Doxazosin plus finasteride reduced clinical progression of benign prostatic hyperplasia more than either drug used alone

McConnell JD, Roehrborn CG, Bautista OM, et al. **The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia.** N Engl J Med. 2003;349:2387-98.

QUESTION

In men with benign prostatic hyperplasia (BPH), what is the long-term effect of doxazosin or finasteride, alone or in combination, on measures of clinical progression?

DESIGN

Randomized (unclear allocation concealment*), blinded (patients and investigators),* placebo-controlled trial with mean follow-up of 4.5 years (Medical Therapy of Prostatic Symptoms [MTOPS] Study).

SETTING

17 clinical centers in the United States.

PATIENTS

3047 men ≥ 50 years of age (mean age 63 y) who had an American Urological Association (AUA) symptom score of 8 to 35 in the pilot phase (changed to 8 to 30 in the full study) and a maximum urine flow rate between 4 and 15 mL/s with a voided volume ≥ 125 mL. Exclusion criteria were previous medical or surgical intervention for BPH, blood pressure < 90/70 mm Hg in the supine position, or serum prostate-specific antigen level > 10 ng/mL. Follow-up was 100%.

INTERVENTION

Patients were allocated to doxazosin, beginning at 1 mg/d and increased to 8 mg/d (n = 756); finasteride, 5 mg/d (n = 768); doxazosin (beginning at 1 mg/d and increased to 8 mg/d; same as for monotherapy) plus finasteride, 5 mg/d (n = 786); or placebo (n = 737), once daily.

MAIN OUTCOME MEASURE

Overall clinical progression of BPH, defined as the first occurrence of an increase from baseline ≥ 4 points in the AUA symptom score, acute urine retention, renal insufficiency, recurrent urinary tract infection, or urinary incontinence.

MAIN RESULTS

Analysis was by intention to treat. Overall clinical progression of BPH was reduced with doxazosin alone, finasteride alone, and their combination more than with placebo (Table). Combination therapy was better than either drug alone (Table).

CONCLUSIONS

In men with benign prostatic hyperplasia, long-term doxazosin plus finasteride combination therapy reduced the risk for overall clinical progression of benign prostatic hyperplasia more than either drug used alone. Both drugs used alone were more effective than placebo.

Sources of funding: National Institutes of Health; Merck; Pfizer.

For correspondence: Dr. C.G. Roehrborn, University of Texas Southwestern Medical Center, Dallas, TX, USA. E-mail claus.roehrborn@utsouthwestern.edu.

*See Glossary.

Doxazosin, finasteride, doxazosin plus finasteride (combination), and placebo for clinical progression of benign prostatic hyperplasia at mean 4.5 years†

Comparisons	Event rates	RRR (95% CI)	NNT (CI)
Doxazosin vs placebo	11% vs 17%	35% (17 to 50)	17 (11 to 39)
Finasteride vs placebo	12% vs 17%	33% (14 to 48)	18 (11 to 45)
Combination vs placebo	6% vs 17%	64% (51 to 74)	9 (7 to 13)
Combination vs doxazosin	6% vs 11%	45% (23 to 60)	20 (13 to 46)
Combination vs finasteride	6% vs 12%	46% (25 to 61)	19 (13 to 40)

†Abbreviations defined in Glossary; RRR, NNT, and CI calculated from data in article.

COMMENTARY

α-blockers and 5-α reductase inhibitors have complementary effects in relieving BPH symptoms. In previous comparison trials with 12 months of follow-up, α-blockers were superior to the 5-α reductase inhibitor finasteride in improving urinary symptoms and flow; finasteride was no better than placebo. Long-term use of finasteride, however, has been shown to reduce the risks for urine retention and need for surgical treatment compared with placebo (1).

The well-designed study by McConnell and colleagues showed that long-term α-blocker use also could prevent clinical progression, including BPH complications. Although the risk for invasive treatment was reduced only with combination therapy, this outcome occurred infrequently. Combination therapy also reduced the risk for clinical progression more than either drug alone. However, among the men with clinical progression, by far the most common event was an increased symptom score. Adverse outcomes from BPH were uncommon: No patient developed renal insufficiency, and few had infectious complications.

Monotherapy with the quicker-acting α-blockers, therefore, is still appropriate. The drugs effectively control symptoms, improve urine flow, and reduce BPH complications. Adding finasteride is reasonable when symptoms progress or for men with a large prostate.

Combination therapy, however, raises a concern about prostate cancer. The placebo-controlled Prostate Cancer Prevention Trial found a higher incidence of poorly differentiated cases of cancer in the finasteride group, even though finasteride reduced the overall incidence of prostate cancer by 25% (2). Although experts debate whether the increased risk for high-grade cancer reflects a true harm from finasteride, this finding should be considered in deciding whether to prescribe the drug.

Richard Hoffman, MD, MPH
Albuquerque VA Medical Center
Albuquerque, New Mexico, USA

References

1. **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.
2. **Thompson IM, Goodman PJ, Tangen CM, et al.** The influence of finasteride on the development of prostate cancer. N Engl J Med. 2003;349:215-24.