, MD
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Dr. Hobbins reports no financial relationships relevant to this field of study.

Overt maternal hypothyroidism and hyperthyroidism each complicate about 3/1000 pregnancies. However, subclinical hypothyroidism can accompany as many as 2.5% of pregnancies. Both problems require careful surveillance because of the potential to cause significant maternal and fetal complications.
Thyroid Physiology

During pregnancy, the maternal thyroid works overtime. A two-fold increase in thyroid binding globulin (TBG), along with elevated hCG levels in the first and second trimesters, stimulates maternal thyroid activity. With this increased work load, the thyroid gland swells by about 20% in size. The fetal thyroid is quiet in the first trimester as the fetus is dependent on maternal free triiodothyronine (fT3) and maternal free thyroxin (fT4) for its needs. By 18 weeks, the fetus is self-sufficient and fetal thyroid hormone production is largely regulated through self-regulation, the levels of fetal thyroid-stimulating hormone (TSH) rise.1

Various thyroid products have different placenta-traversing capabilities. These properties become important when the maternal thyroid is over- or underactive. For example, TSH does not cross the placenta but fT3, fT4, and thyroid-stimulating immunoglobulins (TSI) do. The placenta will de-iodinate much of the fT3 to reverse T3, which is essentially inactive. The fetal thyroid gland is especially busy in later pregnancy when it is more involved in oxygen consumption, carbohydrate metabolism, and fetal growth and development.

Hypothyroidism

This maternal problem is caused by insufficient production of maternal fT3 and fT4. By far, the most common cause in pregnancy is Hashimoto’s thyroiditis, an autoimmune condition associated with thyroid peroxidase (TPO) and/or thyroglobulin antibodies, which have a direct antithyroid effect. Type 1 diabetics are particularly susceptible to hypothyroidism. Mothers with untreated or undertreated hypothyroidism have increased rates of preeclampsia, preterm birth, and low birth weight. Additionally, inadequately treated pregnant women with hypothyroidism have children with increased risk for psychomotor abnormalities and lower IQs (even in a subclinical setting)2 — underscoring the need to recognize hypothyroidism early enough to initiate rather simple preventive treatment.

The signs and symptoms of hypothyroidism can be insidious. Patients generally have an even greater weight gain than expected in pregnancy and complain of symptoms such as fatigue, constipation, hair loss, muscle cramps, dry skin, and insomnia. They may or may not have a goiter. The diagnosis is simply made by demonstrating low levels of maternal fT3 and fT4 and elevated levels of TSH (usually 2.5-fold higher than expected). If caused by Hashimoto’s thyroiditis, the presence of TPO antibodies should clinch the diagnosis.

In women with pre-existing hypothyroidism, treatment consists of simply increasing the once-a-day dose of levothyroxine (Synthroid®) by about 40%. Increasing the dose every 2 to 3 weeks to attain a TSH level that is in the low normal range and a T4 level in the high normal range is also accepted maintenance for pregnant women with established disease. In patients diagnosed for the first time in pregnancy, levothyroxine can be started at 0.1-0.15 mg a day and then the dosage can be altered according to the TSH levels.

Hyperthyroidism

Hyperthyroidism in pregnancy is mostly due to Graves’ disease, another autoimmune abnormality associated with the release of TSI, and increases maternal thyroid activity. TSH-binding inhibitory immunoglobulin is the immunoglobulin involved in about 30% of cases and can stimulate TSH receptors or, less commonly, block them.

Patients with this condition will have typical signs and symptoms of being in a hypermetabolic state, exhibiting hyper-irritability, elevated systolic blood pressures, tachycardia (not affected by a Valsalva maneuver), and exophthalmia. The clinical manifestations are often exacerbated by hyperemesis gravidarum. The diagnosis is easily made by assessing fT3 and fT4 levels, which are usually sky high, and TSH values, which are typically very low.

Most patients with Graves’ disease will have been diagnosed and treated before pregnancy. Managing pregnant women with Graves’ simply involves adjusting the dose of their antithyroid medication. The two most common medications used to counter the production of T3 and T4 are propylthiouracil (PTU) and methimazol. In newly diagnosed cases, the standard PTU starting dose is 100 mg every 8 hours, but it may take 6 weeks to normalize thyroxin output. This dose may be adjusted up or down, depending on fT4 values. Since TSH may be somewhat sluggish to respond, these levels are not used as commonly as fT4 to adjust the PTU dosage. Although easier to use because of a longer half-life, methimazole (with a starting dose of 20 mg/day) is often a second choice because of a very questionable possibility of teratogenicity (aplasia cutis).3 These medications should be adjusted so that fT4 is in the high normal and TSH is in the lower normal ranges.

Permanent treatment of hyperthyroidism involves radioactive iodine (RIA) ablation of the thyroid. This approach has been successful in reversing signs and symptoms while normalizing thyroid function in 80% of patients. However, this is not the treatment of choice in pregnancy, and patients have been conservatively counseled to avoid becoming pregnant for 6 months following ablation.4 Nevertheless, if the patient does become pregnant before this time, the half-life of the RIA is 8 days and, therefore, the risk to the fetus should be low.

Surgery is now used less frequently and can be tricky because of the thyroid’s location near vital structures. In fact, one of our patients was treated with a “total” thy-
Fetal Effects of Maternal Hyperthyroidism

fT3 and fT4 can traverse the placenta, accounting for 30% of thyroid hormone found in the fetal circulation. The IgG antibodies that can cause serious fetal problems are TSI, previously labeled “long-acting thyroid stimulating antibody.” An assay for TSI has been available for a few years, and although the test identifies only the stimulating antibodies, it misses 20% of antibodies capable of causing fetal hyperthyroidism. Another more recently used assay, now in its third generation, is thyrotropin-stimulating receptor antibody (TRab). This test is 95% sensitive for identifying antibodies capable of causing hyperactivity of the fetal thyroid, but the assay also pulls in the antibodies that, on rare occasions, can block these receptors, thereby causing fetal hypothyroidism.

These antibodies can create a hypermetabolic state in the fetus, leading to goiter in about 20% of cases, cardiac failure, and, if not dealt with, intrauterine demise. On occasion, the fetal thyroid gland can grow to a point where it can obstruct the upper airway at the time of birth. These fetuses are hyperactive and most often will have sustained tachycardia. Without treatment, some fetuses can have heart rates in the 180s. Interestingly, 60% of fetuses with hypothyroid goiter had peripheral vascularity and 50% had central vascularity. The entire gland will light up like a Christmas tree. One study from France in 39 patients with Graves’ disease showed that 68% of fetuses with hyperthyroid goiters had peripheral vascularity, and none had central vascularity. Twenty percent of those with hyperactive goiters had peripheral vascularity and 50% had central distribution. Interestingly, 60% of fetuses with hyperthyroid goiter had sustained tachycardia — diminishing the impact of FHR alone as a diagnostic tool. In our experience, however, the hyperthyroid fetuses had sustained heart rates in the 180s.

Hyperthyroid fetuses will mature their epiphysseal centers earlier. For example, normally a distal femoral epiphysis (DFE) will rarely be seen before 33 weeks, and if it is present, it appears as a thin dislike echogenic focus. It thickens into a ball-like structure by about 36 weeks. Our recent hyperthyroid fetuses have had detectable DFEs at 26 weeks and proximal tibial epiphyses (usually appearing after 36 weeks) by 32 weeks.

Occasionally, we have gotten enough mixed messages from the fetus, thereby requiring more precise information through fetal blood sampling (specifically fT4 levels). This will allow adjustment up or down of anti-thyroid medication to fit the thyroid status of the fetus. We have used doses of up to 600 mg of daily PTU to control fetal hyperthyroidism. TSH is sluggish to respond and is less useful diagnostically. In most cases, only one sampling is necessary to get a medication regimen on track and then the fetal status can be monitored noninvasively with ultrasound.

Protocol for Managing Maternal Hyperthyroidism

- At the initial visit, obtain blood levels of T3, T4, TSH, TSI, and TRab and increase the PTU according to the results (if the patient is already on this medication). If the diagnosis is newly made during pregnancy, then begin the regimen suggested above.
- From then on, titrate the PTU according to the patient’s signs and symptoms with the aim to get the TSH levels into the lower normal range and the T4
Ultrasound should be employed every 1-2 weeks, depending upon whether the fetus appears affected.
- The fetal heart rate should be < 160 bpm.
- The fetus should not be hyperactive on subjective assessment.
- Thyroid size should be within normal limits.
- If a goiter is present, the tissue should be devoid of internal vascularity.

If TRab levels are high, begin monitoring weekly.
- If no goiter is noted, then there is less concern for fetal compromise.
- If there is a goiter, if TRab levels are very high, if the heart rate is consistently above 160, and if internal vascularity does not diminish on increased doses of PTU, then consider fetal blood sampling to evaluate the status of T4 and TSH.
- Begin monitoring cardiac function through fetal echocardiography.
- Look for clinical signs of cardiac failure (pericardial effusion, cardiac enlargement, and any early signs of hydrops).

Two of the most difficult aspects of managing this condition are the inability to deal with the fetus directly and the unpredictable placental transfer of medications. There is little in the literature to guide the clinician regarding the adjunctive use of the beta-blockers (which has been used occasionally in the neonate), cardiotropic agents such as digoxin, or steroids to counter antibody production (although definitely a reach). Obviously, if the clinical situation deteriorates despite therapy, then delivery is an option if the fetus is at a salvageable gestational age.

In the past, treating thyroid disease in pregnancy has been difficult and confusing. Now with early recognition and collaborative management strategies, successful treatment and avoidance of neonatal complications is more possible in the pregnant patient with thyroid disease.

References

CME Questions
1. In the study by Lanza et al, DMPA use was associated with all of the following except:
   a. increased risk of bone fracture compared to non-users.
   b. increased risk of extremity fractures compared to spine and hip fractures.
   c. higher risk of bone fracture the longer DMPA was used.

2. In the DEMETER trial, medical therapy with methotrexate was associated with:
   a. the highest overall mortality.
   b. a non-significant 4% lower rate of subsequent pregnancy compared to conservative surgery followed by methotrexate.
   c. the highest rate of subsequent intrauterine pregnancy seen with any treatment.
   d. the lowest rate of subsequent intrauterine pregnancy seen with any treatment.

3. Which of the following does not traverse the placenta?
   a. T3
   b. TSH
   c. T4
   d. TSI

4. Which of the following is not generally associated with a fetal hyperthyroid goiter?
   a. Central vascularity on color Doppler ultrasound
   b. Increased fetal activity
   c. Premature maturation of epiphyseal centers
   d. A fetal blood sample showing low T4

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Extended Treatment of VTE with Dabigatran vs Warfarin


Current recommendations for treatment of uncomplicated venous thromboembolism (VTE) in the absence of persistent risk factors for recurrence (e.g., protein C, protein S deficiency) suggest at least 3 months of antithrombotic therapy, typically with warfarin. Risk of recurrence, however, is not insubstantial, and recent clinical trials have shown that extending the duration of antithrombotic therapy after a course of warfarin (with aspirin, for instance) reduces the risk for recurrent VTE.

When warfarin is used for extended VTE recurrence prophylaxis, serious bleeding risk is about 1% annually. In comparison trials to warfarin, major bleeding rates on dabigatran have been generally comparable to warfarin, and intracerebral bleeding was demonstrably less with dabigatran than warfarin. Since dabigatran does not require monitoring, monthly physician visits, or dietary modulation, and has infrequent potential for drug interaction, it provides an attractive alternative.

Schulman et al report the results of two randomized, controlled, double-blind trials of dabigatran 150 mg twice daily vs warfarin or placebo in patients who had completed at least 3 months of warfarin treatment. Dabigatran was found to be noninferior to warfarin for prevention of recurrent VTE, with less frequent bleeding than warfarin (0.9% vs 1.8%). Dabigatran may be a viable alternative for extending DVT prophylaxis after a “traditional” course of warfarin.

Selection Criteria for Lung Cancer Screening


The national lung screening trial (NLST) reported in 2011 that low-dose CT screening in selected smokers (n = 53,454) reduced mortality from lung cancer by 20%. Entry criteria for the NLST included age 55-74 years with at least a 30 pack-years smoking history (former smokers, if they had quit within the last 15 years, were also enrolled). Subsequently, national organizations have variously endorsed lung cancer screening for persons matching NLST eligibility criteria.

The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) developed a lung-cancer risk prediction model based on 154,901 subjects. The PLCO determined other predictors of lung cancer beyond age and smoking duration used in the NLST, including body mass index, family history of lung cancer, and presence of chronic obstructive pulmonary disease. Because the PLCO duration of follow-up was longer than NLST (9.2 years vs 6.5 years), the strength of the PLCO prediction model might be anticipated to be greater than NLST.

A comparison between the NLST and PLCO prediction models found that the PLCO criteria had greater sensitivity and specificity, ultimately missing 43% fewer lung cancers than NLST. The PLCO prediction model has the potential to improve outcomes for persons at risk of lung cancer.

Special Subgroups in Hypertension: Obese Hypertensives


The inter-relatedness of obesity, hypertension, and cardiovascular (CV) events is complex. Obesity is independently associated with high blood pressure, all-cause mortality, and CV mortality. Yet, some reports have suggested that when parsing out CV events among a secondary prevention population (persons with existing CV disease), subjects with normal body weight bear a disproportionately greater risk than overweight and obese persons.

To further clarify this counterintuitive knowledge base, Weber et al report on an analysis of the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension trial (ACCOMPLISH). ACCOMPLISH was performed to determine the relative efficacy of an angiotensin-converting enzyme (ACE) inhibitor + hydrochlorothiazide (HCTZ) vs ACE + amlodipine (CCB) in patients (n = 11,506) with Stage 2 hypertension (blood pressure > 160 mmHg). The trial ultimately demonstrated that ACE + CCB provided a significant mortality advantage over ACE + HCTZ.

In this report, ACCOMPLISH study subjects were divided into normal weight (body mass index [BMI] < 25), overweight (BMI 25-29), and obese categories (≥ BMI 30). CV events were most...
frequent in the normal weight group, and least frequent in the obese patients in the ACE + HCTZ arm of the trial. In the ACE + CCB arm, there were no differences between weight categories in outcomes.

The seemingly paradoxical relationship between overweight and outcomes in persons with established CV disease (myocardial infarction, cerebrovascular accident, or existing hypertension) is difficult to explain. It may be that obesity-related hypertension is mediated by a different, more benign pathophysiology, hence producing more favorable outcomes, although this concept has been insufficiently explored. Finally, because of relatively higher event rates with ACE + HCTZ in normal-weight patients, clinicians should select ACE + CCB since event reduction is equivalent across weight groups for this combination.

Omalizumab for Asthma in Real Life


In evidence-based medicine terminology, “efficacy” is the term used to reflect results achieved within a clinical trial, whereas “effectiveness” indicates the results seen in “typical practice settings,” commonly called “real-life settings.” Clinical trials are anticipated to provide results superior to those in practice settings, where patients cannot be so readily de-selected or excluded, where resources may be more limited, and where rigorous regimentation for administration of treatment is less abundant.

Omalizumab (OMA) is not generally regarded as a first-line asthma medication, but rather an appropriate add-on when guideline-based foundation therapies (inhaled steroids, long-acting beta agonists, and leukotriene receptor antagonists) are insufficient to provide control. Although only 30-50% of asthmatics have a prominent underlying allergic component, among difficult-to-control asthmatics, the number may be as high as 80%. Clinical trials indicate that OMA, by blocking IgE, is a useful add-on in such resistant asthma cases. But do “real-life” settings reflect similar benefit?

Grimaldi-Bensouda et al report on refractory asthma patients (n = 767) recruited by more than 100 physicians who prescribed OMA as an add-on treatment. During a follow-up period of almost 2 years, study subjects who received any doses of OMA enjoyed a 43% relative risk reduction in likelihood of hospitalization or emergency department visits for asthma. Subjects on treatment with OMA demonstrated an even greater benefit: 60% relative risk reduction.

In real-life settings, OMA provides substantial improvement in clinically important endpoints for patients with difficult-to-treat asthma.

Tenofivir: New Hope for Hepatitis B Patients


Hepatitis B (HEP-B) is responsible for approximately half of hepatic carcinoma cases worldwide. While HEP-B treatment has been shown to reduce risk for liver failure and hepatic cancer in cirrhosis, whether currently available antiviral therapies actually reverse the underlying disease process is less well studied. Indeed, previous prevailing wisdom had opined that the fibrotic changes of cirrhosis might not be amenable to attempts at regression.

Tenofivir (TFV) is a potent HEP-B polymerase/reverse transcriptase inhibitor. Marcellin et al report on the results of an open-label trial of TFV in patients who had completed a 48-week antiviral treatment with either adefovir or TFV. Subjects were subsequently assigned to once-daily TFV for up to 7 years. Approximately one-fourth of patients had cirrhosis at baseline, and all subjects agreed to follow-up liver biopsy in the fifth year of the trial (240 weeks).

TFV was well tolerated and confirmed to be associated with regression of fibrosis (in the cirrhosis group) and improvement in liver histology (in the non-cirrhosis group) at 240 weeks. This large dataset is very supportive of a role for TFV not just in arresting disease progression, but actually in regression of cirrhosis.

H. pylori: Frequency of Recurrence After Successful Eradication


Worldwide, Helicobacter pylori appears to be responsible for the majority of cases of gastric cancer. A Chinese clinical trial of H. pylori eradication through pharmacotherapy noted an almost 40% reduction in gastric cancer over the subsequent 15-year observation period. Initial eradication of H. pylori provides important risk reduction. Of course, initial treatment is sometimes not effective, and even when initial treatment is effective, there is potential for recurrence.

From a population of study subjects (n = 1091) cleared of H. pylori (confirmed by post-treatment negative urea breath tests), only 125 evidenced recurrence over a 1-year follow-up (11.5%). Factors associated with recurrence included non-adherence to H. pylori treatment regimens and methodology of the treatment regimen (i.e., 14-day triple therapy, sequential therapy, or concomitant therapy, with sequential therapy being most successful). These recurrence rates are typical of low-income countries, whereas as recurrence rates are as much as 30% less in high-income countries. Overall, H. pylori treatment is well tolerated, provides important risk reduction for gastric cancer, and is associated with few recurrences that can be managed by appropriate retreatment.
New Study on Chelation Therapy Proves Controversial

In this issue: Chelation therapy for cardiovascular disease; statins and kidney injuries; chlorthalidone for hypertension; and FDA actions.

Does chelation therapy work?

The National Center for Complementary and Alternative Medicine (NCCAM) is attempting to fulfill its mandate to prove or disprove the value of alternative treatments. A division of the National Institutes of Health, NCCAM has done research on everything from supplements to meditation. This latest study looks at chelation therapy in patients with cardiovascular disease. Chelation therapy with ethylene diamine tetra-acetic acid (EDTA) has been used for decades to treat lead toxicity, and it has also been found to reduce metastatic calcium deposits. Despite the fact that small studies have never shown a benefit for chelation in treating cardiovascular disease, many alternative clinics continue to tout its value in this role. A recently published NCCAM-funded study to evaluate the value of chelation enrolled more than 1700 patients ≥ 50 years of age with a history of myocardial infarction (MI) at least 6 weeks prior. The study was a double-blind, placebo-controlled, $2 \times 2$ factorial randomized trial from 2003 through 2011. There were 289 patients who withdrew consent from the study, of which 60% were in the placebo group. The study consisted of 40 EDTA/vitamin infusions vs placebo infusions (given weekly for 30 weeks then at 2-8 week intervals). About 15% of patients in both groups dropped out during therapy. The primary outcome was a composite of total mortality, recurrent MI, stroke, coronary revascularization, or hospitalization for angina. The primary endpoint occurred in 222 (26%) in the chelation group and 261 (30%) in the placebo group (hazard ratio [HR], 0.82; 95% confidence interval [CI], 0.69-0.99; $P = 0.35$). There was no effect on total mortality, but there was slight improvement in other outcomes with chelation. The authors conclude that among stable patients with a history of MI, chelation therapy modestly reduced the risk of adverse cardiovascular outcomes. They conclude that this study provides evidence to guide further research but is not sufficient to support the routine use of chelation therapy in patients with cardiovascular disease (JAMA 2013;309:1241-1250).

Editorialists in the same issue of JAMA immediately leveled strong criticisms, ranging from allegations of noncompliance with regulations for the protection of research participants to questioning the professional credentials of the study sites and investigators. The JAMA editorial board did an extensive review of the data, and despite concerns, decided to publish the study with the caveat that “these findings do not support the routine use of chelation therapy as secondary prevention for patients with previous myocardial infarction and established coronary disease.” (JAMA 2013;309:1291-1292.) Another editorialist, however, suggests that “limitations in the design and execution” of this trial compromise the findings. For example, the high number of withdrawals of consent in the placebo group suggests that the study was not truly blinded. There is also concern about the use of “softer” endpoints such as coronary revascularization and hospitalization for angina.

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Also, the trial design was altered midway through the study because of the length of the trial. Given these concerns, “including missing data, potential investigator or patient unmasking, use of subjective endpoints, and intentional unblinding of the sponsor, the results cannot be accepted as reliable and did not demonstrate a benefit of chelation therapy.” (JAMA 2013;309:1293-1294.)

Statins and renal function

When prescribing a high-dose statin, physicians no longer need to monitor liver function tests, but might want to consider monitoring renal function, at least for the first 3 months. Last year, the FDA removed labeling requiring periodic monitoring of liver enzyme tests, but now a Canadian study suggests that high-potency statins (defined as doses of at least 40 mg simvastatin, 20 mg atorvastatin, or 10 mg rosuvastain) may be associated with acute kidney injury. Researchers reviewed records of more than 2 million patients from nine population-based cohort studies comparing current and past use of high-potency vs low-potency statin therapy. Patients hospitalized for acute kidney injury were matched with 10 controls. About 3% of patients had chronic kidney disease (CKD) at the onset of the study. Within 120 days of starting therapy, there were 4691 hospitalizations for acute kidney injury in patients without CKD and 1896 hospitalizations in patients with CKD. In patients without CKD, current users of high-potency statins were 34% more likely to be hospitalized with acute kidney injury compared to low-potency statin users (fixed effect rate ratio 1.34; 95% CI, 1.25-1.43). In patients with CKD, the increase was about 10% with high-potency statins (risk ratio, 1.10; 95% CI, 0.99-1.23). The authors conclude that use of high-potency statins is associated with an increased rate of acute kidney injury compared to low-potency statins, with the effect strongest in the first 120 days of treatment. The authors further suggest that since there is a relatively small incremental cardiovascular benefit between high-potency and low-potency statins, and given the increased risk of rhabdomyolysis, diabetes, and acute kidney injury, patient selection for risk-benefit is important (BMJ 2013;346:f880).

Chlorthalidone for hypertension

Thiazide diuretics are recommended as first-line treatment for hypertension. Hydrochlorothiazide (HCTZ) is the most commonly used diuretic in North America, but some experts have recommended chlorthalidone in this role, suggesting that it may be superior. A new study, however, suggests that chlorthalidone may cause more electrolyte abnormalities than HCTZ. Nearly 30,000 patients ≥66 years of age who were newly treated for hypertension were evaluated. About one-third were treated with chlorthalidone and the rest with HCTZ. None of the patients had been hospitalized for heart failure, stroke, or MI within the last year. The primary outcome was a composite of death or hospitalization for heart failure, stroke, or MI, and safety outcomes included hospitalization with hypokalemia or hyponatremia. After 5 years of follow-up, there was no difference in the primary outcome between the two drugs — 3.2 events per 100 person years for chlorthalidone vs 3.4 events per 100 person years for HCTZ. However, patients treated with chlorthalidone were three times more likely to be hospitalized with hypokalemia (adjusted HR, 3.06; CI, 0.81-1.06). Hyponatremia was also more common (HR, 1.68; CI, 1.24-2.28). The findings suggest that in typical doses, chlorthalidone is not associated with fewer adverse cardiovascular events or deaths compared to hydrochlorothiazide, but it is associated with a greater incidence of electrolyte abnormalities, especially hypokalemia (Ann Intern Med 2013;158:447-455).

FDA actions

The FDA has issued a warning regarding azithromycin and cardiac toxicity. The drug has been associated with fatal heart rhythms — especially in patients already at risk — including those with prolonged QT intervals, torsades de pointes, congenital long QT syndrome, bradyarrhythmias, or uncompensated heart failure. Other patients may be at risk as well, including those with low potassium or magnesium levels, those using drugs that prolong the QT intervals, and elderly patients with cardiac disease. The warning was based on a study published in The New England Journal of Medicine last year.

An FDA advisory committee is recommending against the use of calcitonin salmon (Miacalcin and Fortical nasal sprays, and Miacalcin injection) for the treatment of osteoporosis in postmenopausal women because the risk of cancer outweighs any potential benefit. The recommendation is based on an FDA review that questions the drug’s effectiveness in reducing fractures. Another review found a small increased risk of cancer associated with the drug. The drug could still be used for Paget’s disease, acute bone loss due to immobilization, and hypercalcemia. The FDA has yet to rule on the advisory committee’s recommendations.