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INSIDE

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ABSTRACT & COMMENTARY

Synopsis: *Only about 12% of patients with new onset atrial fibrillation who did not have apparent contraindications to warfarin treatment filled prescriptions for it.*

Source: Johnson JA, et al. *Arch Intern Med*. 2003;163:1705-1710.

This was a retrospective review of Ohio Medicaid billing data conducted in 1998-2000. There were 11,699 cases of new-onset nonvalvular atrial fibrillation (AF) during that time period. Johnson and colleagues collected and controlled for risk factors for stroke and hemorrhage, as well as many other medical conditions and some socioedemographic factors thought to be relevant. Analysis of data from all providers of medical services to Ohio Medicaid enrollees revealed that only 9.7% of all patients with new-onset AF and only 11.9% of those without apparent contraindications filled prescriptions for warfarin in the 7 days preceding or 30 days following the documented date of diagnosis of AF. Hypertension and congestive heart failure predicted increased likelihood of using warfarin. Age younger than 55 or older than 85 years predicted nontreatment, as did prior intracranial hemorrhage, prior gastrointestinal hemorrhage, predisposition to falls, alcohol, or other drug use, renal impairment, and conditions perceived as barriers to compliance.

COMMENT BY BARBARA A. PHILLIPS, MD, MSPH

I confess that when I first read this title and skimmed this abstract, I thought this paper was about patient acceptance and compliance with medical therapy. It's not. It's about physician compliance with guidelines. Bear with me; it's not as bad as you may be thinking.

The thrust of the article appears to be that there must be something different about the way physicians treat women, Ohioans, or Medicaid patients. In this study, only about 12% of eligible patients with new-onset atrial fibrillation were prescribed warfarin. This is in stark contrast to studies showing that eligible patients with new AF in the Kaiser Permanente system in Northern California[1] and in the Harvard Community Health

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Plan[2] received it 55% and 79% of the time, respectively. The difference is unlikely to be due to the fact that the patients were women; the Medicaid population reported here is about 69% women overall and about 78% women for the group older than 75. The difference is also unlikely to be due to the fact that the study was done in Ohio. As a Kentuckian, I have lived next to Ohio most of my life. They have their quirks, of course, but Buckeye people are pretty much like the rest of us.

So it must be because they are Medicaid recipients that so few patients who might have been expected to benefit from warfarin treatment received it. Johnson et al are careful to point out that they tried to identify known contraindications to anticoagulation such as alcoholism, prior hemorrhage, and falling risk. Patients with these risks were not considered "eligible" and were not part of the 88% of patients with new AF who did not get treated.

One of the most robust predictors of nontreatment with warfarin in this study was what Johnson et al called "Perceived barriers to compliance," defined as mental illness, homelessness, inadequate housing, lack of a caregiver, or known noncompliance. About 30% of patients in this population had one or more of these barriers, and their presence strongly predicted nontreatment with warfarin.

Those of us who have cared for patients on warfarin know that it takes partnership and commitment on both sides. Appointments must be kept, blood levels must be monitored, medication must be taken regularly, and diet, alcohol, and other medication intake needs to be consistent for the titration to be accurate. Anticoagulant overdose is messy, dangerous business, and no physician wants to be part of it. It is also possible—even likely—that the Ohio doctors wrote far more prescriptions for warfarin than patients filled. Johnson et al make little note of the possibility that some patients in this study may simply have failed to fill a prescription, but that is extremely likely. Some data suggest that only about two-thirds of prescriptions that physicians write get filled in a timely manner. So I have some empathy and understanding for those Buckeye MDs who erred on the side of doing no harm in the case of patients who seemed unlikely to be able to be partners in their own care and who probably wrote some prescriptions that never got filled.

On the other hand, this study and others have consistently found that advancing age is strongly associated with reduced likelihood of receiving anticoagulation. This is despite the fact that the risk of AF rises impressively with aging, as does the risk of its most common adverse consequence, strokes. Although the risk of hemorrhage with warfarin is real, substantial evidence indicates that its benefits far outweigh its risks, especially in people older than 75.[4,5] Perhaps the real message from this paper is to reconsider the use of warfarin in those who might appear to be "too old." ■

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A Visit to a Dangerous PAD

ABSTRACT & COMMENTARY

Synopsis: *Peripheral arterial disease is common. Screening with measurement of the ankle-brachial index will improve detection.*

Source: Collins TC, et al. *Arch Intern Med.* 2003;163: 1469-1474.

Focusing on the populations of 3 primary care clinics and a Veterans Affairs Medical Center, Collins and colleagues sought to determine the prevalence of peripheral arterial disease (PAD). They enrolled patients who were scheduled for an appointment with their primary care physician (PCP). Inclusion criteria included age older than 50 years; after enrolling 17 patients between the ages of 50 and 54 years and discovering that none had PAD, they raised the age criterion to 55. Other criteria were ethnic and racial self-identification and having a PCP. They excluded patients who could not complete a consent form, who were demented, who had chronic obstructive pulmonary disease requiring oxygen, who were recently diagnosed with a non-skin cancer malignancy, who had leg ulcers or gangrene, who could not be contacted by telephone or who lived outside of Texas. After approaching 457 patients, 403 agreed to participate. Those who refused were more likely to be African American and younger than those who agreed.

All patients completed 4 questionnaires: the San Diego Claudication Questionnaire (SDCQ), which detects intermittent claudication; the Walking Impairment Questionnaire (WIQ), which assesses patient-reported walking ability; the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36), which measures health-related quality of life; and the Lifestyle and Clinical Survey (LCS), a complete health history questionnaire. Collins et al defined PAD as an ankle-brachial index (ABI) < 0.9. The ABI is the ratio of systolic blood pressure (SBP) in the ankle to SBP in the arm.

The patients were 34% African American, 48% male, average age 64 years, and relatively impoverished (only 5% had an annual income > $50,000). There were 67 patients (16.6%) with PAD. Patients with PAD were more likely to smoke (29.9% vs 16.7%), to be afflicted with diabetes mellitus (55.2% vs 34.5%), to be hypertensive (82.1% vs 66.4%), and to have a higher average systolic blood pressure (156.5 mm Hg vs 145.4 mm Hg). They were less likely to exercise daily (13.4% vs 25.6%), but there was no difference in the proportion that walked daily (31.3% vs 32.1%). However, patients with PAD were more likely to report the presence of intermittent claudication and atypical leg symptoms as measured by the SDCQ (62.7% vs 50.6%). A small number (1.5%) of patients without PAD reported intermittent claudication. PAD patients scored lower on the WIQ and the SF-36. There was no statistical difference between the patients with regard to use of antiplatelet drugs (38.8% vs 31.9%). Gender, age, and income did not influence results.

Only 17.9% of patients with PAD were aware of their diagnosis. A sizable proportion of them (37.3%) had no leg symptoms. When the patients were grouped by ethnicity, 13.2% of whites, 22.8% of African Americans, and 13.7% of Hispanics had PAD. This did not meet the level of statistical significance ($P = 0.6$). However, when the white and Hispanic populations were combined and compared with the African-American population, it was significant ($P = 0.2$).

COMMENT BY ALLAN J. WILKE, MD

Most of the results of this study are old news,[1,2] but they reinforce the lessons we learned in medical school: PAD is pervasive, but often undiagnosed. It is more common in African Americans. It is often asymptomatic. There is a lot of overlap between patients with PAD and without when considering common chronic illnesses such as diabetes, hypertension, and hyperlipidemia.

Why is the diagnosis of PAD important, and is it important enough to warrant widespread screening? PAD is a marker for other vascular disease, especially coronary and cerebral artery disease. Patients with PAD have decreased longevity, dying more frequently from heart attacks and stroke.[3] The National Cholesterol Education Program's Adult Treatment Panel III (ATP III) identifies "other clinical atherosclerotic disease" as a risk factor equivalent to established coronary heart disease, diabetes, cigarette use, and hypertension. The diagnosis of PAD could tip the scales in favor of more aggressive treatment of hyperlipidemia. Measuring ABI fulfills most, if not all, of the frame criteria for a good screening test.[4]

This study raises other unanswered questions. Why were so few patients taking antiplatelet medications? Only about one-third of these patients reported antiplatelet therapy, despite having conditions (diabetes, heart disease, stroke, etc) that warranted it. Why were patients with PAD less likely to exercise? Simplistically, one could argue that the condition itself hindered exercise (especially walking), but there was no difference in

the percentage of patients who walked daily, notwithstanding a difference in the percentage who had leg symptoms. Why did some patients *without* PAD (ie, ABI > 0.9) have symptoms of intermittent claudication? Might they have microvascular disease with relatively normal large vessels?

This study can be faulted in its design. Some information was self-reported and not verified by chart review. By selecting patients from appointment lists, Collins et al did not examine that part of the population who wasn't motivated to visit their PCP. Arguably, they were healthier and their inclusion would have lowered the incidence of PAD. Since patients with higher incomes weren't studied, do the results apply to them? The patients who declined to participate were younger African Americans. Their inclusion presumably would have lowered the incidence of PAD in that group. I thought that Collins et al went overboard in their statistical analysis. For instance, they reported that patients with PAD had average ABIs less than patients without (0.72 vs 1.13). As my kids might say, "Well, duh!" If ABI is the variable that defines PAD, it stands to reason that people with PAD would have a lower ABI. ■

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The Skinny On Low-Fat and Low-Carbohydrate Diets

ABSTRACTS & COMMENTARY

Synopsis: *The low-carbohydrate diet produced a greater weight loss than did the conventional diet for the first 6 months, but the differences were not significant at 1 year.*

Sources: Samaha F, et al. *N Engl J Med*. 2003;348:2074-2081; Foster GD, et al. *N Engl J Med*. 2003;348:2082-2089.

THE MARKED INCREASE IN THE NUMBER OF PEOPLE who are obese and the alarming increase in the incidence of type 2 diabetes have resulted in an amazing number of new books on diet. A great deal of controversy has arisen over the benefits of a low-carbohydrate, high-protein diet. The Atkins diet in particular has received much attention despite limited long-term controlled studies relating to its benefit.

Two recent studies examining the benefits of a high-protein, high-fat, low-carbohydrate diet vs a high-protein, low-fat, high-carbohydrate diet, appeared in the same issue of the *New England Journal of Medicine*.

Bonow and Eckel succinctly summarized these studies in their accompanying editorial.[1] "Each group of investigators randomly assigned obese subjects to either a low-carbohydrate diet (with high protein and fat content) or a more standard, reduced-fat diet (with fat constituting less than 30 % of the total caloric intake but more than in some extremely low-fat diets). Each study was designed to follow subjects for more than 90 days. Samahah and colleagues followed severely obese subjects (mean body-mass index, 43) with a high prevalence of diabetes (39%) or of the metabolic syndrome without diabetes (43%), whereas Foster and associates studied subjects with less severe obesity (mean body-mass index, 34), none whom had diabetes. Samaha et al used fixed-carbohydrate restriction (30 g or less per day), and Foster et al used the Atkins diet.

Despite these differences in study population and dietary approaches, both studies demonstrated significantly greater weight reduction with the low-carbohydrate diet than with the reduced-fat diet during the first 6 months (average reduction, 6 to 7 kg vs 2 to 3 kg); however, the magnitude of the weight loss difference (4 kg in both studies) was relatively small and adherence in the 2 diet groups was low. In addition, in the study by Foster et al, there was no longer a significant difference in the weight loss between the subjects in the low-carbohydrate group and those in the reduced-fat group at 12 months.

■ COMMENT BY RALPH R. HALL, MD, FACP

The dropout rate in both studies was significant—53 of 132 patients in the Samaha et al group and 24 of 63 patients in the Foster et al group. The patients who dropped out were not followed in order to determine their ultimate weight loss or gain. Some studies have shown that a number of subjects who drop from a study continue to follow the diet and lose weight.

The subjects on the low-carbohydrate diet, in both groups, had a reduction in risk factors for coronary heart disease, ie, drops in triglycerides and insulin resistance, and the Foster et al group had a rise in the high density cholesterol level. Subjects on the low-fat diet had a drop in their LDL cholesterol.

Another important diet study which Eckel, one of the authors of the editorial, was involved, was just reported at the American Diabetes Association meeting.[2] Cornier

and Eckel examined insulin-sensitive (IS) and insulin-resistant (IR) female obese subjects' response to both a high-carbohydrate, low-fat (HC/LF) and a low-carbohydrate, high-fat diet (LC/HF), (400 kg/d deficit). The study lasted 16 weeks. IR women in the HC/LF diet lost a significantly greater amount of weight than those randomized to the LC/HF diet (11.47 kg vs 6.12 kg; $P < 0.01$). IR women randomized to the LC/HF lost significantly more weight than those randomized to the HC/LF diet (11.46 kg vs 6.12 kg; $P = 0.05$).

Triglycerides decreased significantly in all groups except the IR women on the HC/LF diet. In summary, obese IS women lose more weight on a diet that is low in fat content, while IR women lose more weight on a diet that is low in carbohydrate and high in fat. Insulin sensitivity was determined by a fasting, blood insulin.

The marked differences in weight loss when women, and likely men, are given a diet matched to their insulin sensitivity has great potential. The remaining problem is how long can we keep patients on a high-fat diet without increasing the risk of vascular disease? The ill effects of long-term, high-fat diet have been repeatedly demonstrated. The paucity of fruits and vegetables in the high-fat diet removes nutrients that have long been demonstrated to have significant health benefits. ■

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SAH Risk May Be Reduced By Healthy Lifestyle

ABSTRACT & COMMENTARY

Synopsis: *The association of caffeine and nicotine in pharmaceutical products and aneurysmal SAH warrants further study.*

Source: Broderick JP, et al. Stroke. 2003;34:1375-1381.

Subarachnoid hemorrhage (SAH) due to a ruptured cerebral aneurysm is a disorder that is without apparent cause and is generally impossible to predict. This study suggests that there are a number of SAH risk factors related to lifestyle that are, in fact, modifiable.

The Hemorrhagic Stroke Project (HSP) compared 312 cases of aneurysmal SAH with 618 controls, without SAH, matched for age, sex, and race. Among cases, 66% were cigarette smokers compared with 30% of controls (generating an adjusted odds ratio of 3.73). Cocaine use was identified among 3% of cases and no controls (OR = 25). Other independent risk factors included hypertension, low body mass index, family history, low educational achievement, and caffeine or nicotine in pharmaceutical products.

COMMENT BY ALAN Z. SEGAL, MD

These data from the HSP are important in that they emphasize that a seemingly unavoidable event, a spontaneous aneurysm rupture, may be influenced by modifiable lifestyle factors. While certain risk factors, such as family history or educational level, are difficult or impossible to change, other factors are associated with harmful behaviors and habits. Despite links with both atherosclerotic disease and cancer, young people continue to smoke cigarettes. These data, among individuals aged 18-49, further emphasize additional unrecognized deleterious effects of tobacco use. Similarly, for hypertension, the importance of treating blood pressure to prevent heart disease and stroke is well appreciated. This study further suggests that untreated hypertension in young people may also put them at increased risk for SAH. ■

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Reduced Cardiac Risk for Breast Cancer Survivors

ABSTRACT & COMMENTARY

Synopsis: *Women who survive breast cancer may be at a lower risk of developing coronary artery disease compared with women without a history of breast cancer.*

Source: Lamont EB, et al. Cancer. 2003;98:2-10.

Estrogen is strongly associated with both health and disease in women. Comparatively high estrogen exposure is protective against some diseases (eg, coronary heart disease and osteoporosis) but contributory to others (eg, breast and endometrial carcinoma). Recently, Lamont and associates from the University of Chicago have demonstrated that breast cancer survivors have reduced rates of osteoporosis. In the current report, an examination of coronary artery disease as

manifest by acute myocardial infarction was undertaken in postmenopausal women who have survived breast cancer. The report details an investigation of the National Cancer Institutes Surveillance, Epidemiology and End Results (SEER) Medicare Program. Elderly women survivors of stage 0, I, or II breast carcinoma (n = 5980) diagnosed between the ages of 55 and 64 were compared with age-matched women without a history of cancer (n = 23165) derived using the Medicare 5% Noncancer File. In addition to age, Lamont et al controlled the analyses for race, socioeconomic status, geographic location, cohort entry year, and medical comorbidity.

The hazard of hospitalization for acute myocardial infarction (AMI) for breast cancer survivors relative to the comparison group was 0.66 (95% CI, 0.49-0.88). The apparent cardioprotective effect was stronger in breast cancer survivors with documented cardiac risk factors. Lamont et al conclude that survivors of early stage, postmenopausal breast cancer are at significantly lower risk of hospitalization for acute myocardial infarction than women who do not have a history of breast cancer. Lamont et al call for further investigation into the mechanisms of this cardioprotective effect.

COMMENT BY WILLIAM B. ERSHLER, MD

This is a very interesting observation that may have public health implications. Lamont et al have identified a subset of women who have a 34% reduction in the disease that accounts by far for the largest numbers of deaths in elderly women in the United States. If additional work identifies the mechanism behind this reduction in cardiac risk in breast cancer survivors, the finding may be applicable to the cardiovascular health of the general population.

Three possible explanations come to mind. First, breast cancer survivors by virtue of the rigors of intensive surgical and medical management may be more health conscious and modify those controllable factors relevant to the development of coronary artery disease and acute myocardial infarction (eg, smoking, diet, etc). However, Lamont et al suggest that this explanation is less likely because their data demonstrated that hospitalization rates for other illnesses (eg, pneumonia) were not different in the 2 cohorts. Secondly, estrogens may be etiologic in the development of breast cancer yet protective in atherosclerosis, particularly coronary artery disease. Or, thirdly, a common therapy for breast carcinoma (eg, tamoxifen) may be associated with cardiac protection. Neither the SEER records nor the claims data would allow an accurate estimation of lifetime estrogen exposure or tamoxifen use, and therefore, although quite possibly the case, this association could not be satisfactorily addressed using the resources available. Additional research focused on mechanisms to explain this cardioprotective phenomenon would require data enriched with clinical variables such as tamoxifen use and the influence thereon of certain cardiac risk factors.

Despite the constraints and inherent problems of exploring claims data, the findings that elderly women with a history of postmenopausal breast cancer have a 34% lower hazard of hospitalization for acute myocardial infarction is of great interest. It is quite possible that the cardiac protection relates to the use of SERM's and, therefore, the data may have public health implications for women without a history of breast cancer. Further evaluation to define the mechanisms of this cardioprotective effect is warranted. ■

Dr. Ershler is an Oncologist at the INOVA Fairfax Hospital Cancer Center, Fairfax, VA; Director, Institute for Advanced Studies in Aging, Washington, DC.

Pharmacology Update

Atazanavir Sulfate Capsules (Reyataz)

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

THE FDA HAS APPROVED THE FIRST ONCE-DAILY PROtease inhibitor (PI) for the treatment of HIV-1 infections. Atazanavir (Bristol-Myers Squibb) is the newest PI to enter this relatively crowded class. It is marketed under the trade name Reyataz.

Indication

Atazanavir is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infections.[1]

Dosing

The recommended dose is 400 mg (2 × 200 mg) capsules daily taken with food. If didanosine (buffered formulations) is included in the regimen, atazanavir should be taken with food 2 hours before or 1 hour after didanosine. If efavirenz is included in the regimen, atazanavir 300 mg, ritonavir 100 mg, and efavirenz 600 mg should taken together with food as a single dose. Food improves and reduces variability in the bioavailability of atazanavir.[1]

Atazanavir is available as 100-mg, 150-mg, and 200-mg capsules.

Potential Advantages

Atazanavir is dosed once daily with low pill burden and may improve compliance.[2] The drug does not appear to be associated with clinically significant increases in total cholesterol, LDL-cholesterol, and triglycerides.[1,3] In two 48-week studies the change in total cholesterol from baseline ranged from +2% to +9%, and triglycerides ranged from -9% to +1.5% for atazanavir.[1,3] In contrast, changes in total cholesterol and triglycerides were +27.8% and +42.2% for nelfinavir and +21% and +23% for efavirenz. Hyperlipidemia is a common adverse effect of PIs with 50% or greater affected with hypertriglyceridemia being more common.[4] However, it is not certain if the favorable lipid effects of atazanavir will result in a lower incidence of lipodystropy.[6]

Potential Disadvantages

Side effects include nausea, vomiting, diarrhea, headache, abdominal pain, somnolence, insomnia, and fever. Thirty-five to 47% of patients experience hyperbilirubinemia, and about 15-24% of patients show jaundice or scleral icterus.[1] Atazanavir has been shown to prolong PR interval in some patients. Atazanavir is an inhibitor of cytochrome P450 isoenzyme 3A, 1A2, and 2C9 and may increase plasma levels of drugs metabolized via this metabolic pathway. Atazanavir is metabolized by CYP 3A, and drugs that are inhibitors of inducers of this isoenzyme may affect its drug levels. Coadministration of atazanavir with triazolam, midazolam, ergot-containing products, and pimozide is contraindicated, and co-administration with irinotecan, bepridil, indinavir, lovastatin, simvastatin, rifampin, St. John's Wort, and antisecretory drugs is not recommended. Patients with hepatitis B, hepatitis C, or elevated liver transaminase levels may be at greater risk for further transaminase level elevation or hepatic decompensation.[1]

Comments

Atazanavir, the newest PI, offers the potential advantage of once-daily dosing and lower risk of lipid abnormalities. In antiretroviral treatment-naïve patients, atazanavir in combination with lamivudine and zidovudine has been shown to be similar in efficacy in a 48-week study to efavirenz and lamivudine and zidovudine.[1] In another similar study the combination of atazanavir and lamivudine and stavudine was similar to nelfinavir and lamivudine and stavudine.[1] In patients who have failed one or more prior PI-regimen the results were somewhat equivocal. In a 24-week study, patients who have failed only one prior PI-regimen, atazanavir 400 mg daily (plus 2 NNRTs) was less efficacious compared to lopinavir/ritonavir (plus 2 NNRTs). In another study of patients who have failed several drug therapies, however, atazanavir (300 mg daily) boosted with ritonavir (100 mg) appears to be comparable to lopinavir and ritonavir.[5] All patients were also on tenofovir and a NRTI. The results of the latter study were submitted late to the FDA and were not reviewed in time before the user fee deadline. As with other PIs, various drug interactions can be problematic. The most common laboratory abnormality is reversible hyperbilirubinemia. In vivo resistant data indicate that 15% of isolates in treatment-naïve patients were susceptible to atazanavir, and 80% of these isolates develop mutation that keeps them susceptible to other PIs. In contrast, 51% of isolates from treatment-experienced patients were resistant to atazanavir.[1,5] The wholesale cost of atazanavir is $662 per month.

Clinical Implications

Atazanavir offers another PI option. Once-daily dosing and current resistant data suggest a role in treatment-naïve patients. For treatment-experienced patients the role is not yet defined, as noninferiority has been established. Findings from the boosted atazanavir study may help clarify this issue as this regimen more closely reflects the future clinical use of atazanavir in this population.[5] ■

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CME Question

9. Which of the following statements about nonvalvular atrial fibrillation is true?

a. There actually is no increased risk of stroke associated with nonvalvular atrial fibrillation.
b. Its prevalence peaks in middle age and decreases after about the age of 55.
c. Treatment with warfarin has consistently been documented to occur in 80-90% of those with new-onset atrial fibrillation.
d. Age older than 75 is a relative contraindication for warfarin treatment, because the risks outweigh the benefits.
e. There is wide variation in the rate of warfarin treatment by patient age and insurance status.

Answer: 9 (a)

By Louis Kuritzky, MD

A Strategy to Reduce Cardiovascular Disease by More Than 80 Percent

DESPITE IMPRESSIVE RESULTS IN cardiovascular risk reduction by applying an individual treatment (eg, statin, antihypertensive), the effect of multiple risk factor reduction has been much more elusive to quantify. Wald and Law suggest that the literature supports consideration of a combination product they call the Polypill which is a multicomponent pill containing treatments which have demonstrated efficacy to reduce CV end points by means of LDL reduction, blood pressure control, attenuation of platelet aggregability, and reduction of homocysteine (although data referable to homocysteine is predominantly observational at this time). They base their suggested composition of the Polypill upon numerous large randomized, controlled trials and meta-analyses.

Their suggested Polypill would contain either atorvastatin 10 mg or simvastatin 40 mg, 3 different antihypertensives at half-standard dose (thiazide + ARB + CCB would be best tolerated, but thiazide + beta blocker + ACE would be less expensive, albeit at almost triple that adverse effect incidence profile), folic acid 800 µg and 75 mg of ASA. Wald and Law are remarkably optimistic in their anticipation of benefits for persons older than 55 without previous CV end points: They claim, "As 96% of deaths from IHD or stroke occur in people aged 55 and over, treating everyone in this group would prevent nearly all such deaths." They go on to opine that risk factor measurement prior to institution of the Polypill would be unnecessary, since risk reduction has been demonstrated regardless of initial risk level. Wald and Law acknowledge the radical nature of their suggestions, but support the rationale with highly attractive potential benefits. ■

Wald NJ, Law MR. Prog Cardiovasc Dis. 2003;46:31-38.

Pearly Penile Papules: Still No Reason for Uneasiness

IT IS NOT UNCOMMON FOR ADULT MEN to present to clinicians with lesions on their penis, which ultimately turn out to be pearly penile papules (PPP). These lesions appear around the margins of the glans and have been sometimes mistaken for condylomata from human papilloma virus (HPV). Indeed, some early reports misattributed PPP to HPV. Recent polymerase chain reaction specimens have failed to demonstrate HPV in PPP. Pathologic and histologic studies have shown that these small, punctuate lesions are angiofibromata, are covered with normal squamous epithelium, and may occur on the glans or corona of the penis. Because these are normal structures, patients who present with PPP should be reassured that no treatment is required.

In this trial, Hogewoning et al assayed PPP lesions in adult men (n = 71) and were unable to find any association between PPP and HPV. In the occasional case where HPV was detected in other, non-PPP skin lesions, the HPV varieties were those of low risk for carcinogenesis. PPP is an innocent cutaneous lesion, which does not have precancerous potential, nor does it predict involvement with HPV. Clinicians should reassure concerned patients about the benignity of the disorder. ■

Hogewoning C, et al. J Am Acad Dermatol. 2003;49:50-54.

The Epidemiology of Major Depressive Disorder

THE FIRST MAJOR NATIONAL POPULATION survey to establish the demographics of depression using DSM III criteria occurred 1990-1992 and reported a lifetime prevalence of 14.9%, with 12 month prevalence of 8.6%. Since that report, an evolution of diagnostic criteria (ie, DSM IV) coupled with an enhanced public and professional awareness of the seriousness, prevalence, and treatability of depression, have occurred. These changes were pertinent for a new national survey to update prior information. The National Comorbidity Survey (NCS) is data collected from face-to-face interviews with a representative cross-section of the adult American public (n = 9090) in 2001-2002.

According to NCS data, the lifetime prevalence for major depressive disorder was 16.2%, which equates to 32-35 million Americans affected during their lifetime. Disturbingly, the number of days "out of role" because of depression was more than twice that seen for most other chronic conditions. Of all the persons who had suffered depression within the last 12 months, slightly more than half had received treatment for it. Depression remains a prevalent and costly condition in America. ■

Kessler RC, et al JAMA. 2003;289: 3095-3105.

In Future Issues: **Life Can Be Less Risky!**