Benign Prostatic Hyperplasia

Re: Clinical Outcomes After Combined Therapy With Dutasteride Plus Tamsulosin or Either Monotherapy in Men With Benign Prostatic Hyperplasia (BPH) by Baseline Characteristics: 4-Year Results From the Randomized, Double-Blind Combination of Avodart and Tamsulosin (CombAT) Trial

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Objective: To investigate the influence of baseline variables on the 4-year incidence of acute urinary retention (AUR), benign prostatic hyperplasia (BPH)-related surgery and overall clinical progression in men treated with tamsulosin, dutasteride, or a combination of both. Patients and Methods: The 4-year Combination of Avodart® and Tamsulosin (CombAT) study was a multicenter, randomized, double-blind, parallel-group study of clinical outcomes in men aged ≥50 years with symptomatic (International Prostate Symptom Score [IPSS]≥12) BPH, with prostate-specific antigen (PSA) levels of ≥1.5 ng/mL and ≤10 ng/mL, and a prostate volume (PV) of ≥30 mL. Eligible patients received tamsulosin 0.4 mg, dutasteride 0.5 mg, or a combination of both. The primary endpoint was time to first AUR or BPH-related surgery. Secondary endpoints included clinical progression of BPH and symptoms. Posthoc analyses of the influence of baseline variables (including age, IPSS health-related quality of life [HRQL], PV, PSA, IPSS, peak urinary flow rate [Q_{max}] and body-mass index [BMI]) on the incidence of AUR or BPH-related surgery, clinical progression of BPH, and symptoms were performed. Results: There were 4844 men in the intent-to-treat population. Overall baseline characteristics were similar across all patient groups. Regardless of baseline subgroup, the incidence of AUR or BPH-related surgery was higher in men treated with tamsulosin than in those treated with dutasteride or combined therapy. Combined therapy was statistically better than tamsulosin in reducing the risk of AUR or BPH-related surgery in subgroups of baseline PV >42.0 mL, in all subgroups of baseline PSA level, and all other baseline subgroups (P ≤0.001). Across treatment groups, the incidence of clinical progression was highest in men with a baseline IPSS of < 20 or IPSS HRQL score of < 4. The incidence of clinical progression was also higher in men receiving tamsulosin than dutasteride or combined therapy in all baseline subgroups, except for men with a baseline PV of <40 mL. Combined therapy reduced the relative risk (RR) of clinical progression compared with tamsulosin across all baseline subgroups and compared with dutasteride across most baseline subgroups. Symptom deterioration was the most common progression event in each treatment group regardless of baseline subgroup, except in those men with an IPSS of ≥20 at baseline. Combined therapy reduced the RR of symptom deterioration compared with tamsulosin across all but one baseline subgroup (the reduction was not significant for men with a baseline PV of <40 mL) and compared with dutasteride in most subgroups. Conclusions: Men with a baseline PV of ≥40 mL and any baseline PSA level of ≥1.5 ng/mL had greater reductions in the RR of AUR or BPH-related surgery and greater reductions in the RR of clinical progression and symptom deterioration on combined therapy or dutasteride monotherapy than on tamsulosin monotherapy. These analyses support the long-term use of combined therapy with dutasteride plus tamsulosin in men with moderate-to-severe BPH symptoms and a slightly enlarged prostate.

Editorial Comment: This is another in a series of reports from the CombAT database. The strengths and weaknesses of the trial design have been examined here and elsewhere. The role of combination therapy with a 5alpha-reductase inhibitor and alpha-blocker continues to evolve, in large part because urologists simply do not accept that the cutoffs used by GlaxoSmithKline to define a large prostate (30 gm or greater) are accurate. Virtually the entire dutasteride database contains men with prostate volumes 30 gm or greater. As we have previously indicated, this group excludes virtually half of the men who present to

urologists throughout the world with lower urinary tract symptoms secondary to BPH. Notwithstanding this glaring omission, there is considerable debate regarding what prostate volume constitutes "enlargement." Throughout my travels around the world I have been struck by an almost universal definition of a large prostate as at least 50 gm.

While the CombAT database suggests statistical significance at 30 gm, the data reported in this post hoc analysis shed new and important light on how the data are driven, ie it is the extremely large prostates that drive the statistical database. When dividing the group into tertiles, one is struck that the lowest is represented by prostate volumes 42 gm or less. More than two thirds of patients had prostate volumes greater than 42 gm, with the largest tertile greater than 57.8 gm. Clearly CombAT is not representative of the typical population one sees in general urological practice.

One other point that is striking is that there is no statistically significant advantage of combination therapy vs monotherapy in prostate volumes 42 gm or less regarding decreasing the risk of urinary retention or the need for BPH surgery. This finding was partly due to the fact that the incidence of BPH progression, as defined by acute retention or need for surgery, in men with volumes less than 40 gm was only 3.4% during 4 years. In fact, in that cohort of men the incidence of BPH progression was lower in the tamsulosin than the dutasteride monotherapy arm. Furthermore, in the largest prostates not only did combination therapy work better to reduce BPH risk related events, but so did alpha-blocker monotherapy. The notion that men with prostates 30 gm or larger should be routinely started on combination therapy is not supported and makes little clinical, much less economical, sense. The take home message is that combination therapy with a 5alpha-reductase inhibitor and alpha-blocker has no real advantage in the typical man who presents with lower urinary tract symptoms unless the prostate is markedly enlarged.

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Re: Comparison of Dutasteride and Finasteride for Treating Benign Prostatic Hyperplasia: the Enlarged Prostate International Comparator Study (EPICS)

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Objective: To assess the efficacy and safety of dutasteride compared with finasteride in treating men with symptomatic benign prostatic hyperplasia (BPH) for 12 months. Patients and Methods: The Enlarged Prostate International Comparator Study was a multicentre, randomized, double-blind, 12-month, parallel-group study. Men aged ≥ 50 years with a clinical diagnosis of BPH received once-daily treatment with dutasteride 0.5 mg (n = 813) or finasteride 5 mg (n = 817). After a 4-week placebo run-in period, patients were randomized to receive dutasteride or finasteride for 48 weeks, followed by an optional 24-month, open-label phase, during which patients received dutasteride 0.5 mg once daily. The primary endpoint was change in prostate volume, and the secondary endpoints included improvement in American Urological Association Symptom Index (AUA-SI) scores, improvement in maximum urinary flow rate (Q_{max}) and long-term safety in the 24-month open-label phase. Results: Both dutasteride and finasteride were effective at reducing prostate volume with no significant difference between the two treatments during the study. Similar reductions in mean AUA-SI scores and Q_{max} were also observed for men in both treatment groups. A similar percentage of adverse events was experienced by patients of both treatment groups, and no new adverse events were reported in the open-label phase. Conclusion: Dutasteride and finasteride, when administered for 12 months, were similarly effective in reducing prostate volume and improving Q_{max} and urinary symptoms associated with BPH in men with an enlarged prostate.

Editorial Comment: Following much prodding, and more than a decade after completion of this double-blind study, the data from EPICS have finally been published. The study was designed to determine if there were any differences in prostate volume reduction between