POEMs

PATIENT ORIENTED EVIDENCE THAT MATTERS

Practice Recommendations from Key Studies

Vaccine prevents genital herpes in subgroup of women

Stanberry LR, Spruance SL, Cunningham AL, et al. Glycoprotein-D-adjuvant vaccine to prevent genital herpes. N Engl J Med 2002; 347:1652–61.

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PRACTICE RECOMMENDATIONS

The herpes simplex virus (HSV) type-2 vaccine studied here prevented genital herpes only in women who were seronegative for HSV-1 and HSV-2 at baseline. Ten of these women would need to be vaccinated to prevent 1 case of genital herpes. The vaccine did not prevent infection with HSV-2 in these women. It did not prevent genital herpes in women with other HSV serologic status or in men.

The usefulness of this vaccine is limited by the small subgroup in which it is efficacious. Determining which women fall into this subgroup could prove costly. It is possible that asymptomatic infected persons may spread HSV more readily. Emphasis on the use of condoms and antiviral agents should still be the first line in preventing the spread of genital herpes.

BACKGROUND

Can a vaccine prevent genital herpes? HSV infection occurs worldwide and is epidemic in some populations, despite the availability of antiviral agents and condoms. Genital HSV infection may be asymptomatic or severe with painful skin lesions and complications. Infection can also cause significant psychological illness.

POPULATION STUDIED

Subjects had regular sexual partners with genital herpes. Study 1 subjects (N=847) were seronegative for HSV-1 and HSV-2 at baseline. Study 2 subjects (N=1867) were of any HSV status. Treatment and control groups did not differ significantly from one another. Most patients were white and heterosexual with a mean age of 30 to 34 years. Just over a third of study participants were women. About 10% of the participants did not complete the 3-dose series.

STUDY DESIGN AND VALIDITY

Two double-blinded, randomized trials were performed using an HSV type 2 glycoprotein-D-subunit vaccine in subjects whose sexual partners had genital herpes. Participants were randomized to receive the vaccine or placebo at 0, 1, and 6 months.

Study 1 subjects had 9 follow-up visits over 19 months, with serologic analysis at each visit. Study 2 subjects had 6 follow-up visits over 19 months with blood samples at 0, 7, and 19 months. Sexual partners agreed not to use suppressive antiviral therapy in Study 1 and could use such therapy in Study 2.

Results were analyzed by intention-to-treat. Method of randomization and blinding of concealment was not mentioned in the article, and this information could not be obtained from the authors.

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What is a POEM?

Each month, the POEMs (Patient-Oriented Evidence that Matters) editorial team reviews 105 research journals in many specialties, and selects and evaluates studies that investigate important primary care problems, measure meaningful outcomes, and have the potential to change the way medicine is practiced. Each POEM offers a Practice Recommendation and summarizes the study's objective, patient population, study design and validity, and results. The collected POEMs are available online at www.jfponline.com.

Condoms and antiviral agents are still the best prevention for genital herpes

■ OUTCOMES MEASURED

The initial primary outcome for both studies was development of genital herpes in all subjects. After Study 1 results were analyzed but before Study 2 results were known, the primary outcome for Study 2 was changed to the development of genital herpes in HSV-2 seronegative females.

■ RESULTS

Vaccine efficacy was defined as the reduction in the rate of genital herpes in immunized subjects compared with nonimmunized subjects. Study 1 showed no efficacy in preventing HSV infection in subjects who were HSV-1 and HSV-2 seronegative (efficacy=38%; 95% confidence interval [CI], –18 to 68).

Study 2 showed no efficacy in the primary outcome of preventing genital herpes in females who were HSV-2 seronegative (efficacy=42%; 95% CI, –31 to 74) but showed efficacy in females who were seronegative for both HSV-1 and HSV-2 (efficacy=74%; 95% CI, 9 to 93). In this subgroup, the transfer rate of genital herpes was 3.5% in the treatment group and 13.3% in the placebo group, giving a number needed to treat of 10.

Efficacy was not seen in females who were HSV-1 seropositive but HSV-2 seronegative (efficacy= –106%; 95% CI, –723 to 9) or in HSV-2 seronegative males (efficacy= –10%; 95% CI, –127 to 47). The vaccine did not prevent infection with HSV-2, even in the women that were prevented from getting genital herpes (efficacy=23%; 95% CI, –17 to 49).

Adverse events were mostly limited to pain at the site of injection. Pain severe enough to limit normal activities was greater among immunized subjects (5% vs. 3% in Study 1, 5% vs. 2% in Study 2). There was a nonsignificant trend towards increased genital herpes and HSV-2 infection in men who received the vaccine.

Detriments of tPA for acute stroke in routine clinical practice

Bravata DM, Kim N, Concato J, Krumholz HM, Brass LM. Thrombolysis for acute stroke in routine clinical practice. Arch Intern Med 2002; 162:1994–2001.

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■ PRACTICE RECOMMENDATIONS

Under optimal conditions, tissue plasminogen activator (tPA) may be a viable option for treatment of acute ischemic stroke; however, this study showed that protocol is not adhered to in practice and that these protocol deviations are associated with increased mortality and other adverse events. Based on these findings, tPA should not be used in routine clinical practice to treat acute stroke until individual hospitals develop protocols to guarantee the medication's appropriate use.

■ BACKGROUND

What are the benefits and harms of tPA in routine clinical practice? Thrombolytic agents have been used in acute stroke to limit the progression of ischemia caused by the thrombus. Previous publications have suggested that the generalized use of tPA for stroke outside of the study setting may result in higher complication rates. Strict adherence to protocol is believed to be necessary to avoid adverse events such as intracranial hemorrhage and death. The topic of interest in this study was the incidence of deviation from protocol and the related occurrence of adverse events of tPA therapy in routine clinical practice.

■ POPULATION STUDIED

The study examined 16 acute care hospitals in Connecticut; any patient who had received tPA for the diagnosis of acute ischemic stroke was included. The outcomes of these patients' clinical courses were compared with the results of the National

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Institute of Neurological Disorders and Stroke (NINDS) study (n=312). Significant differences in baseline characteristics included a decreased incidence of previous stroke, aspirin use, and an increased proportion of white race in the Connecticut cohort.

STUDY DESIGN AND VALIDITY

A retrospective medical record review was performed on all patients who had received tPA for acute ischemic stroke. Data were collected via an extraction form developed for the study by 2 of the authors. Any discrepancies in the data extraction process were resolved by consensus of 3 of the authors. Strokes were classified according the National Institutes of Health Stroke Scale criteria, and protocol was defined according to the American Heart Association Guidelines for Thrombolytic Therapy for Acute Stroke.

This study was well designed to measure the outcomes of interest. Criteria were well defined to limit investigator bias, and medical records were thoroughly researched. In general, a retrospective review is a weaker study design, but in this case it allowed insight into usual practice adherence to the protocols being investigated without influencing prescriber decision-making. The comparison of in-hospital mortality erred toward a lower rate in the Connecticut group.

OUTCOMES MEASURED

The primary outcomes measured were adverse events (in-hospital mortality, intracranial hemorrhage, and extracranial hemorrhage). Adherence to protocol was also measured; deviations were defined as major (contraindication in the tPA package insert) or minor (other deviations from protocol, inappropriate monitoring, etc). Process errors included not recording weight, no record of rectal examination, and similar omissions. Clinicians' awareness of breaches of protocol was recorded.

RESULTS

Sixty-three patients were identified who had received tPA for acute ischemic stroke. Nearly all (97%) cases had had at least 1 protocol deviation. Overall, 55 major and 84 minor protocol deviations occurred in the 63 patients.

In-hospital mortality was significantly higher in the Connecticut cohort than in the NINDS study (16/63, 25%, vs 40/312, 13%; *P*=.01; number needed to harm [NNH]=8). In-hospital mortality increased with increasing number of major protocol deviations (3/21, 14%, with no major protocol deviations; 9/31, 29%, with 1 major deviation, NNH=7; and 4/11, 36%, with ≥2 major deviations, NNH=5). Mortality also increased with minor protocol deviations (1/6, 17%, with no minor protocol deviations; 8/35, 23%, with 1 minor deviation, NNH=17; and 7/22, 32%, with ≥2 minor deviations, NNH=7).

No difference in in-hospital mortality was found between the NINDS cohort and the cases with no major protocol deviations (40/312, 13%, vs 3/21, 14%; *P*=.85). Process errors were evident in 40 (64%) patients. Protocol deviations were consistent across all hospitals studied. For 19 (30%) patients, the physicians documented awareness of protocol violations, but this documentation did not affect mortality.

Comparing celecoxib with traditional nonsteroidal anti-inflammatory drugs

Deeks JJ, Smith LA, Bradley MD. Efficacy, tolerability, and upper gastrointestinal safety of celecoxib for treatment of osteoarthritis and rheumatoid arthritis: systematic review of randomized controlled trials. BMJ 2002; 325:619–23.

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PRACTICE RECOMMENDATIONS

Celecoxib is as effective as other nonsteroidal anti-inflammatory drugs (NSAIDs) for treating the symptoms of osteoarthritis or rheumatoid arthritis. However, patients taking celecoxib are less likely to

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discontinue the medication because of gastrointestinal upset than patients taking traditional NSAIDs. Nevertheless, celecoxib does not decrease the incidence of serious gastrointestinal adverse events with long-term therapy.

BACKGROUND

Is celecoxib more effective or better tolerated than traditional nonsteroidal anti-inflammatory medications? NSAIDs are often used for arthritis symptom relief. Unfortunately, they may cause serious adverse effects. Researchers have developed celecoxib to provide symptom relief without the NSAID-associated gastrointestinal toxicity via cyclooxygenase 2–specific inhibition. This systematic review compared the efficacy, safety, and tolerability of celecoxib with other NSAIDs.

POPULATION STUDIED

The study analyzed data from studies of 15,187 patients with osteoarthritis or rheumatoid arthritis. Patients with osteoarthritis were older, had fewer concomitant illnesses, and took fewer other medications than did patients with rheumatoid arthritis. Most trials excluded patients with active gastrointestinal, renal, hepatic, or coagulation disorders.

STUDY DESIGN AND VALIDITY

This systematic review included all published and unpublished data, identified by extensively searching the literature and reviewing data on file with the manufacturer. These blinded, randomized trials compared celecoxib with placebo or an NSAID for at least 12 weeks and reported efficacy, tolerability, and gastrointestinal safety outcomes. The studies used various celecoxib doses, including supratherapeutic doses. Meta-analyses compared information for each outcome. Safety and tolerability analyses, but not the efficacy analysis, included data from celecoxib 800 mg per day. Comparator NSAIDs included diclofenac 75 mg twice daily, ibuprofen 800 mg 3 times daily, or naproxen 500 mg twice daily. The authors evaluated data for effectiveness for osteoarthritis separately from data for rheumatoid arthritis.

The review assessed each trial according to predefined criteria. All 9 trials used concealed treatment allocation. Also, each study analyzed data by intention to treat. The authors used original data obtained from the researchers rather than data obtained from the peer-reviewed publication. Endoscopic studies documented all gastropathy, although many ulcers are asymptomatic and do not lead to complications. One potential study limitation was that no long-term follow-up was included (1 large study assessed symptomatic upper gastrointestinal disease at 26 weeks).

OUTCOMES MEASURED

Standardized indices measured efficacy and tolerability outcomes. Osteoarthritis trials used the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index, and rheumatoid arthritis studies used the American College of Rheumatology Responder Index (ACR-20). Rates of withdrawal due to any adverse effect determined the tolerability outcome, and the combined outcome of symptomatic ulcers or episodes of bleeding, perforation, and obstruction at 12 and 24 weeks determined gastrointestinal safety. The authors also evaluated the incidence of endoscopically identified gastric ulcers. However, this outcome was not related to subsequent development of more serious ulceration or symptoms. The US Food and Drug Administration does not consider this outcome to be a valid surrogate marker for NSAIDs.

RESULTS

In all trials, celecoxib was more efficacious than placebo and equally efficacious compared with traditional NSAIDs. For osteoarthritis, celecoxib reduced WOMAC composite scores to the same extent as naproxen. The composite includes pain, stiffness, and physical function. For rheumatoid arthritis, celecoxib improved ACR-20 responder rates similarly to diclofenac and naproxen. The

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ACR-20 measures improvement in painful, tender, or swollen joints.

In evaluating tolerability, celecoxib had a higher withdrawal rate than did placebo due to any adverse event (relative risk [RR], 1.49; 95% confidence interval [CI], 1.15–1.92) and any gastrointestinal adverse event (RR, 1.68; 95% CI, 1.07–2.65).

Withdrawal rates suggest that adverse events did not differ among celecoxib and the other NSAIDs, although fewer patients taking celecoxib discontinued due to gastrointestinal adverse events, mainly abdominal pain and dyspepsia (RR, 0.54; 95% CI, 0.42–0.71; number needed to treat [NNT]=35 at 3 months).

Endoscopic evaluation detected a much lower rate of ulcers at 12 weeks with celecoxib use than with NSAID use (RR, 0.29; 95% CI, 59–79%; NNT=6 at 3 months). One study found similar reductions at 24 weeks. The incidence of serious gastrointestinal events was evaluated in 1 study, which found no difference between celecoxib and ibuprofen or diclofenac.

Screening for and treating asymptomatic bacteriuria not useful in women with diabetes

Harding GK, Zhanel GG, Nicolle LE, Cheang M. N Engl J Med 2002; 347:1576–83.

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PRACTICE RECOMMENDATIONS

Women with diabetes mellitus should not be screened or treated for asymptomatic bacteriuria. Unlike other clinical conditions in which screening for asymptomatic urinary tract infection (UTI) has proved valuable (pregnancy, urologic surgery, renal transplantation), women with diabetes derive no meaningful benefit. Previous recommendations by the US Preventive Services Task Force neither recommended for or against screening or treatment of asymptomatic bacteriuria in diabetic women.

BACKGROUND

Should we screen for and treat asymptomatic bacteriuria in women with diabetes mellitus? Women with diabetes mellitus have more frequent and often more severe UTIs when compared with their nondiabetic peers. Moreover, these same women are 3 times more likely to exhibit asymptomatic bacteriuria. In an attempt to prevent the morbidity associated with UTIs in these patients, some experts recommend screening for and treatment of bacteriuria in diabetic women.

POPULATION STUDIED

The investigators recruited adult women with diabetes (approximately 80% had Type 2) referred to endocrinology clinics at 2 tertiary-care teaching hospitals. Eligible women had to have demonstrated bacteriuria (at least 10^5 colony-forming units of an organism per mL) on 2 consecutive urine cultures over a 2-week period while remaining asymptomatic. The placebo and antibiotic treatment groups were similar in baseline characteristics, including age (mean 57.0 and 53.7 years, respectively) and recent blood glucose control (mean A1C 13.2% and 12.7%, respectively). Comparable percentages of women in each group were sexually active and had a history of UTI.

STUDY DESIGN AND VALIDITY

From an initial screening group of 1900 women, 108 who met the inclusion criteria were randomized, using concealed allocation, into this double-blind trial. After the initial 6 weeks of the study, the blinding of the participants and the study coordinators was discontinued for the remainder of the follow-up (up to 36 months). Patients randomized to antimicrobial treatment received trimethoprim-sulfamethoxazole 160 mg/800 mg (TMP/SMX, Bactrim DS) orally twice a day for 14 days.

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Patients allergic to TMP/SMX or who had resistant organisms on culture received ciprofloxacin (Cipro) 250 mg orally 2 times a day. A planned treatment arm of 3 days of therapy was discontinued after the first 6 patients randomized to it had an early relapse. Active treatment patients with symptomatic UTI or reinfections were managed using longer courses of therapy and/or low-dose antimicrobial prophylaxis. Therapy was credited with a bacteriologic cure if a pretherapy isolate had not recurred after 4 weeks.

The investigators performed suitable statistical analysis using an intention-to-treat approach. Two of the patients were lost to follow-up, and one was excluded because outcomes could not be assessed. In the end, the outcomes analysis consisted of data from 105 participants.

OUTCOMES MEASURED

The investigators assessed the time to the first episode of a symptomatic UTI and its frequency as primary outcomes. Secondary outcomes were many, including: hospital admission for a UTI or other causes; patient's response to the first course of antibiotics; the number of days of antibiotic therapy; occurrence of new episodes of asymptomatic bacteriuria; and adverse effects of antibiotic therapy.

RESULTS

Antimicrobial therapy provided no benefit compared with placebo in terms of time to first symptomatic UTI or number of infections per 1000 days. Likewise, hospitalization for UTI or other causes did not change because of therapy. The antimicrobial therapy group actually received 5 times the number of days of antibiotics compared with the control group—a difference that was completely attributable to the attempted eradication of asymptomatic bacteriuria. Not surprisingly, placebo and treatment arms did differ in days of antibiotic therapy per 1000 days of follow-up (33.7 vs 158.2; $P<.001$) and adverse effects from antibiotic therapy (3 vs 10 women; $P=.05$; number needed to harm=8).

Negative ELISA D-dimer assay can miss pulmonary embolism

Dunn KL, Wolf JP, Dorfman DM, Fitzpatrick P, Baker JL, Goldhaber SZ. Normal D-dimer levels in emergency department patients suspected of acute pulmonary embolism. J Am Coll Cardiol 2002; 40:1475–8.

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PRACTICE RECOMMENDATIONS

This evaluation of the use of enzyme-linked immunosorbent assay (ELISA) D-dimer test in routine clinical practice supports other evidence that the assay has a high sensitivity to exclude pulmonary embolism in patient populations in which there is clinical suspicion. Nevertheless, the assay incorrectly excluded the diagnosis of pulmonary embolism in 2 cases.

Other examples of clinical decision-making exist for which the acceptable negative predictive value for screening is set at 100%—eg, the diagnosis of phenylketonuria in newborns.

Physicians who do not want to miss cases of acute pulmonary embolism when they clinically suspect the diagnosis should not rely solely on negative D-dimer assay results when the value to rule out the diagnosis is set at 500 ng/mL. If a lower value is used to define normal—eg, 250 ng/mL, as used in other studies—no cases of acute pulmonary embolism would have been missed in this group of patients. Regardless of the cutoff used, the assay will yield many false-positive results.

BACKGROUND

In patients with clinically suspected acute pulmonary embolism, does a negative ELISA D-dimer assay correctly exclude pulmonary embolism? Physicians do not want to miss cases of pulmonary embolism. Because imaging tests to rule out the diagnosis (lung scans, chest computed tomography, or pulmonary angiography) are inexact, expensive, or invasive, physicians seek a sensitive screening assay to reduce the

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number of patients needing additional testing.

Although the ELISA D-dimer test is known to identify far too many false-positive cases to be useful as a positive screen, some proponents believe the test has sufficient negative predictive value to accurately identify individuals without acute pulmonary embolism. This study evaluated this question.

POPULATION STUDIED

The authors enrolled all patients presenting to the emergency department of the Brigham and Women's Hospital during 2000 who were initially evaluated for suspected pulmonary embolism. The authors evaluated 1106 D-dimer levels: 311 from men and 795 from women. They did not define the emergency department physicians' criteria for suspected pulmonary embolism and did not specify any inclusion or exclusion criteria. The prevalence of pulmonary embolism over the course of the year was 5.0%.

STUDY DESIGN AND VALIDITY

This evaluation of the negative predictive value of a normal D-dimer assay mandated that emergency department physicians order the assay for all patients suspected of acute pulmonary embolism. No other procedural change was required in how physicians chose to work up, treat, or follow up suspected pulmonary embolism. Because no imaging test was performed on all subjects as a gold standard for the diagnosis, the authors chose to follow up every subject for 6 months to determine whether pulmonary embolism was subsequently diagnosed.

The greatest weakness in this report is the insufficient detail on how the study was conducted. An example is the lack of clear eligibility and exclusion criteria. Presumably the screening test was applied whenever the clinical suspicion of pulmonary embolism was moderate or high and no patients were excluded, regardless of comorbidities; but these presumptions could not be confirmed. With the exception of providing mean age and sex distribution of subjects by test result, the authors did not describe the demographic characteristics of their subjects.

Whatever cutoff is used, the ELISA D-dimer assay will yield many false-positive results

By making the assay results from all cases of suspected pulmonary embolism in the emergency department the sole requirement, the study became an observation of normal clinical practice. Emergency department physicians chose to evaluate 350 of the 559 patients with positive screening results and 132 of the 547 with negative results by imaging. Imaging modalities included lung scan, computed tomography, or pulmonary angiogram.

To verify that no cases of pulmonary embolism were missed, the authors followed all patients in whom pulmonary embolism was excluded for 6 months to verify the absence of acute pulmonary embolism. This follow-up identified 5 of the 55 pulmonary embolism patients; all had initial D-dimer values exceeding 500 ng/mL.

OUTCOMES MEASURED

The primary outcomes were the sensitivity and specificity of the ELISA D-dimer assay (VIDAS assay, bioMerieux) in detecting pulmonary embolism in symptomatic patients presenting to the emergency department.

RESULTS

Of 547 patients who screened negative with the D-dimer assay, 2 had acute pulmonary embolism; of 559 positive screens, 53 patients had acute pulmonary embolism. These results translated into a sensitivity of 96.4%, a specificity of 52.0%, a positive predictive value of 9.5%, and a negative predictive value of 99.6%.

Of the patients who had a positive screen, 9.5% had pulmonary embolism, whereas 99.6% of those with a negative screen did not have pulmonary embolism.

Self-examination does not reduce breast cancer mortality

Thomas DB, Gao DL, Ray RM, et al. Randomized trial of breast self-examination in Shanghai: final results. J Natl Cancer Inst 2002; 94:1445–7.

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PRACTICE RECOMMENDATIONS

Breast self-examination does not decrease breast cancer mortality, according to the results of this randomized controlled trial of 266,000 women who were given intensive instruction in breast self-examination. These findings correspond with the US Preventive Services Task Force policy not to recommend breast self-examination for the reduction of breast cancer mortality.

BACKGROUND

Does breast self-examination reduce breast cancer mortality? Previous studies have shown that breast cancer detected from breast self-examination is smaller and at an earlier stage than breast cancer detected through other means. However, whether practicing breast self-examination actually reduces mortality from breast cancer is still unclear. The US Preventive Health Services Task Force has concluded that there is too little evidence to either recommend or discourage breast self-examination. This study evaluated the role of breast self-examination in the reduction in breast cancer–related mortality.

POPULATION STUDIED

At enrollment, all women were permanent residents of Shanghai, were 33 to 66 years old, and were employed by or retired from the Shanghai Textile Industry Bureau. The study was conducted in Shanghai to avoid contamination; mammography is unavailable and breast self-examination instruction is not routinely provided for the women employed by the bureau or in China in general. Women were excluded if they failed to complete the initial study questionnaire, if they were judged to be mentally or physically unable to participate (no criteria were given for this exclusion), or if they had a history of breast cancer. The women were recruited through the factories' health care facilities, where they received their primary health care.

STUDY DESIGN AND VALIDITY

This study was a randomized, controlled, single-blinded trial. Women were randomized to receive an intensive instructional program on breast self-examination or to be in a control group, based on their employment in 1 of 519 textile factories (randomization occurred by factory, not by individual). A total of 266,064 women were enrolled in the study.

The instruction in breast self-examination was thorough and probably more scrupulous than that provided by most physicians. Participants in the intervention arm were taught a 3-step breast self-examination technique that included breast inspection in front of a mirror for evidence of asymmetry and dimpling, and breast palpation in standing and supine positions. Palpation was taught by using a circular motion with the pads of the 3 middle fingers while pressing firmly, with the ipsilateral arm above the head. Participants were taught to palpate the axilla and squeeze the nipple to detect any discharge. The instruction sessions provided the participants one-on-one instruction, including practice on a silicone breast model and on themselves. Reinforcement instruction sessions occurred at 1 and 3 years after the initial sessions.

At 1 and 2 years after the initial instruction, women were brought together in groups of 10 to watch a video that reviewed what they had

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learned and emphasized the importance of self-examination. At 1, 3, 6, and 9 months after the initial instruction, the factory medical workers scheduled the participants to come to the factory medical clinic to practice breast self-examination under supervision.

Starting at month 12, supervised self-examinations were done every 6 months for 5 years. The medical workers were told to correct the women's technique but not to examine the women's breasts unless the women reported a finding. In addition, the medical workers were encouraged to devise their own methods to remind the women to practice breast self-examination.

The women in the control group did not receive information on breast cancer screening or self-examination. When the intervention group received follow-up reinforcements, the control group attended sessions on prevention of low back pain.

This study was well done. All subject inclusion and exclusion decisions, diagnoses, and determination of cause of death were made by researchers who were blinded to subjects' study arm. The study used an intention-to-treat design.

OUTCOMES MEASURED

The primary outcome of this study was death from breast cancer. To determine deaths from breast cancer, a physician reviewed clinical and hospital records of deceased participants. Secondary outcomes included proficiency of self-examination.

RESULTS

Eight years after initial instruction, the rates of breast cancer mortality in the intervention and control groups were identical (0.10% in both groups). The instruction group was more proficient in breast self-examination. However, the ability to find a lump was greatest immediately after the videos and declined to the before-video level 1 year later.

Digoxin increases mortality among women with congestive heart failure

Rathore SS, Wang Y, Krumholz HM. Sex-based differences in the effect of digoxin for the treatment of heart failure. N Engl J Med 2002; 347:1403-11.

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PRACTICE RECOMMENDATIONS

Digoxin increases mortality in women with congestive heart failure, compared with men; however, the clinical significance of this is unknown since gender is a nonmodifiable risk factor. More importantly, there is a suggestion of harm when looking at women treated with digoxin versus placebo. Since there are other therapies with definite benefit in congestive heart failure (angiotensin-converting enzyme inhibitors, beta-blockers, spironolactone), it is prudent to reconsider the use of digoxin in women with ejection fractions less than 45%.

BACKGROUND

Is there a difference in the effect of digoxin for heart failure between women and men? This study is a subgroup analysis of the Digitalis Investigaton Group Trial (DIG), which, in 1997, showed that digoxin did not affect mortality in the treatment of heart failure. This subgroup analysis reexamined the data and looked for sex-based differences, which is important because women account for the majority of deaths from congestive heart failure.

POPULATION STUDIED

The researchers from the original DIG trial enrolled 6800 patients who had stable heart failure with an ejection fraction of 45% or less and who were in normal sinus rhythm. Overall, the women in the study were older than the men, had a shorter duration of heart failure, had a higher median ejection fraction, and had greater disease

severity as classified by the New York Heart Association system. The reported results, however, adjust for these differences.

STUDY DESIGN AND VALIDITY

This is a post hoc analysis of the DIG trial, a randomized, double-blinded, placebo-controlled study of 5281 men and 1519 women randomized to receive either digoxin or placebo. This reanalysis of the DIG data looked at the outcomes separately for men and women.

This analysis (based on sex) was not planned when the trial was conceived. There is considerable risk with a post hoc analysis of this type. The authors statistically controlled for baseline differences between the sexes. Unfortunately, the study was not originally set up to evaluate differences by sex, and there was a disproportionate number of men. Another limitation is that it relies a great deal on statistical adjustments. There is also a risk that an association may occur by chance to multiple analyses.

OUTCOMES MEASURED

The primary outcome was death from any cause within an average of 37 months (range 24 to 48 months). Other outcomes included death from cardiovascular disease, death from worsening heart failure, and hospitalization for heart failure.

RESULTS

The investigators reported that women on digoxin had a significantly higher mortality compared with men (33.1% vs 35.2%, *P*=.034). Mortality was not significantly higher in women receiving digoxin compared with women receiving placebo (33.1% vs 28.9%, respectively; 95% confidence interval [CI], 20.5 to 8.8). However, after adjusting for other factors (eg, age, race, ejection fraction), digoxin use was associated with a significant increase in mortality in women compared with men (hazard ratio 1.23; 95% CI, 1.02–1.47; number needed to harm=22; 95% CI, 11–227).

There was no overall increase in mortality in men taking digoxin versus placebo. There was no significant difference between men and women regarding the secondary outcomes of death from cardiovascular disease or death from worsening heart failure. Higher rates of hospitalization in women with worsening heart failure approached statistical significance when compared with men (30.2% vs 25.8%, *P*=.053). There was no significant difference in rate of hospitalization for other causes.

Duct tape removes warts

Focht DR III, Spicer C, Fairchok MP. Efficacy of duct tape vs cryotherapy in the treatment of verruca vulgaris (the common wart). Arch Pediatr Adolesc Med 2002; 156:971–4.

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PRACTICE RECOMMENDATIONS

Duct tape (or any durable, occlusive, tacky tape) appears to be at least as effective as traditional cryotherapy for removal of the common wart. It is an unusual and welcome event in health care when a common ailment is proven equally amenable to an inexpensive, tolerable, and safe alternative therapy.

BACKGROUND

Is the application of duct tape as effective as cryotherapy in the treatment of common warts? The common wart occurs in 5% to 10% of all pediatric patients. Cryotherapy with liquid nitrogen is currently the treatment of choice in many pediatric offices. However, anecdotal reports in the literature have suggested that tape occlusion therapy also may be effective.

POPULATION STUDIED

A total of 61 patients between the ages of 3 and 22 years were initially enrolled over a period of 9 months. Each was an outpatient of the Madigan Army Medical Center and was scheduled for treatment of common warts or was observed to have them.

Patients were excluded if warts were located on the face or on the periungual, perianal, or genital areas; if previous cryotherapy had been performed on the same wart; or if they were immunodeficient or had a chronic skin disease.

STUDY DESIGN AND VALIDITY

In this randomized, single-blinded trial, cryotherapy was compared with duct tape for the treatment of common warts. Patients were randomized by using a computer-generated code after nursing personnel measured the initial diameter of the study wart. The report did not indicate whether treatment allocation was withheld from the enrolling researcher.

The cryotherapy group returned to the clinic every 2 to 3 weeks for a maximum of 6 treatments or until wart resolution (maximum treatment period of 15 weeks). The day before evaluation and retreatment, patients were to debride the wart with an emery board.

The duct tape group was required to return to the clinic every 4 weeks for a maximum of 2 months, but only if the wart was still present as determined by the patient.

A piece of duct tape the size of the wart was applied for 6 days. After 6 days, the tape was removed, and the wart was soaked in water and then debrided. Tape was left off overnight and then new tape was applied for another 6 days.

Before a clinic visit, the tape was removed to keep nursing personnel blinded. However, once a wart was evaluated, nurses became unblinded to determine which group the patient was in for further therapy. Further visits could conceivably consist of an evaluation by the unblinded nurse. It is also appears that patients in the tape group who reported wart resolution within the first 4 weeks never had wart resolution visibly confirmed by nursing personnel.

OUTCOMES MEASURED

The primary outcome measured was complete resolution of the study wart. A secondary outcome measure was time to resolution.

RESULTS

Of 61 patients initially enrolled in the study, 51 were included in the final analysis (26 in the duct tape group and 25 in the cryotherapy group). Nine patients were not available for follow-up (3 in the duct tape group and 6 in the cryotherapy group), and 1 patient from the tape group suffered a traumatic amputation of the toe with the study wart.

More patients receiving duct tape therapy experienced complete resolution of their warts than those receiving standard cryotherapy (85% vs 60%; number need to treat=4; 95% confidence interval, 2–91). Of the 22 warts that resolved with duct tape therapy, 73% disappeared within the first 4 weeks. Of the 15 warts that resolved with cryotherapy, 60% resolved during approximately the same period.

HRT and vitamins C and E do not improve coronary disease in women

Waters DD, Alderman EL, Hsia J, et al. Effects of hormone replacement therapy and antioxidant vitamin supplements on coronary atherosclerosis in postmenopausal women. A randomized controlled trial. JAMA 2002; 288:2432-40.

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PRACTICE RECOMMENDATIONS

Hormone replacement therapy (HRT) and antioxidant vitamin supplements (vitamins E and C) do not provide cardiovascular benefit for postmenopausal women with known coronary heart disease. Moreover, a potential for harm exists with each of the treatments. Therefore, neither should be prescribed specifically for cardiovascular benefit for postmenopausal women with coronary heart disease.

BACKGROUND

Are HRT and antioxidant vitamins useful for the secondary prevention of coronary events in postmenopausal women? While epidemiological studies have demonstrated a positive association between HRT (estrogen alone or in combination with progestin/progesterone) and cardiovascular health benefits, neither of the 2 randomized controlled studies examining this relationship has demonstrated such benefits.

Likewise, antioxidants (dietary or vitamin supplements) have been epidemiologically associated with similar cardiovascular health benefit. A number of randomized controlled studies of vitamin E only in patients with or at risk for coronary disease have reported no cardiovascular benefit. Nevertheless, 1 randomized controlled study combining vitamins E and C suggested cardiovascular benefit, raising questions about possible synergistic effects of these vitamins.

POPULATION STUDIED

A total of 423 postmenopausal women with coronary disease (documented by angiogram), recruited over 2 years at 7 clinical sites in the US and Canada, were studied. Stringent exclusion criteria included:

- HRT use within 3 months
- concurrent use of ≤60 mg/d of vitamin C or ≥30 IU/d of vitamin E
- evidence of potential cervical, uterine, or breast cancer
- uncontrolled hypertension or diabetes
- myocardial infarction (MI) within 4 weeks or planned coronary artery bypass graft
- fasting triglycerides >500 mg/dL
- creatinine >2.0 mg/dL
- symptomatic gallstones
- New York Heart Association class IV heart failure
- history of hemorrhagic stroke, bleeding diathesis, pulmonary embolism, or idiopathic deep vein thrombosis
- untreated osteoporosis.

STUDY DESIGN AND VALIDITY

Using a double-blind (concealed allocation assignment), 2x2 factoral, randomized control design, study participants were assigned to 4 equally sized treatment groups, stratified by clinical center and previous hysterectomy status. Subjects were given either 400 IU of vitamin E and 400 mg of vitamin C or a matching placebo to be taken twice daily with or without HRT. Women with prior hysterectomy were given 1 tablet of conjugated equine estrogen (0.625 mg/d) or a matching placebo; those with no hysterectomy were given 1 tablet of conjugated equine estrogen (0.625 mg/d) and medroxy-progesterone acetate (2.5 mg/d) or matching placebo.

Follow-up was at 3 months after randomization and then every 6 months through the end of the trial for a mean of 2.8 years. Although 306 subjects (72%) completed the study with an exit angiogram, 336 (79%) were included in the primary analysis. The 30 subjects without an exit angiogram had either died or had an MI before completing the study; for analysis, they were assigned the worst rank of angiographic outcome.

The group with the smallest percentage of completers (72%) was that receiving HRT placebo and the vitamins. The group with the largest percentage of completers (85%) was that receiving HRT and vitamins. Data were analyzed by intention-to-treat.

OUTCOMES MEASURED

The primary outcome was the annualized mean (SD) change in minimum lumen diameter from baseline to concluding angiogram of all qualifying coronary lesions, averaged for each patient. Secondary outcomes measured included all-cause mortality and cardiovascular events.

RESULTS

Neither HRT nor antioxidants provided cardiovascular benefit; in fact, potential harm from their use was suggested. Based on coronary angiographic change, the increased risk associated with HRT was statistically significant (P=.045),

and the increased risk associated with antioxidant vitamins was of borderline statistical significance (*P*=.09). All-cause mortality was significantly higher in women assigned to antioxidant vitamins compared with vitamin placebo (*P*=.047). There were no significant differences between the 4 groups in cardiovascular events, cancer, or other noncardiovascular events.

Densitometry identifies women in whom treatment will reduce fracture risk

Nelson HD, Helfand M, Woolf SH, Allan JD. Screening for postmenopausal osteoporosis: review of the evidence for the US Preventive Services Task Force. Ann Intern Med 2002; 137:529–41.

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PRACTICE RECOMMENDATIONS

Despite lack of research on the effectiveness of osteoporosis screening to reduce fractures, there is sufficient evidence that bone density measurements accurately predict short-term fracture risk and that treating asymptomatic women with osteoporosis reduces fracture risk.

According to this report, a reasonable recommendation is to screen all women older than 65 years and postmenopausal women younger than 65 years who have low weight (or body mass index) or who have never used hormone replacement therapy.[1]

The US Preventive Services Task Force noted that the optimal screening frequency has not been studied, but suggested a frequency of not more than every 2 years for older women or every 5 years for younger postmenopausal women. Also of note: other sources, notably the bisphosphonates package labeling, advise against monitoring therapy with repeated dual-energy x-ray absorptiometry or other methods.

BACKGROUND

Does osteoporosis screening decrease fracture risk in postmenopausal women? Osteoporosis results in 1.3 million fractures annually in the US.[2] Of the approximately 25 million American women with osteoporosis, 8 million have had a documented fracture.

Although half of postmenopausal women will have an osteoporosis-related fracture, whether the evidence is sufficient to warrant screening for osteoporosis in postmenopausal women remains unclear.

POPULATION STUDIED

The authors examined all information available from English-language abstracts that contained original data about postmenopausal women and osteoporosis and addressed screening or the effectiveness of risk factor assessment, bone density testing, or treatment.

STUDY DESIGN AND VALIDITY

This systematic review included relevant studies identified from multiple searches of MEDLINE (1966 to May 2001), HealthSTAR (1975 to May 2001), and Cochrane databases; reference lists of systematic reviews; and experts. Two reviewers read each abstract to determine its eligibility. The authors highlighted studies that were applicable to current practice standards, had high-quality internal validity ratings, and were most generalizable to the US population of postmenopausal women under consideration for screening. The authors excluded studies of primary prevention of osteoporosis and secondary causes of osteoporosis.

The authors used comprehensive methods for locating relevant studies and described independent selection of the studies to be included. Their inclusion criteria were relevant to most forms of primary care clinical practice. The exclusion criteria appeared appropriate given the constraints of the review. The authors used the same criteria used by the US Preventive Services Task Force for determining the internal validity of articles considered for inclusion.

The authors did not describe reviewing the refer-

ence lists of articles considered and may have missed important information by limiting the search to the English-language and therapeutic trials that used medications other than bisphosphonates.

OUTCOMES MEASURED

A radiographically verified, nontraumatic fracture was the primary outcome used in the evaluation of therapeutic trials included in this review.

RESULTS

The authors were unable to identify studies concerning the effectiveness of screening in reducing osteoporotic fractures. The authors reviewed articles on risk factor assessment, bone density tests, and osteoporosis treatment with bisphosphonates. They then created an outcomes table based on assumptions from the reviewed articles to estimate the effect of screening 10,000 postmenopausal women for osteoporosis on reducing hip and vertebral fractures.

For women 65 to 69 years of age, the numbers needed to screen were 731 to prevent 1 hip fracture in 5 years and 248 to prevent 1 vertebral fracture. For women with low bone density, the number needed to treat (NNT) was 88 to prevent 1 hip fracture and 30 to prevent 1 vertebral fracture. The analysis of NNT became more favorable as age advanced.

In addition, they found 3 clinical risk factors that consistently predicted increased risk of fracture: advanced age, low weight or body mass index, and nonuse of hormone replacement therapy. The presence of any of the 3 risk factors increased the risk for fracture by 70% (relative risk, 1.7).

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