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INSIDE

The DVT Limbo Rock: How Low Can You Go?

ABSTRACT & COMMENTARY

Synopsis: *Keeping the INR in the range of 1.5 to 2.0 is safe and effective.*

Source: Ridker PM, et al. *N Engl J Med*. 2003;348:1425-1434.

Warfarin use in deep-vein thrombosis (DVT) is the prototypical "rock and a hard place"; don't use it, and you risk a recurrence of DVT. Use it, and you risk major and minor bleeding. Current guidelines recommend periodic monitoring of the patient's international normalized ratio (INR) with the goal of keeping it between 2.0 and 3.0 (moderate intensity). The Prevention of Recurrent Venous Thromboembolism (PREVENT) trial was designed to determine if long-term, low-intensity therapy with a target INR of 1.5 to 2.0 could reduce the risk of recurrent DVT. This would be desirable because, intuitively, a lower INR would be associated with a reduced risk of major hemorrhage. Eligible patients were older than 30 years; had an idiopathic DVT; had already completed 3 months of moderate-intensity warfarin; had no history of metastatic cancer, major gastrointestinal hemorrhage, or hemorrhagic stroke; had a life expectancy greater than 3 years (to accommodate study follow-up); were not taking dipyridamole, ticlopidine, clopidogrel, heparin, more than 325 mg of aspirin or any other drug known to affect prothrombin time; and did not have known lupus anticoagulant or antiphospholipid antibodies.

This study randomized 578 patients to placebo or warfarin. The randomization was double blinded. All patients were seen every 2 months for office visits at which time an INR was drawn and the warfarin dose adjusted; placebo patients had sham dose adjusting. The placebo group (253) and the warfarin group (255) were similarly composed. The average age was 53 years; 47% were female. The racial make-up was comparable, predominantly non-Hispanic white with African Americans and Hispanics represented. Average body-mass index was 29.9. There were equivalent numbers of diabetics. More than a quarter of patients in both groups were positive for Factor V Leiden or a prothrombin mutation. The patients were followed for an average of 2.1 years with the longest follow-up at 4.3 years.

VOLUME 25 • NUMBER 8 • APRIL 29, 2003 • PAGES 57-64

Patients in the warfarin group took a median dose of 4 mg and had a median INR of 1.7. The primary end points were recurrent DVT, pulmonary embolism, and major hemorrhage (a bleeding event that resulted in hospitalization or transfusion). Strokes and a composite end point of recurrent DVT, major hemorrhage, and death were also followed. The independent data and safety monitoring board terminated the study when it became apparent that patients on low-dose warfarin enjoyed a "large and statistically extreme benefit." In the placebo group there were 37 recurrent DVTs (7.2 per 100 person-years). In the warfarin group there were 14 (2.6 per 100 person-years). Patients with Factor V Leiden or a prothrombin mutation derived similar benefit, 8.6 vs 2.2 DVTs per 100 person-years. Two patients in the placebo group had a major hemorrhage vs 5 patients in the warfarin group, a nonsignificant difference. There were 8 deaths and 2 strokes in the placebo group vs 4 deaths and 1 stroke in the warfarin group (not statistically significant).

COMMENT BY ALLAN J. WILKE, MD

Moderate-dose warfarin (INR, 2.0 to 3.0) is effective in preventing DVT,[1] but at a cost: risk of bleeding, frequent blood tests, and dose tweaking. Duration of therapy has received the most attention recently. Current recommendations, based on the circumstances of the DVT, are 3 months (DVT occurring in someone with a reversible cause [eg, immobility]), 6 months (first idiopathic DVT), and 12 months (recurrent idiopathic DVT). The current study indicates that we may be able to have our cake and eat it, too. The inclusion/exclusion criteria are not overly stringent, but applying the results to someone with lupus anticoagulant or antiphospholipid antibodies should be done with caution; these patients generally need a higher INR (2.5-3.5). It is important to remember, too, that all patients received moderate-dose warfarin for 3 months before randomization. An editorialist notes that a study in press that compares low-intensity to moderate-intensity warfarin shows that moderate-intensity warfarin performed significantly better than low-intensity warfarin with no increase in adverse effects.[2] Perhaps we will need a study of placebo vs low-intensity warfarin vs moderate-intensity warfarin to sort it all out.

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Internal Medicine Alert, ISSN 0195-315X, is published twice monthly by American Health Consultants, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

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GST Registration Number: R128870672.

Periodicals postage paid at Atlanta, GA.

POSTMASTER: Send address changes to ***Internal Medicine Alert***, P.O. Box 740059, Atlanta, GA 30374.

Back issues: $20. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

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Subscription Prices

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1 year *with* free AMA Category 1 credits: $289
(Student/Resident rate: $145).

Multiple Copies
1-9 additional copies: $215 each; 10 or more copies: $191each.

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Internal Medicine Alert has been approved by the American Academy of Family Physicians as having educational content acceptable for prescribed credit hours. Term of approval covers issues published within one year from the beginning distribution date of January 1, 2003. This volume has been approved for up to 45 prescribed credit hours. Credit may be claimed for one year from the date of this issue.
The program is also approved by the American Osteopathic Association for 40 Category 2B credit hours.

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Are We Failing Our Heart Failure Patients?

ABSTRACT & COMMENTARY

Synopsis: *Adding continuous positive airway pressure (CPAP) to medical therapy in patients who have obstructive sleep apnea and congestive heart failure both improves systolic function and lowers blood pressure.*

Source: Kaneko Y, et al. *N Engl J Med*. 2003;348:1233-1241.

This was a controlled study of 24 patients who had heart failure and obstructive sleep apnea (OSA). Inclusion criteria included a history of ischemic or non-

ischemic dilated cardiac myopathy (a.k.a. heart failure), left ventricular ejection fraction less than 45%, New York Heart Association (NYHA) functional class II to IV, optimal treatment with medications, and obstructive sleep apnea. In this study, obstructive sleep apnea was defined as an apnea plus hypopnea index (AHI) of at least 20 events per hour of sleep. Patients with primary valvular heart disease, pacemakers, unstable angina, and recent (within 3 months) myocardial infarction or cardiac surgery were excluded. All patients had sleep studies and cardiac evaluations including digital photoplethysmography and 2-dimensional echocardiography at baseline and after 1 month. Those randomized to receive CPAP underwent a second night of sleep testing (after the first diagnostic test) to establish optimum CPAP pressure.

All of the subjects were habitual snorers, and most were middle-aged obese men (21/24 men, mean age about 55 years). These people were not particularly sleepy, as evidenced by normal Epworth Sleepiness Scores. Treatment and control groups were not different in baseline measures. Those who received CPAP required an average of 8.9 ± 0.7 cm H_20 pressure.

After 1 month, the control group had not changed in any of the reported measures, but the 12 patients who were treated with CPAP had significant improvements in measures of sleep-disordered breathing and in nocturnal oxygen saturation. More importantly, they also had significant improvements in daytime systolic blood pressure (from 126 ± 6 to 116 ± 5 mm Hg; $P = 0.02$), in heart rate (from 68 ± 3 to 64 ± 3 beats per minute; $P = 0.007$), in left ventricular ejection fraction (from 25.0 ± 2.8% to 33.8 ± 2.4%; $P < 0.001$), and a 35% increase in left ventricular end-diastolic and end-systolic volumes ($P = 0.009$). All of these changes were significant compared with the control group. Improvements were similar both in those who were and those who were not taking beta-blockers, and in those with ischemic and nonischemic cardiomyopathy.

COMMENT BY BARBARA A. PHILLIPS, MD, MSPH

Wow! A nonpharmacologic treatment for congestive heart failure that is cheap and has minimal side effects! Heart failure is a prevalent and expensive condition with high morbidity and mortality. Patients with heart failure have high rates of both obstructive and central sleep apnea; it is likely that obstructive sleep apnea is the cause of the heart failure, and central sleep apnea is the result.[1,2] No matter; CPAP is a highly effective treatment for both![3,4]

This is the first controlled study to demonstrate that nocturnal CPAP significantly improves the daytime cardiac function of optimally treated heart failure patients. It also demonstrates a dramatic (10 mm Hg) fall in daytime systolic blood pressure and heart rate, suggesting that reduced afterload is one likely mechanism of its beneficial effect.

It is notable that these patients were not very sleepy; no one had an Epworth Sleepiness Score of more than 10, which is felt to be the cut-off range for normal. Yet they wore CPAP anyway and benefited significantly. In addition to improving cardiac function and sleepiness, CPAP can lower blood pressure,[5] improve daytime cognition,[6] reduce car wrecks,[7] improve quality of life,[8] and reduce health care costs.[9] Yet, the vast majority of patients with obstructive sleep apnea are probably not being treated.[10] There are many barriers to treatment of sleep apnea, including limited access to sleep testing, the requirement to spend 1 or 2 nights in the sleep laboratory, third-party payers, and lack of awareness both by patients and by physicians.

With the growing body of evidence that sleep apnea causes significant cardiovascular morbidity and mortality and that treatment with CPAP can reduce this health burden, it is becoming increasingly difficult to justify the delays and cost of our current approach to sleep apnea diagnosis. This is especially true since many of those with sleep apnea can be diagnosed with simple clinical tools such as a history, physical examination and/or questionnaires![11-18] As awareness grows, it is likely that careful clinical evaluation, home monitoring and auto-titrating (or "smart") CPAP will improve access and patient convenience. In the meantime, we owe it to our patients to look for this very treatable condition. ■

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How Much Protein Should We Consume?

ABSTRACT & COMMENTARY

Synopsis: *A high intake of nondairy protein may accelerate renal function decline in women with mild renal insufficiency.*

Source: Knight EL, et al. *Ann Intern Med.* 2003;138: 460-467.

In individuals with moderate-to-severe renal insufficiency, low protein intake may slow renal function decline. However, the long-term effect of protein intake on renal function in persons with normal renal function or mild insufficiency is unknown.

This study involved 1624 women enrolled in the Nurses' Health Study who were aged 42-68 years in 1989 and gave blood samples in 1989 and 2000. Ninety- eight percent of the women were white, and 1% were African American. Their protein intake was measured in 1990 and 1994 by using a semi-quantitative food frequency questionnaire. Creatinine concentration was used to estimate glomerular filtration rate (GFR) and creatinine clearance.

A high protein intake was not significantly associated with change in estimated GFR in women with normal renal function. In women with mild renal insufficiency (defined as an estimated GFR of > 55 mL/min per 1.73m^2 but < 80 mL/min per 1.73 m^2), increase in protein intake was significantly associated with a decline in renal function. A high intake of nondairy animal protein was associated with a significantly greater decrease in GFR.

COMMENT BY RALPH R. HALL, MD, FACP

There are several limitations to this study. Since participants were not randomly assigned to a specific protein intake and since only 2 estimations of protein intake were taken during the 11 years of the study, the dietary intake may have varied more than estimated. The population studied was predominately white; therefore, the results apply only to this population.

Another significant study that confirms and compliments this study was carried out by Wrome and associates.[1] They studied the relationship between dietary protein and microalbuminuria (MA). The study included participants from the third National Health and Nutrition Examination Survey (NHANES III) and included large numbers of young men and women, elderly, black and Mexican Americans. There were 15,779 subjects aged 20-80 years with available measurements of dietary protein (DPI), urinary albumin, and creatinine. The dietary recall used assessed protein intake of animal and plant sources separately. DPI was not associated with an increase in MA in healthy persons or those with isolated hypertension or in diabetics without hypertension. However, in diabetics with hypertension there was an increase in MA in those on high-protein diets.

MA is associated with a significantly increased risk of cardiovascular disease. It is not a cause of cardiovascular disease but serves as a marker for those at increased risk. It is caused by glomerular capillary injury and is probably the result of endothelial disfunction.

As Knight and colleagues note, the potential consequences for the large number of undiagnosed diabetes and hypertensive patients and of patients with mild undiagnosed renal failure who are inclined to embark on a high-protein weight-loss diet are significant. ■

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Rheumatoid Arthritis: A New CAD Risk Factor

ABSTRACT & COMMENTARY

Synopsis: *Rheumatoid arthritis should be recognized as a marker of increased risk for myocardial infarction.*

Source: Solomon DH, et al. *Circulation*. 2003;107: 1303-1307.

It is well known that there is increased morbidity and mortality in individuals with rheumatoid arthritis (RA), the most common systemic autoimmune disease, affecting 2 million Americans, most of whom are women. Recently, several studies have suggested

increased rates of cardiovascular disease in these patients, potentially contributing to the reduced longevity in RA. In that atherothrombosis is an inflammatory process, it is a rational hypothesis that the chronic inflammation in RA may adversely affect blood vessels. Furthermore, it is well known that inflammatory markers, such as C-reactive protein (CRP) and other cytokines, are elevated in RA.

This observational investigation from the the Nurses' Health Study (NHS), sought to assess whether RA was associated with increased cardiovascular events. In the NHS, women were enrolled in 1976 between the ages of 30 and 55 years and underwent questionnaire follow-up every 2 years. A total of 141,342 women remained after baseline exclusion of RA, CV disease, and cancer, of which 7786 women reported RA on at least 1 biannual questionnaire between 1978 and 1996. Solomon and colleagues pursued the RA diagnosis by a connective tissue disease screening questionnaire, followed up by careful review of medical records in the 2170 women with symptoms on the questionnaire suggestive of RA. The cardiovascular end points were myocardial infarction and stroke, both fatal and nonfatal, all verified by medical review. Associated confounding risk factors were adjusted for, including all potential major coronary artery disease (CAD) risk factors, as well as physical activity, BMI, folate, omega-3, and vitamin intake. Use of corticosteroids and nonsteroidal antiinflammatory drugs (NSAIDs) was examined for possible associations. (The data on corticosteroids are available only since 1994 and for NSAIDs, 1990). The primary analysis examined the age-specific incidence rates of stroke and myocardial infarction. The duration of follow-up was calculated as the interval between the 1976 questionnaire and the first diagnosis of myocardial infarction, stroke, or death, or conclusion of the study in mid-1996. Relative risks were computed for individuals with and without RA who had cardiovascular end points. A pooled logistic regression technique was used to adjust for multiple potential confounders, including a wide variety of risk factors. Several other analyses were used, all of which produced the same results as the main analysis.

Based upon medical record reviews, 527 women developed RA during the follow-up out of the 114,000 women in the observational study, representing more than 2 million years of follow-up. There were 2296 myocardial infarctions and 1326 strokes. The women with RA were similar to those without RA with respect to CAD risk factors, with some variation. Three percent of the RA patients reported corticosteriod use since the data were documented beginning with the 1994 survey. The age-adjusted risk of myocardial infarction was 2-fold for patients with RA compared to those without (RR, 2.07). After adjustment for multiple confounders, the relative risk was identical at 2.0, roughly comparable for fatal and nonfatal infarction. These risk ratios were highly significant. However, adjusted stroke rates did not achieve significance, although there was a trend approaching 50% more stroke in the RA women. Duration of disease seemed to be important; women with less than 10 years of known RA had an adjusted relative risk of 1.16 (NS), while those with > 10 years of exposure to RA had a risk of myocardial infarction of 3.1. Solomon et al point out that the relative increased risk of RA of 2- to 3-fold is comparable to that suggested in smaller studies in the literature. They emphasize that the risk association remained after adjustment for known CAD risk factors. Laboratory analyses and markers of inflammation are not available from the NHS. Solomon et al point out, however, that, "many of the cells comprising the inflammatory infiltrate in the joint lining are likewise found in atherosclerotic plaque." CRP and other cytokine markers of inflammation are known to be elevated in RA. Furthermore, one recent study reported a decrease of cardiovascular mortality in patients treated with methotrexate, suggesting that immunosuppressive therapy was beneficial for the vascular wall. Solomon et al point out that there may be inadvertent confounders, such as reduced physical activity, the various medications taken for RA, and perhaps differential use of cardiovascular prevention medications. They emphasize that medications used for RA have the potential for both inducing and protecting from thrombotic events and atherogenesis. Efforts to control for use of corticosteriods and NSAIDs were carried out, with the risk of MI persisting. Solomon et al concluded, "RA should be recognized as a marker of increased risk for myocardial infarction." They believe that treatment medications for RA and perhaps less-than-adequate CAD prevention therapy may contribute to the increased risk in these women. They concluded, "It would be prudent to consider aggressive cardiac prevention measures in patients with RA to address established coronary heart disease risk factors."

COMMENT BY JONATHAN ABRAMS, MD

This is an interesting analysis, which seems not surprising given our current knowledge and the focus on inflammation and its relationship to atherothrombosis and unstable plaque. In this large,

observational cohort, it is difficult to establish the effects of various potent drugs used for RA. Furthermore, the recent controversy about COX-2 inhibitors and the suggestion that nonselective NSAID may be safer point out the complexity of anti-inflammatory medications. Aspirin use was less common in the RA patients, 41.5% vs 52.2%. Hormone replacement therapy was slightly greater in RA, 33% vs 27%; as expected, NSAID use approached 67% in the RA patients vs 22% in non-RA women. Physical activity, measured in estimated mets per week, was somewhat less in the RA women but not strikingly so. No data were provided for CRP in these women, and one wonders if the banked plasma stored at the beginning of the study could be analyzed for CRP. It is clear that many to most patients with RA will have elevations of CRP and other inflammatory markers. Many believe that CRP itself may play an adverse role in the vasculature and is not just a marker of increased vascular risk. Thus, chronic elevation of cytokines in this autoimmune disease over many years may induce or exacerbate events in the vessel wall in promoting atherothrombosis and perhaps unstable plaque.

I agree firmly with the conclusions of Solomon et al that aggressive CAD preventive measures should be considered in RA, and I would suggest that this approach be mandated. We are currently treating diabetes without obvious overt vascular disease as a CAD risk equivalent (ie, diabetics should be treated with the same target goals of blood pressure and lipid modification as individuals with established CAD or a previous stroke). It is logical that for the RA patient, one should aim for an LDL target of 100 mg/dL or less; aspirin should be used in all; COX-2 NSAID use should be avoided until the current controversy is resolved; blood pressure should be controlled, with a target of 130/80 or less; an optimal "heart healthy diet" is recommended; and as much physical activity as can be carried out should be. With the complexity of this illness and its treatment, it may be difficult to carry out randomized trials looking at CAD risk prevention, particularly since the major adverse vascular effects of RA are seen only after 10 or more years of exposure. Thus, RA is now added to the pantheon of conditions for which very aggressive CAD prevention approaches are warranted. In this case, it is unlikely that a "smoking gun" trial of aggressive prevention therapy vs "usual care" will be carried out. ■

Dr. Abrams is Professor of Medicine, Division of Cardiology, University of New Mexico, Albuquerque.

Pharmacology Update

Enfuvirtide (Fuzeon—Roche Pharmaceuticals)

By William T. Elliott, MD, FACP, and James Chan, PharmD, PhD

THE FDA RECENTLY APPROVED A NEW CLASS OF ANTIretroviral drug for treatment of patients with resistant HIV infections. Enfuvirtide (T-20), a synthetic 36-amino acid peptide fusion inhibitor, received an accelerated approval by the FDA. In contrast to existing antiretroviral agents that inhibit replication of HIV-1, enfuvirtide inhibits the entry of the virus into cells by inhibiting the fusion of viral and cellular membranes. The drug, which has made news because of its $20,000 per year price tag, will be marketed by Roche Pharmaceuticals as "Fuzeon."

Indications

Enfuvirtide is approved for use in combination with other retroviral agents for the treatment of HIV-1 infection in treatment-experienced patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy. It is approved for use in adults and children 6 years of age or older.[1]

Dosage

The recommended dose in adults is 90 mg given subcutaneously twice daily. The drug can be injected into the upper arm, anterior thigh, or abdomen. Injection should be given at a different site from the preceding site. The dose in pediatric patients (aged 6-16) is 2 mg/kg twice daily up to a maximum of 90 mg per dose. Body weight should be monitored so that the dose could be adjusted.[1]

Enfuvirtide is available as 90-mg single-use vials.

Potential Advantages

Enfuvirtide provides a new site of action and is the first approved fusion inhibitor of HIV entry. It provides an option for patients who have used other antiretroviral drugs and shows evidence of continual viral replication. The addition of enfuvirtide to an optimized combination resulted in improved virologic and immunologic response compared to an optimized regimen alone.[3-5] HIV-1 isolates resistant to other antiretroviral agents such as nucleoside reverse transcriptase inhibitors, nonnucleoside reverse transcriptase inhibitors, and protease inhibitors have been found to be susceptible to enfuvir-

tide in vitro.[1] Enfuvirtide does not affect drugs metabolized by CYP450 isoenzymes and it does not appear to interact with other antiretroviral agents.

Potential Disadvantages

Enfuvirtide requires twice-daily subcutaneous injection. Injection-site reactions were the most common adverse events as 98% of patients experienced at least 1 reaction. Pain/discomfort requiring analgesics occurred in 9% of patients. Other local adverse events included induration, erythema, and nodules and cysts. About 3% of patients discontinued treatment due to local adverse events.[3-5] A higher incidence of bacterial pneumonia has been reported in phase III clinical trials compared to the control. Risk factors for pneumonia include low initial CD4 cell counts, high viral load, intravenous drug use, smoking, and prior respiratory disease. Hypersensitivity reactions and immune-mediated adverse events have also been reported. Resistant isolates have been recovered from patients treated with enfuvirtide.[1] The long-term effectiveness of enfuvirtide is not known at this time.

Comments

Enfuvirtide is the first in a new class of antiretrovirals, the fusion inhibitors, drugs which block gp-41-mediated fusion of HIV-1 to the D4+ host cell.[2] The accelerated approval of enfurvirtide was based on two 24-week phase III studies involving about 1000 patients. TORO-1 (T-20 vs Optimized Regimen Only [OB]) was conducted in North America and Brazil and TORO-2 in Europe and Australia.[3-5] Eligible patients had greater than 3 months (TORO-2) or 6 months (TORO-1) prior experience with 3 classes of antiretroviral drugs and HIV-1 RNA of at least 5000 copies/mL. They were randomized to an optimized regimen of 3-5 agents that was based on prior history and baseline genotypic and phenotypic resistance with or without enfuvirtide. Analysis at 24 weeks was based on intent to treat and last observation carried forward. In TORO-1, viral RNA had a reduction of 1.696 log for enfuvirtide compared to a reduction of 0.764 log for OB alone ($P < 0.0001$). The median baseline viral load was 5.2 logs for each arm.[3,4] Mean changes in CD4+ were +76 cells/mm^3 and 32 cells/mm^3, respectively ($P < 0.0001$). In TORO-2, viral RNA was reduced by 1.43 log for enfuvirtide compared to 0.65 for OB ($P < 0.0001$). Both arms had a baseline viral RNA of 5.1 log.[5] Overall 52% of enfuvirtide patients had a 1 log or greater reduction in HIV RNA compared to 26% for OB, and 23% of enfuvirtide patients had HIV RNA < 50 copies/mL compared to 9% for OB.[1] Patients who discontinued treatment ranged from 11.3% to 17% for enfuvirtide and 5% to10.9% for OB. The drug has also been studied in 35 pediatric patients, aged 6-16 years in 2 open-label trials with viral response similar to adults.[1] Enfuvirtide is expected to cost about $20,000 per year.[6] The drug will be provided through a progressive distribution plan and will be shipped through a sole distributor.

Clinical Applications

Enfuvirtide provides an effective option to patients as an add-on to an optimized background regimen in treatment-experienced patients with viral replication despite continuing antiretroviral therapy. Roche indicated that the supply of enfuvirtide would be limited, and it expects to have enough for 12,000 to 15,000 patients in 2003 and up to 32,000 in 2004.[6] ■

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CME Questions

19. When compared to placebo, long-term, low-intensity warfarin therapy for prevention of recurrent venous thromboembolism:

a. caused more major bleeding.
b. resulted in statistically significant fewer deaths.
c. was associated with more DVT recurrences.
d. was not effective in persons with Factor V Leiden.
e. None of the above

20. In patients with heart failure and sleep apnea, continuous positive airway pressure (CPAP) improves:

a. cardiac function but only in patients who are sleepy.
b. blood pressure but only in patients who are hypertensive.
c. measures of sleep-disordered breathing, but not of cardiac function.
d. cardiac function but only in those with ischemic (as opposed to nonischemic) cardiomyopathy.
e. ejection fraction, blood pressure, heart rate, and end-diastolic volume.

Answers: 19 (e); 20 (e)

By Louis Kuritzky, MD

Detection of Alzheimer's Disease and Dementia in the Preclinical Phase

ALZHEIMER'S DISEASE (AD) IS THE most common form of dementia in America, but often escapes clinical attention until symptoms compromise quality of life, activities of daily living, or safety. Interventions might be enhanced by early detection of AD, but little investigation of early detection techniques has been done.

Palmer and colleagues evaluated 1435 persons aged 75-95 years who were without dementia at baseline. All persons underwent evaluation at baseline, 3 years, and 6 years with 3 different tools; subjects were asked, "Do you currently have any problems with your memory?" Additionally, each subject underwent mini-mental status examination, and neuropsychological testing assessed cognitive function.

At follow-up, almost 20% of survivors had dementia. All 3 screening tools, if positive, increased relative risk of AD. Having a memory complaint at baseline doubled the relative risk of subsequent dementia, and cognitive impairments increased relative risk of dementia by 2- to 5-fold.

Although using all 3 tools had a high predictive value if positive, the tools are too insensitive for routine employment, since only 18% of persons who ultimately developed dementia were identified using this 3-step process. That we can identify, with some reliability, a subgroup of persons likely to progress to dementia is promising. For broader applicability, more sensitive screening tools will be required. ■

Palmer K, et al. BMJ. 2003;326: 245-247.

Shoe Design and Plantar Pressures in Neuropathic Feet

CLINICIANS HAVE TRIED A VARIETY of maneuvers to reduce the incidence and effect of neuropathic foot ulcers in an attempt to reduce their subsequent morbidity. Since a substantial proportion of diabetics will ultimately develop distal sensory neuropathy and be at risk of foot ulcers, learning which type of footwear might help minimize the consequences of this neuropathy is of great importance. The most commonly used orthopedic shoe for diabetic neuropathy is the "rocker bar" variety (RB shoe), others suggest that a simple extra depth shoe, which is typically less expensive, more cosmetically pleasing, and more readily accessible, may be equally effective.

Praet and colleagues studied 10 diabetic women suffering from peripheral sensory neuropathy, but without evidence of foot deformity or ulceration. Women were tested in 3 categories of shoes: Category A were simple popularly styled traditional shoes, category B were extra depth shoes, and category C were specially crafted (based upon plaster casts of feet) shoes with rocker bottoms.

Overall, only the RB shoes effectively reduced forefoot pressure more than traditional "over the counter" footwear. Praet et al acknowledge that choosing footwear for any one individual diabetic remains a difficult choice and that shoe-specific pressure measurements in different types of footwear may be the best alternative for some patients, especially for those who balk at use of the less cosmetically acceptable RB shoes. ■

Praet S, et al. Diabetes Care. 2003;26: 441-445.

Serum Thyroid Stimulating Hormone in Assessment of Severity of Tissue Hypothyroidism in Patients with Overt Primary Thyroid Failure

ALTHOUGH THERE IS GOOD AGREEment that thyroid stimulating hormone (TSH) is the most appropriate indicator of hypothyroidism, it is little understood whether absolute levels of TSH correlate either with degree of tissue effect of hypothyroidism, or levels of thyroid hormone. Meier and colleagues used a composite of clinical score, ankle reflex time, CK, and total cholesterol as markers of what they term "thyroid hormone action at the tissue level." They then correlated TSH with thyroid hormone levels and tissue parameters.

The correlation of tissue parameters and TSH was weak. This review suggests that there is a poor correlation between levels of TSH and clinical or metabolic severity of hypothyroidism. Meier et al have no quarrel with the sensitivity and diagnostic accuracy of TSH to discern the presence or absence of hypothyroidism. Rather, they hypothesize that once TSH is maximally stimulated, no further increase will occur, despite progressively greater degrees of hypothyroidism. Meier et al suggest that thyroxine treatment should be guided by clinical signs and thyroid hormone concentrations, rather than solely by TSH concentration. ■

Meier C, et al. BMJ. 2003;326: 311-312.

In Future Issues: One-Year Outcomes in Survivors of ARDS