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Is Patience a Virtue?

ABSTRACTS & COMMENTARY

Synopsis: *Radical prostatectomy reduces the risk of death from prostate cancer when compared to watchful waiting, but it does not confer a survival advantage.*

Sources: Holmberg L, et al. *N Engl J Med.* 2002;347:781-789; Steineck G, et al. *N Engl J Med.* 2002;347:790-796.

HOLMBERG AND COLLEAGUES IN SCANDINAVIA ENROLLED MEN with early prostate cancer and then randomized them to either radical prostatectomy or watchful waiting. These men were, by protocol, younger than 75 (average age, 64.7 years) and were expected to have a life expectancy of an additional 10 years (to allow for follow-up). They had no other cancers. Their prostate cancers had to be newly diagnosed and previously untreated. Cytology, histology, or both confirmed the diagnoses. The definition of "early" prostate cancer was tumor in stage T0d or T1 (clinically unapparent), T2 (confined to the prostate), or T1c (diagnosed by needle biopsy prompted by an elevated prostate-specific antigen [PSA] level). The tumors had to be well- or moderately well-differentiated with a low Gleason score (< 10). Additionally, before a patient could be enrolled, his bone scan had to show no sign of metastases, there could be no sign of urologic obstruction, and his PSA had to be less than 50 ng/mL.

The watchful waiting group received no immediate therapy, although some of the men were diagnosed after receiving a transurethral resection of prostate (TURP). Patients in the intervention group first had pelvic lymph node dissection. If, on frozen section, the nodes were positive (ie, metastatic disease), no further surgery was performed. No one received adjuvant or systemic therapy. If there was symptomatic local progression, men in the watchful waiting group could get a TURP. Men in the intervention group could have chemical or surgical castration. Men in both groups received the same treatment for disseminated disease. All patients had an examination and laboratory work (hemoglobin, creatinine, PSA, and alkaline phosphatase) twice in years 1 and 2, and then yearly. They also had annual chest x-rays and bone scans. Cause of death, distant metastases, local progression, and local recurrence were rigorously defined. The study had 3 end points: disease-specific mortality (the

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time to death from prostate cancer), the rate of distant metastasis (the time to diagnosis of distant metastases), and death from causes other than prostate cancer.

Six hundred ninety-eight men, who were similar at baseline, were enrolled with equal numbers in both groups. After randomization, 2 men were excluded because the prostate cancer diagnoses were wrong and one man was excluded because he previously had Hodgkin's disease. The patients were followed for up to 8 years (median, 6.2 years). No one was lost to follow-up. Analysis was by intention-to-treat. Thirty watchful-waiting men eventually had treatment with intent to cure, and 25 men in the intervention group did not have prostatectomies. In all, 115 men died, 62 from the watchful waiting group and 53 in the intervention group. The relative hazard of death from any cause was 0.83, a nonsignificant finding because the 95% confidence interval (CI) was 0.57-1.2. The deaths due to prostate cancer (disease-specific mortality) were 31 and 16, respectively. The relative hazard was 0.5, which was significant (CI, 0.27-0.91). The absolute difference at 8 years was 6.6% (number needed to treat [NNT] = 17). Only 1 of these 47 men did not have clinically apparent distant metastases. Only 2 men died within 1 month of randomization, 1 in each group. This effectively rules out operative or postoperative complications as the cause of the higher death rate from other causes in the intervention group. Men in the intervention group were also significantly less likely to develop distant metastases and local progression.

COMMENT BY ALLAN J. WILKE, MD

The decision to undergo radical prostatectomy is a very personal one. As primary care physicians, our patients turn to us for guidance and advice. However, we have not had good information on which to base our counsel. Thus, the results of this trial were eagerly awaited. The answers are not all in, but at this point we can tell our patients that radical prostatectomy will probably reduce their chances of death from prostate cancer, developing distant metastases, and local progression, but will not reduce their chance of death overall. We will have to treat 17 men with radical prostatectomy and wait 8 years to prevent 1 death from prostate cancer.

Will they feel better? In a companion article, Steineck and colleagues looked at quality of life in about half of the men in the study. Not surprisingly, men from the intervention group had worse erectile dysfunction (ED; 80% vs 45%, number need to harm [NNH] = 3), better urinary bladder function (28% with weak stream vs 40%, NNT = 8), and worse urinary leakage (49% vs 21%, NNH = 4). Bowel function and psychological symptoms showed a nonsignificant trend toward advantage in the intervention group.

Now, the fine print. This study enrolled Scandinavians exclusively. There was no racial breakdown given, but the number of men of African ancestry undoubtedly was very small. In this country, black men are twice as likely to die of prostate cancer as white men[1] (48.7 vs 19.6 per 100,000). Only lung cancer causes more cancer deaths. The men in this study were followed for a median 6 years; the mortality curves separated at about 2½ years and grew farther apart as the study progressed. What will the next 6 years show? These men had the very best kind of prostate cancer—well or moderately well differentiated with no evidence of local or distant spread—and they were healthy enough to be expected to live 10 more years. The results for patients with more advanced disease or other co-morbidities are likely to be worse. The participants did not receive any adjuvant local or sys-

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

United States
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.

Canada
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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, 2002. This volume has been approved for up to 40 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.

Statement of Financial Disclosure

In order to reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, we disclose that Dr. Brunton is a consultant for Andrx, Reliant, and AstraZeneca and serves on the speaker's bureau of Janssen, Schering, Aventis and AstraZeneca. Dr. Hall is a consultant for Aventis. Dr. Kuritzky is a consultant for GlaxoSmithKline and is on the speaker's bureau of GlaxoSmithKline, 3-M, Wyeth-Ayerst, Pfizer, Novartis, Bristol-Myers Squibb, AstraZeneca, Jones Pharma, and Boehringer Ingelheim. Dr. Lipsky is a consultant for and is on the speaker's bureau of Aventis and AstraZeneca. Dr. Ost is on the speaker's bureau of Merck, Roche, and Boehringer Ingelheim and does research for the American Lung Association. Dr. Phillips serves on the speaker's bureau of Cephalon, Boehringer Ingelheim, Merck, Res Med, and GlaxoSmithKline and is a consultant for Boehringer Ingelheim, Wyeth-Ayerst, and Res Med. Dr. Robinson serves as a consultant for TAP, Pfizer, Janssen, Eisai, J&J-Merck, and Procter & Gamble, is on the speaker's bureau of Janssen, Eli Lilly, Solvay, TAP, and Aventis, and does research for Forest Labs, Wyeth-Ayerst, AstraZeneca,and Centocor. Drs. Chan, Elliott, Ferris, Grauer, Karpman, Wiese, and Wilke report no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study.

temic therapy. Holmberg et al note in their discussion that they did not stress nerve-sparing prostatectomy. Had they, it is possible that there might have been less ED.

More studies need to be published before we have definitive answers. Until then, this study gives us information we can share with our patients. Some men will consider ED a fair trade for easier bladder emptying. Others will weigh urinary incontinence against distant metastases and roll the die. We will be there for them in any case to support their decisions. ■

Reference

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Is Normal Pressure Hydrocephalus a Valid Concept in 2002?

ABSTRACT & COMMENTARY

Source: Bret P, et al. *J Neurol Neurosurg Psychiatry.* 2002; 73:9-12.

1. Is CSF pressure really normal in patients with NPH?

The actual readings of CSF are often moderately and physiologically high because of anxious muscle tension in the patient. Then, with the needle remaining in place, the patient relaxes and CSF fluid pressure drops 15-20 mm of CSF with the patient supine and the manometer erect. It can be argued, however, that a single CSF measurement by lumbar puncture may not adequately reflect the true intracranial pressure, or the presence of numerous B waves.

2. Is NPH really a cause of curable dementia?

Bret wisely says "no" to this question. He states bluntly, "patients with NPH do not fit the criteria of degenerative (Alzheimer-type) or arteriosclerotic dementia." This is largely a semantic argument. Most neurologists accept the premise that NPH is a cause of curable dementia, particularly if strict criteria are used in establishing the diagnosis. As pointed out by Bret and colleagues this criteria includes:

- Presence of a clearly identified etiology;
- Predominant gait difficulties with mild or absent cognitive impairment;
- Substantial improvement after CSF withdrawal (CSF tap test);
- Normal sized or occluded sylvian fissures and cortical sulci on CT or MRI;
- Absent or moderate white matter lesions on MRI.

3. Is CSF diversion the only treatment modality?

Ventriculoperitoneal shunts have become standard treatments although ventriculoatrial shunts are still a second-line treatment. Lumboperitoneal shunts have never gained widespread acceptance in the treatment of patients with NPH, probably because they are strictly limited to communicating forms of hydrocephalus. Whatever the type of shunt, the major nuisance is the high rate of complications. Thus far, only truly satisfactory ventricular drainage is effective. Third ventriculostomy in patients with aqueductal stenosis may be effective but only a few patients and their surgeons have experience with this technique.

Conclusion

Bret concludes his commentary with a number of points.

A. Some carefully selected patients respond to shunting which remains the standard today. Nevertheless, complications are high, although newer programmable shunts eliminate some of the difficulties.

B. Presently, the term "normal pressure hydrocephalus NPH" is an oxymoron, indicating a static illness. The problem lies that in reality NPH is likely to be a dynamic process that gradually and insidiously disrupts the intracranial structures.

C. It has become obvious that the other elements of the historical concept of NPH need to be revised. NPH should not be regarded as an age-related disease specific to the adult and elderly population. A similar condition may be encountered during childhood, with a clinical presentation that does not differ basically from that of the adult and may be erroneously ascribed to "arrested hydrocephalus," which is a distinct condition. More important, the term NPH is questionable because it matches neither the real conditions nor the current diagnosis. This is established in most institutions on the basis of the clinical and CT presentation only, without assessment of the ICP nor the actual CSF manometric profile of such patients. This is acknowledged by the results of dynamic tests that showed a general trend to increased, albeit compensated, pressure levels or at least an inability of compensatory mechanisms to dampen a sudden increase of ICP in patients with NPH.

■ COMMENT BY FRED PLUM, MD

Bret proposes a more relevant nosographic designation for the NPH syndrome by renaming it "chronic hydro-

cephalus" without reference to age and CSF pressure. Although this proposal is attractive, it is unlikely to be adopted after many decades of neurologists being taught that NPH is one of the rare treatable causes of dementia. NPH is an active process that results from failure of the resorptive mechanisms of the CSF. It may be regarded as an intermediate state of balance between uncompensated hypertensive hydrocephalus and asymptomatic hydrocephalus (in which compensatory systems are fully effective). As proved by follow-up monitoring of shunted patients, insertion of a shunt in those suffering from chronic hydrocephalus often provides a clinical cure without changes in their ventricular size. Shunting may, therefore, be regarded as an additional compensatory system allowing chronic hydrocephalus in turn to become asymptomatic hydrocephalus, which may be the only condition that really deserves the label NPH. What is truly needed to revolutionize the treatment of NPH is improved means of identifying patients who will respond to shunts. The initial results at New York Presbyterian Hospital—Weill Cornell Medical College suggest that this may be possible using sophisticated new MRI imaging techniques. ■

Dr. Plum is University Professor, Department of Neurology, Cornell University Medical College, New York, NY.

Lung Cancer Screening Using Low-Dose Spiral CT

ABSTRACT & COMMENTARY

Synopsis: *In this nonrandomized screening study of 7956 individuals, the study found that low-dose spiral CT was a good screening test for detecting early lung cancer. This study also showed that annual screening should be done only in selected individuals.*

Source: Nawa T, et al. *Chest.* 2002;122:15-20.

Lung cancer is currently the leading cause of death due to malignancy in the United States, but screening has been a major issue. In the past, the opinion was that chest roentgenograms and sputum cytology could prove to be useful for early detection of lung cancer, but several studies failed to demonstrate efficacy and CXR screening subsequently has fallen out of favor.

This was a prospective, nonrandomized, institutional study in Japan screening 7956 individuals for primary lung cancer, which extended for 29 months. Based on the results of this thoracic CT screening, the following data were extracted: a) prevalence of lung cancer detected at baseline screening and its incidence at the repeat screening; b) detectability of small, early lung cancer; and c) selection of suitable candidates. Demographics were as follows: age range 50-69, 77.1% of males in the study population were smokers, 4.3% of females in the study population were smokers, 79% of the total population were male and 21% female. Nodules that showed extensive calcification or clustered in the same lobe in groups of 6 or greater were considered to be benign and excluded from the study.

Noncalcified solid pulmonary nodules (SPN) measuring 8-10 mm were examined with detailed CT (thin cut CT chest) 1 month later, and if the size of the nodule was 5-7 mm, an annual repeat CT screening was recommended. If the detailed CT demonstrated a noncalcified SPN 8-10 mm in size, a detailed CT was repeated every 3 months for 6 months, and if no growth was noted, annual screening CT was recommended. If at any point growth of the nodule was noted, a further study was recommended: bronchoscopy, video-assisted thoracoscopy (VATS) biopsy, and/or serum tumor markers.

Results of the baseline screening showed that 2099 of 7956 (26.3%) patients had noncalcified SPN, and 541 of 2099 patients (6.8% of 7956) had a detailed CT. Subsequent bronchoscopy was done in 64 of 541 (11.8%) individuals and VATS biopsy was subsequently performed in 51 of these 64 patients (9.4% of 541 individuals with detailed CT). Of the 541 (6.7%) individuals who were identified to have noncalcified nodules measuring 8 mm or greater on a detailed CT, 36 (6.2%) were diagnosed with primary lung cancer. Therefore, the prevalence of primary lung cancer at baseline was 0.44% for the 7956 individuals. Of those patients diagnosed with lung cancer, 9 (25%) individuals were smokers.

The staging of lung cancer at baseline screening ranged as follows: stage IA (28/36; 77.7%); stage IB (3/36; 8.3%); stage IIA (3/36; 8.3%); stage IIB (1/36; 2.7%); and stage IIIA (1/36; 2.7%). Histologically, the tumors were determined to be well-differentiated adenocarcinoma (27/36), moderately differentiated adenocarcinoma (7/36), large cell carcinoma (1/36), and carcinoid (1/36).

A follow-up screening with low-dose CT was repeated a year later in 5568 individuals who had no evidence of noncalcified pulmonary nodules at baseline, and 148 of 5568 individuals were recommended to have a detailed CT for noncalcified nodules greater than or equal to 8 mm. Of those individuals with detailed CT, 7 of 148 (4.7%) had additional diagnostic tests (bronchoscopy and/or VATS), and 4 of 148 (2.7%) were diagnosed to have primary lung cancer. The incidence of primary lung cancer was 0.07%. All of these individuals were smokers.

Primary lung cancer detected on the annual screening

follow-up was stage IA in all 4 cases, with 2 well differentiated and 2 moderately differentiated adenocarcinomas.

COMMENT BY DAVID OST, MD, & ANDREAS KYPRIANOU, MD

Previous authors have found no improvement in mortality of lung cancer by screening patients with chest roentgenograms and sputum cytology,[1] but recently encouraging results of low-dose spiral CT have been reported.[2] Nawa and colleagues have demonstrated that low-dose spiral CT can be a good screening test for early primary lung cancer, especially for adenocarcinoma and large cell cancer, but not for squamous cell or small cell lung cancer. Further prospective studies are warranted to demonstrate improved mortality and to assess cost effectiveness of using low-dose spiral CT as a screening test for lung cancer. This study supports the theory that annual lung cancer screening may be useful when applied to selected populations. In particular, the limited data available suggest that it might be targeted at individuals with a history of smoking. ■

Dr. Kyprianou is a Fellow in Pulmonary/Critical Care Medicine, Northshore University Hospital, Manhasset, NY.

References

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2. Kaneko M, et al. *Radiology.* 1996;201:798-802.

Oral vs. Sub Q Vitamin K

ABSTRACT & COMMENTARY

Synopsis: *Oral vitamin K lowers high INR more rapidly than subcutaneous administration.*

Source: Crowther MA, et al. *Ann Intern Med.* 2002;137:251-254.

THE ANTICOAGULANT EFFECTS OF WARFARIN FREquently need to be reversed for bleeding complications, excessively high INR values, or preprocedures. Although withholding warfarin is eventually effective, occasionally faster reduction in INR is necessary. Crowther and associates tested the hypothesis that oral vitamin K would reduce high INRs faster than subcutaneous vitamin K. Patients with an INR between 4.5 and 10.0 were randomized to receive 1 mg of vitamin K either orally or subcutaneously and warfarin was withheld. The primary outcome was INR on the day after vitamin K. In the 51 patients studied, the mean INR was 6. The INR had decreased to the 1.8-3.2 range the next day in 58% of the oral vitamin K group and 24% of the subcutaneous groups (odds ratio, 4.3; 95% CI, 1.1-17.4; $P = .015$; number needed to treat = 3). Two patients who received subcutaneous vitamin K had an increased INR the next day; this did not occur in the oral therapy group. Conversely, 3 patients who received oral vitamin K had INR < 1.8, whereas none of the subcutaneous group did. Crowther et al concluded that oral vitamin K lowers high INR more rapidly than subcutaneous administration.

COMMENT BY MICHAEL H. CRAWFORD, MD

The use of vitamin K to reverse a high INR is to prevent bleeding complications. The risk of major bleeding in patients with INR > 6.0 is reported to be 4%.[1] In this study no episodes of bleeding were observed, so the incidence may actually be lower. Some have been reluctant to use vitamin K to reverse high INRs for fear of overshooting and precipitating thrombosis, such as in patients with prosthetic valves. Again in this study no episodes of thrombosis were observed, but 3 patients did have INR < 1.8 after oral vitamin K. The results of this study suggest that in patients with a high risk of bleeding complications and no excessive risk of thrombosis, ie, prosthetic valve, and an INR > 4.5, that low-dose oral vitamin K administration should be considered. Patients with high INR and a low risk of bleeding, such as many preprocedure patients, should merely have warfarin withheld. ■

Dr. Crawford is Professor of Medicine, Mayo Medical School, Consultant in Cardiovascular Diseases and Director of Research, Mayo Clinic, Scottsdale, Ariz.

Reference

1. Hylek EM, et al. *Arch Intern Med.* 2000;160:1612-1617.

Pharmacology Update

Clindamycin 1% and Benzoyl Peroxide 5% Topical Gel (DUAC)

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

THE FDA HAS APPROVED A NEW TOPICAL GEL FOR the treatment of acne. The DUAC gel combines 2 time-tested ingredients, clindamycin and benzoyl peroxide. The once-daily product will be marketed by

Stiefel Laboratories.

Indications

Clindamycin/benzoyl peroxide gel is indicated for the topical treatment of inflammatory acne vulgaris.[1]

Dosage

The gel should be applied once daily in the evening. The skin should be gently washed, rinsed with warm water, and patted dry before application.[1]

The product should be stored in a cool place; refrigeration is preferred.

DUAC will be supplied as a 45 g tube.

Potential Advantages

Clindamycin/benzoyl peroxide gel formations are generally more effective in reducing inflammatory lesions (papules and pustules) than clindamycin or benzoyl peroxide alone in patients with moderate to moderately severe facial acne vulgaris.[1-4]

Clindamycin/benzoyl peroxide gel has been shown to produce 91% inhibition (> 1 $\log^{10}/cm^2$ from baseline) of *Propionibacterium acnes* 24 hours after application compared to 31% for clindamycin solution 1%.[5] This organism is one of the primary factors in the pathogenesis of acne vulgaris. The side effects of clindamycin/benzoyl peroxide gel are similar to that of either ingredient alone.[2]

Potential Disadvantages

Clindamycin/benzoyl peroxide gel does not appear to be any more effective than benzoyl peroxide alone in treating noninflammatory (comedones) acne lesions.[1,2] Benzoyl peroxide can reduce the stability of clindamycin, therefore, the formulation should be stored in a cool place and refrigeration is preferred.[3] Benzoyl peroxide may promote tumor growth and the effect of the combination is not known. The manufacturer is required by the FDA to conduct postmarketing studies on UV-induced skin cancer and dermal carcinogenicity.[6] Clindamycin/benzoyl peroxide carries the same warning for pseudomembrane colitis risk due to potential systemic absorption of clindamycin.

Comments

Combining benzoyl peroxide and clindamycin has been shown to improve effectiveness of treating acne, and may also decrease the emergence of resistant strains of *P acnes*.[7] In general, the combination was more effective than the individual ingredients in reducing inflammatory lesions.

DUAC has been shown to be more effective than benzoyl peroxide, clindamyin, or vehicle in 3 of 5 studies involving a total of 1319 subjects.[1] Effectiveness was based on mean percent reduction of inflammatory lesion counts and investigator's global assessment in 11-week studies. Mean reduction for DUAC ranged from 42-65%, benzoyl peroxide from 36-57%, clindamycin from 30-49%, and vehicle from 0-29%. Global assessment values were not reported by the manufacturer. Data from other clindamycin/benzoyl gel studies suggest a similar trend in relative effectiveness as assessed by physician and patients. In one study (n = 480), a higher percent of patients rated themselves as having moderate or excellent improvement at 10 weeks for the combination, 54% compared to 35% for benzoyl peroxide, 37% for clindamycin, and 18% for vehicle.[4] The corresponding physician assessment was 64%, 37%, 26%, and 9%, respectively.

In another 10-week study (n = 287), physicians and patients rated the combination better than clindamycin and vehicle but similar to benzoyl peroxide.[2] The wholesale cost for DUAC topical gel is $79.00 for a 45-g tube.

Clinical Implications

Benzoyl peroxide/clindamycin gel provides another topical option for the treatment of acne vulgaris. The individual ingredients have been used successfully for decades. The combination is more effective than clindamycin alone and modestly better than benzoyl peroxide alone but may reduce the emergence of resistant strains of *P acnes*. ■

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CME Question

21. In the study of radical prostatectomy vs. watchful waiting for early prostate cancer:

a. men who had prostatectomies lived longer.
b. men who had prostatectomies had a greater chance of local recurrence.
c. men in the watchful waiting group were more likely to die of prostate cancer.
d. men in the watchful waiting group were less likely to develop distant metastases.

By Louis Kuritzky, MD

Homocysteine-Lowering Therapy with Folic Acid, Vitamin B_{12}, and Vitamin B_6 and Clinical Outcome after Percutaneous Coronary Intervention

HOMOCYSTEINE (HCST) HAS RECENTLY obtained substantial attention as a modifiable cardiovascular risk factor. Elevated levels of HCST have been associated with adverse cardiovascular outcome in a linear fashion, similar to cholesterol. It is suggested that elevations of HCST alter patterns of vascular smooth muscle cell growth and migration, endothelial function, lipoproteins, and coagulability. Hence, modification of HCST might favorably affect outcomes in high-risk CAD patients, such as those undergoing coronary angioplasty.

Schnyder and associates studied patients who underwent PCTA on at least 1 vessel for underlying stenosis > 50%, evaluating the effect of treatments known to reduce HCST: a combination of folic acid, vitamin B_{12}, and vitamin B_6. After PCTA, subjects were randomly assigned to the supplements or placebo, administered for 6 months. The primary study outcome was a composite of death, MI, and need for repeat revascularization for as long as 6 months after administration of the supplements.

At baseline, no patients had severe elevations of HCST, but mild-moderate increases were found in 29% of subjects. HCST-lowering therapy was associated with a risk reduction of 32% in the composite end point, mostly due to a 38% relative reduction in need for revascularization. This inexpensive multiple vitamin intervention holds promise in reducing cardiovascular risk among persons undergoing PCTA. ■

Schnyder G, et al. JAMA. 2002;288: 973-979.

Effect of Cataract Surgery on Motor Vehicle Accidents in Older Adults

OLDER ADULTS SUFFER VISUAL impairment due to cataract (CAT) more often than any other single cause. More than half of adults older than age 65 have cataract, which is slightly more frequent in African Americans. Retrospective reviews have shown that among older drivers, presence of CAT was associated with an increased frequency of a recent motor vehicle accident (MVA) when compared with persons free of CAT.

The per capita MVA rate in older licensed drivers (40/1000) is substantially less than in persons younger than 25 (140/1000), but this is largely a result of the many fewer miles driven by older persons than younger. Hence, the per-mile driven rate of MVA among older drivers is actually comparable to that of the highest risk younger drivers. Whether correction of CAT results in improvements of MVA risk was the subject of this report.

Owsley et al prospectively compared patients (n = 277) with CAT who underwent intraocular lens implantation after CAT excision to untreated CAT patients, followed 4-6 years. During follow-up, the MVA rate/million miles traveled in the surgically treated group was less than half that seen in the untreated group. Though the trial was not randomized, the data are highly supportive of the potential favorable effect of CAT surgery on highway safety. ■

Owsley C, et al. JAMA. 2002;288: 841-849.

Inflammatory Biomarkers, Hormone Replacement Therapy, and Incident Coronary Heart Disease

THE ROLE OF HORMONE REPLACEment therapy (HRT) in menopausal women is an area of current controversy, primarily due to the discordance between observational data that suggested cardiovascular benefits associated with HRT, and recently completed interventional trials that have shown increases in venous and arterial thrombotic end points early after HRT initiation. Among the possible mechanisms for deleterious effects of HRT upon cardiovascular risk, changes in C-reactive protein (CRP) and interleukin (IL-6) might play a role.

Pradhan and associates studied subjects from the Women's Health Initiative (n = 75,343) who had suffered an incident coronary heart disease event (n = 304). In their analysis, they compared CRP and IL-6 levels in persons with incident CHD vs. controls.

Although both baseline CRP and IL-6 were found to predict (independently) CHD events, only CRP levels were increased by the use of HRT. Comparatively, baseline CRP and IL-6 levels demonstrated greater effect on subsequent CHD events than did use or nonuse of HRT. Pradhan et al observe that it is the CRP level, rather than use of HRT, which is the primary determinant of subsequent risk for CHD events. ■

Pradhan AD, et al. JAMA. 2002;288: 980-987.

Mobitz II in a Patient on Digoxin

By Ken Grauer, MD

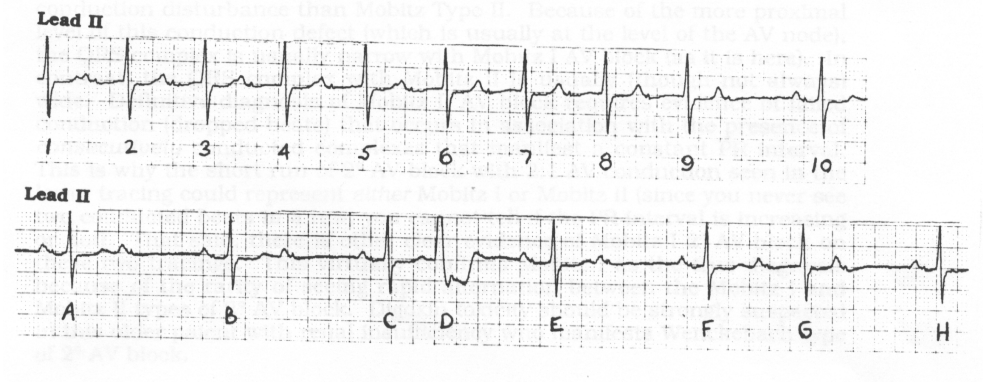

Figure. Nonsequential lead II rhythm strips obtained from a 71-year-old man with heart failure.

Clinical Scenario: The nonsequential rhythm strips shown in the Figure were obtained from a 71-year-old man with a history of congestive cardiomyopathy and renal insufficiency. The patient was admitted for an exacerbation of heart failure. Digoxin was among the many medications he was taking. Assessment of the bottom rhythm strip was 2:1 AV block, Mobitz Type II. Do you agree?

Interpretation: Use of calipers will greatly facilitate interpretation of the 2 tracings shown in the Figure. Except for the very first T wave in the top tracing, virtual superposition of P waves on top of T waves masks atrial activity until the last beat (beat #10) in the top tracing. Inspection of the T wave of this beat #10 reveals the true shape of what T waves would look like without a superimposed P wave. Knowing this allows us to "walk out" with calipers—an essentially regular atrial rhythm (at a rate of 75-80/minute) throughout both rhythm strips.

With the exception of premature beat D in the lower tracing (which is a premature ventricular contraction [PVC]), the QRS complex is narrow in both rhythm strips. Upright P waves are present in these lead II rhythm strips and appear to be conducting, albeit with a PR interval that is not always constant. Second degree (2°) AV block is present because a number of P waves on these tracings do not conduct. Concern about the presence of 2° AV block, Mobitz Type II is raised because of the short run of 2:1 AV block with a constant PR interval (beats A through F in the bottom tracing). However, Mobitz II 2° AV block is *not* present. Instead, one can definitively diagnose Mobitz I (2° AV block of the Wenckebach type). Distinction between these 2 forms of AV block is important clinically because of the generally much more serious prognostic implications of Mobitz II, which in the acute setting is usually indication for immediate pacemaker placement.

Statistically, Mobitz Type I 2° AV block is a much more common conduction disturbance than Mobitz Type II. Because of the more proximal level of this conduction defect (which is usually at the level of the AV node), the QRS complex is usually narrow with Mobitz I AV block (as it is here). In contrast, the QRS complex with Mobitz II is usually (though not always) wide. Definitive diagnosis of Mobitz II AV block requires evidence of failed conduction (dropped beats) that occurs in association with the presence of *consecutively* conducted complexes that manifest a constant PR interval. This is why the short run of 2° AV block with 2:1 AV conduction seen in the lower tracing could represent *either* Mobitz I or Mobitz II (since you never see 2 conducted beats in a row, you cannot tell if the PR interval is increasing or not). That said, there is other clear evidence of Mobitz I 2° AV block on these 2 tracings. This virtually confirms Mobitz I as the true diagnosis because of the rarity of seeing rapid alternation between the Mobitz I and Mobitz II types of 2° AV block. Digoxin toxicity should be strongly suspected in this older patient with renal insufficiency who manifests Wenckebach type of 2° AV block. ■

In Future Issues: **Effect of Lipid-Lowering Therapy on Coronary Artery Calcification**

PHARMACOLOGY WATCH

Forgot Your Ginkgo? Forget About It, Study Shows

The $15 billion dietary supplement industry took a bruising in the last month with reports that some of the most popular over-the-counter treatments are little more than expensive placebo. Ginkgo, the commonly used memory enhancing agent, was evaluated in 230 men and women older than the age of 60 who had normal memory and were in good health. Patients were randomly assigned to receive ginkgo 40 mg 3 times a day or matching placebo for 6 weeks. Neuropsychological tests were administered at the end of the study, which revealed no significant differences between treatment groups on any of the outcome measures including verbal and nonverbal learning and memory, attention and concentration, naming and expressive language, self-reported memory, and companion scoring. The study concluded that ginkgo did not facilitate learning memory tension or concentration in adults older than the age of 60 (*JAMA*. 2002;288:835-840). In a separate study from The Netherlands, 652 adults older than age 60 were given a multivitamin/mineral supplement, 200 mg of vitamin E, both, or placebo in a study to evaluate whether the supplements would reduce the incidence and severity of acute respiratory tract infections. Patients were followed for nearly 1.5 years. No difference was found among any of the groups with regard to incidence or severity of acute respiratory infections, except for the finding of worsening severity of disease in the vitamin E group (19 days illness with vitamin E vs 14 days illness with placebo; $P = 0.2$). (*JAMA*. 2002;288:715-721.)

On the other hand, a homocysteine-lowering therapy with a combination of B vitamins effectively improves clinical outcomes after percutaneous coronary interventions. Folic acid, vitamin B_{12}, and vitamin B_6 were tested in a randomized, double-blind, placebo-controlled trial involving more than 550 patients in Switzerland who had undergone successful angioplasty. The participants received a combination of folic acid 1 mg/d, vitamin B_{12} 400 µ/d, and vitamin B_6 10 mg/d, or placebo. The main outcome measure was the composite outcome of major adverse events including death, nonfatal myocardial infarction, and the need for repeat revascularization evaluated at 6 months and 1 year. The composite end point was significantly lower at 1 year in the vitamin-treated patients (15.4%) compared to the placebo group (22.8%) (RR, 0.68; 95% CI, 0.48-0.96; $P = .03$) primarily due to reduce rate of revascularization. (*JAMA*. 2002;288:973-979).

Celebrex OK for Asthma Patients

Celecoxib (Celebrex®) may be safe to use in patients with a history of aspirin-induced asthma. Patients with known aspirin sensitivity, or aspirin-exacerbated respiratory disease (AERD), are generally unable to take aspirin or any NSAID. In a study from San Diego, 60 patients with AERD were challenged with celecoxib, a COX-2 inhibitor, or placebo over 48

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hours. During the study period, none of the 60 patients experienced any symptoms or changes in nasal examinations or declines in FEV_1. The following day, all 60 patients were exposed to aspirin and all showed sensitivity. The study concluded that inhibition of COX-1 is the critical initiating event in respiratory reactions in patients with AERD (*Arthritis Rheum*. 2002;46:2201-2206).

Losartan Not Superior to Captopril

The angiotensin II receptor blocker losartan is not superior to the ace inhibitor captopril after complicated acute myocardial infarction. The large OPTIMAAL trial (Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan) looked at 5477 patients in 7 European countries with confirmed acute myocardial infarction and heart failure. Patients were randomly assigned and titrated to target dose of losartan 50 mg once daily or captopril 50 mg 3 times daily. The primary end point was all-cause mortality. During a mean follow-up of 2.7 years, there were 499 (18%) deaths in losartan group and 447 (16%) in the captopril group (RR 1.13; 95% CI, 0.99-1.28; $P = 0.07$). Because of this nonsignificant trend in total mortality in favor of captopril, the study suggests that losartan cannot be generally recommended in this population. It is noted however that losartan was better tolerated than captopril, and associated with significantly fewer discontinuations (*Lancet*. 2002;360:752-760).

Alfa-Interferon Could Help Fight West Nile

The number of West Nile virus cases is mounting in the United States, Canada, and Mexico where 37 deaths have been attributed to the virus, now the first case has been reported in California, and other cases are the result of organ donation from infected donor. Researchers are hoping that alfa-interferon may be of help. The drug has been effective against St. Louis encephalitis, a similar virus, and is the drug of choice for treatment of hepatitis C. Researchers are enrolling patients in the New York area where the virus first appeared 3 years ago. Although infection with the mosquito-borne virus rarely causes serious illness (< 1%), the elderly and chronically ill are particularly prone to encephalitis. alfa-interferon will be given for 2 weeks and should be started within the first few days of illness, prior to the onset of encephalitis. Research is also progressing on 3 West Nile virus vaccines, which should be in human trials by 2003.

Sertraline Effective Against Depression

Depression is common in patients with coronary artery disease and represents a significant independent risk factor for both first myocardial infarction and cardiovascular mortality. A new study shows that the selective serotonin reuptake inhibitor sertraline is safe and effective for treating major depression in patients with recent myocardial infarction or unstable angina. A total of 369 patients on 3 continents with major depressive disorder were enrolled and randomized to sertraline 50-200 mg/d or placebo in a double-blind fashion for 24 weeks. The main outcome was change in left ventricular ejection fraction (LVEF) while other outcomes included surrogate cardiac measures and cardiovascular adverse events. Sertraline had no significant effect on LVEF, and also did not increase ventricular premature complex runs, QTc intervals, or other cardiac measures. The incidence of severe cardiovascular adverse events was 14.5% with sertraline and 22.4% with placebo. Depression scores were better in the sertraline group. The authors conclude that sertraline is safe and effective for trading depression in patients with recent MI or unstable angina (*JAMA*. 2002;288:701-709).

FDA Actions

Procter & Gamble has announced that it expects an over-the-counter form of omeprazole (Prilosec) to be available by early 2003. The company has received an approval letter from the FDA but needs to clarify language on the package label so that consumers will clearly understand how to use the drug. Procter & Gamble is planning a study to make sure consumers understand the drug labeling, a process which will take several months. The FDA has approved fluoxetine (Prozac) for the treatment of panic disorder. The indication was previously only granted to paroxetine (Paxil) and sertraline (Zoloft), and it has been heavily promoted by the manufacturers of these drugs. Fluoxetine is also recently approved for long-term treatment of bulimia. The drug has been been available as a generic for more than a year, and as such represents a lower cost alternative for patients with these conditions. ■