which have proven cardiovascular and mortality benefits for patients with hypertension. While the mounting evidence about the potential harm of CCBs has frequently been attributed only to short-acting drugs, this study also raises concern about the long-acting variety. We therefore recommend that antihypertensive treatment focus on effective and inexpensive medications (such as diuretics and beta-blockers), or medications such as ACE inhibitors with potential benefit for patients with diabetes, and avoid medications such as CCBs that are both costly and potentially harmful.

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FINASTERIDE FOR BPH

McConnell JD, Bruskewitz R, Walsh P, et al. The effect of finasteride on the risk of acute urinary retention and the need for surgical treatment among men with benign prostatic hyperplasia. N Engl J Med 1998; 338:557-63.

Clinical question **Does finasteride reduce symptoms, the incidence of acute urinary retention, and the need for surgery in men with benign prostatic hyperplasia (BPH)?**

Background Fifty percent of 50-year-old men have BPH, and the incidence increases by approximately 10% every decade. Finasteride, a selective 5α-reductase inhibitor, has previously been shown to modestly improve urinary symptoms and reduce the gland volume in men with enlarged prostates because of BPH. However, the long-term effectiveness of any medical therapy for BPH has not been previously studied.

Population studied Predominately white men with moderate to severe BPH symptoms (scores of 8 to 34 on a "quasi-American Urologic Association [AUA] Symptom Score"), maximum flow rates <15 mL per second, and an enlarged prostate on digital rectal examination (DRE) were studied. Men taking alpha-blockers or antiandrogens and those with a history of chronic prostatitis, recurrent urinary tract infections, prostate cancer, bladder cancer, or a prostate-specific antigen (PSA) of 10 ng/mL or more were excluded.

Study design and validity This was a 4-year, randomized, double-blind, placebo-controlled trial. Patients were randomized to receive either finasteride 5 mg or placebo daily. Symptoms, side effects, and urinary flow rates were assessed every 4 months. After the initiation of the study, the AUA symptom score was adopted as the standard symptom assessment tool. Answers to the original questionnaire were adjusted to approximate the AUA symptom score. Serum PSA levels were measured every 4 months for 1 year and every 8 months thereafter. Patients with baseline PSA levels of 4 ng/mL or higher required a negative prostate biopsy to be admitted into the study. Biopsies were repeated at the study's end. Physical examinations, including DRE and routine blood work, were performed yearly. The intervention and control groups were similar at baseline and subjects were analyzed in the groups to which they were assigned (intention-to-treat analysis). Follow-up was available for 92% of subjects. Shortcomings of this study include that the duration of complaints and previous treatments were not documented, patient satisfaction was not evaluated, there was no description of how the decision for surgery was made, and there was no comparison to alpha-blockers (another common treatment for BPH).

Outcomes measured The primary outcome was the self-administered "quasi-AUA Symptom Score." The secondary endpoints were the need for prostate surgery and the occurrence of acute urinary retention.

Results Of the 3040 men who were randomized, 524 (34%) of the finasteride group and 633 (42%) of the placebo group discontinued treatment, most commonly because of adverse drug effects or treatment failures. The mean decrease in symptom score was 2.6 in the finasteride group and 1.0 in the placebo group. Acute urinary retention developed in 99 men in the placebo group and 42 men in the treatment group (7% vs 3%). The most clinically relevant estimate of effect is the number needed to treat (NNT). In this case, 25 patients would have to be treated for 4 years to prevent one episode of urinary retention (NNT = 25). Surgery was performed on 152 patients in the placebo group and 69 in the finasteride group (10% vs 5%, NNT = 20). Potential harm can be expressed in a similar manner with the number needed to harm (NNH). There was a clinically significant increase in the incidence of impotence (NNH=33) and decreased libido (NNH=23) during the first year of use. These adverse effects were not seen in the second and fourth years of the study.

Recommendations for clinical practice **In this Merck-sponsored study (the makers of finasteride), the finasteride group had a 1.6 point absolute improvement in their symptom score over placebo. While statistically significant, this is not clinically significant: Patients usually report symptomatic improvement only when this score improves by 3 or more. While there was a clinically significant decrease in acute urinary retention and the need for surgery, this is balanced by an equally significant increase in impotence and**

decreased libido in the first year of use. In a 1-year study of terazosin (an alpha-blocker), finasteride, both drugs, or placebo, terazosin modestly improved AUA symptom scores, while finasteride was no better than placebo.[1] Alpha-blockers are less expensive than finasteride and reach their maximum effect in 4 to 6 weeks. In contrast, it may take months for patients taking finasteride to perceive any effect and years to see the maximum benefit. Alpha-blockers are therefore a better first choice for the medical treatment of BPH. For patients with palpably enlarged prostates and moderate to severe symptoms who do not respond to an alpha-blocker, finasteride may offer an alternative to surgery. Patients should be informed of the length of time necessary to notice an improvement and the possibilities of decreased libido and impotence.

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Potentiation of Warfarin by Acetaminophen

Hyiek EM, Heiman H, Skates SJ, Sheehan MA, Singer DE. Acetaminophen and other risk factors for excessive warfarin anticoagulation. JAMA 1998; 279:657-62.

Clinical question **Can the anticoagulant effect of warfarin be potentiated by the concurrent use of acetaminophen (Tylenol)?**

Background Warfarin anticoagulation is used in many patients at increased risk for thromboembolic events. Hemorrhagic complications are more common as the international normalized ratio (INR) increases above 3.0. Minimal information is available on causes of very high INR levels (>6.0) in clinical practice.

Population studied Patients who had been taking warfarin for more than 1 month with a target INR between 2.0 and 3.0 were identified from an outpatient anticoagulant therapy unit. Case patients had an INR >6.0 and controls had an INR between 1.7 and 3.3. In both the case and control groups the mean age was 70 years, approximately 50% were women, and nearly all were white. Conditions leading to anticoagulation did not differ between groups. For most cases, their high INR value represented a recent deterioration (<1 month) in control of anticoagulation. All of the case patients and controls had started taking acetaminophen since their previous INR.

Study design and validity Case patients with an INR >6.0 during the study period were identified from daily INR logs. Controls were randomly selected during the same period from patients with INR between 1.7 and 3.3. All subjects were contacted by phone within 24 hours of their blood draw and questioned about recent medication use, dose change, diet, illness, alcohol consumption, and warfarin compliance. Patients were not specifically informed of their INR value or the true purpose of the study. Half of the cases had previously been informed of their abnormal result through the usual clinic mechanisms. It is not clear if the interviewers were blinded to the patients' INR value.

This case-control study design is appropriate given the infrequent occurrence of cases. This method is, however, susceptible to more bias than randomized controlled trials or cohort studies. In the research business, this type of study is known as a "fishing expedition," an exploratory study designed to find possible links that need further study with more rigorous methods. The finding of a dose-response relationship in the interaction between acetaminophen and warfarin and the fact that this effect has been reported in other studies adds credence to this study's results.

Outcomes measured Outcomes measured included medication use, recent diet, illness, alcohol consumption, and actual warfarin use. Other patient-oriented outcomes, including significant hemorrhage and death, were not studied.

Results A total of 111 case patients were identified and 93 of these were interviewed. An additional 279 controls were identified, of which 196 were interviewed. Cases and controls did not differ in terms of age, sex, race, indication for anticoagulation, length of warfarin therapy, dosage of warfarin, or INR value preceding the study period. A dose-response relationship was found between more than 7 tablets per week of acetaminophen and an increased risk for an INR >6.0. If the dose of acetaminophen was greater than 28 pills per week, the risk of having an INR >6.0 was 10-fold higher than controls (OR = 10.0; 95% CI, 2.6 - 37.9). Other risk factors independently associated with an elevated INR included taking a new medication known to potentiate warfarin, taking more warfarin than prescribed, diarrhea, advanced malignancy, and decreased oral intake. Intake of foods rich in vitamin K and moderate alcohol intake appeared to be moderately protective.

Recommendations for clinical practice **This study presents compelling data that point to acetaminophen (Tylenol) intake as a risk factor for elevations of INR levels in patients taking warfarin. Occasional intake did not confer risk, but patients**