**Table 3.** Data Extraction of Selected RCTs for Synthesis and Analysis

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| **Authors (year)** | **Study design** | **Intervention & control group** | **Sample size & age profile** | **Inclusion criteria** | **Clinical outcomes** | **Statistical analysis** | **Clinical considerations** |
| Chung et al, 2012 [e1] | Multinational, multicenter, double-blind, parallel-group, randomized controlled trial (RCT).  | Free combination of tamsulosin 0.4 mg + dutasteride 0.5 mg vs. tamsulosin 0.4 mg monotherapy vs. dutasteride 0.5 mg monotherapy | Asian (n = 325), Caucasian (n = 4, 259). Patients aged ≥ 50 years old | 1) 325 Asian & 4,259 Caucasian men with moderate-to-severe LUTS/BPH; 2) Patients with IPSS of 12 - 35; 3) PV ≥ 30 mL; 4) PSA level ≥ 1.5 ng/mL; 5) Qmax > 5 mL/s and ≤ 15 mL/s; 6) Minimum voided volume ≥ 125 mL | Primary outcome at the 2nd year: 1) Asian men: differences were not statistically significant; 2) Caucasian men: significantly lower in combination therapy vs. tamsulosin monotherapy (P < 0.001), which did not differ significantly between combination therapy and dutasteride monotherapy.  | Data analysis was performed in the statistical analysis process on an intent-to-treat population basis. A two sides P value less than 0.05 was defined as statistical significance in data analysis of combination therapy vs. monotherapy in Asian and Caucasian men. Primary outcome of incident rate at the 2nd year were analyzed among two subpopulations using the log-rank and Mantel-Haenszel tests. Secondary outcome of disease progression was analyzed similarly using the log-rank and Mantel-Haenszel tests. Additional *t*-test from general linear model used for IPSS, Q max and BII comparison within two subpopulation groups. | 1) In long-term treatment, combination therapy provides significantly superior and sustained reduction in BPH symptoms, however, decreased activity of 5AR and variability in the gene encoding the 5AR type 2 enzyme in Asian men resulted in lower sensitivity to dutasteride in combination therapy and monotherapy. 2) Lower PV and PSA levels was found in Asian men, which leads to a clinical feature that each volume unit of prostate gland, might require greater release of PSA as well as higher risk of BPH compared with Caucasian men. |
| Post-hoc investigation of CombAT study. | Free combination: drugs administered concomitantly |
| Secondary outcome at 4th year: 1) Significantly lower incidence rate in combination therapy vs. tamsulosin monotherapy in both populations (P < 0.05); 2) Significantly lower in combination therapy vs. dutasteride monotherapy in Caucasian men; 3) Did not differ significantly between combination therapy and dutasteride monotherapy in the Asian men |
| Once daily dose |
| Roehrborn et al, 2014 [e2] | Multinational, multicenter, double-blind, parallel-group, randomized controlled trial (RCT). | Free combination of tamsulosin 0.4 mg + dutasteride 0.5 mg vs. tamsulosin 0.4 mg monotherapy vs. dutasteride 0.5 mg monotherapy | 325 Asian men + 4,259 Caucasian men ≥ 50 years old divided into 8 subgroups: 1) PSA ng/mL: 1 - 2.5 (n = 1,323); 2.5 - 4: (n = 1,557); ≥ 4: (n = 1,925). 2) PV mL: 30 - 40: (n = 1,353); 40 - 60: (n = 2,003); 60 - 80: (n = 879). 3) IPSS QoL: < 4: (n = 2,294); ≥ 4: (n = 2,545). 4) Age years: < 66: (n = 2,264); ≥ 66: (n = 2,578). 5) IPSS: < 16: (n = 2,341); ≥ 16: (n = 2,497); < 20: (n = 3,347); ≥ 20: (n = 1,391). 6) Qmax mL/s: < 10.4: (n = 2,419); ≥ 10.4: (n = 2,425). 7) BMI kg/m2: < 26.8: (n = 2,396); ≥ 26.8: (n = 2,427). 8) BII: < 5: (n = 2,069); ≥ 5: (n = 2,769) | 1) Patients with IPSS of 12 - 35; 2) PV ≥ 30 mL; 3) PSA level ≥ 1.5 ng/mL; 4) Qmax > 5 mL/s and ≤ 15 mL/s; 5) Minimum voided volume ≥ 125 mL | 1) Combination therapy resulted in a significantly greater improvement from baseline IPSS at 4 years vs. tamsulosin monotherapy. 2) Compared to dutasteride monotherapy, the superiority of combination therapy was observed in subgroups with lower baseline PV < 60 mL & PSA < 4 ng/mL. 3) In subgroups with PV ≥ 60 mL & PSA ≥ 4 ng/mL, dutasteride monotherapy and combination therapy group have a similar improvement in LUTS. 4) Combination therapy group showed a significant improvement in Qmax than tamsulosin monotherapy but not to dutasteride monotherapy. 5) In QoL assessment, QoL ≤ 2 at 4 years was significant greater with combination therapy than patients with PV 40 - 60 mL & PSA level < 4 ng/mL in dutasteride monotherapy. | Data analysis was performed in the statistical analysis process on an intent-to-treat population basis. A generalized linear model was used in comparison of IPSS, Qmax improvement from baseline to 2nd year within all 8 subgroups; additional approach of last observation carried forward (LOCF) was applied to the change in IPPS, Qmax from bassline up to 4th year in all subgroups. P ≤ 0.01 was defined as statistical significance in data analysis of the change of IPSS, Qmax. Mantel-Haenszel Chi-squared test used in subgroups with a IPSS QoL score ≤ 2 and IPSS < 12. The Wilcoxon rank-sum test was used to analyze symptoms improvement that relevant to IPSS change. | 1) Patient with high PV score ≥ 30 mL and high PSA level ≥ 1.5 ng/mL should consider taking long-term combination therapy. 2) A comprehensive and appropriate baseline assessment should be conducted by physicians prior to medication prescribing as various baselines show different LUTS. |
| Post-hoc analysis of CombAT study. | Free combination: drugs administered concomitantly |
| Once daily dose |
| Roehrborn et al, 2015 [e3] | Multicenter, open-label, parallel-group randomized controlled trail (RCT) | Fixed-dose of tamsulosin 0.4 mg +dutasteride 0.5 mg + lifestyle advice vs. watchful waiting + lifestyle advice | Fixed-dose combination therapy (n = 369). Watchful waiting with initiation of tamsulosin if symptoms did not improve (n = 373). Men aged ≥ 50 years old. | 1) Asian men aged ≥ 50 years; 2) Diagnosed BPH and moderate LUTS; 3) IPSS of 8 - 19; 4) PV ≥ 30 mL; 5) PSA level of ≥ 1.5 ng/mL | Primary outcome: measured by IPSS; was significantly greater for fixed-dose combination therapy than watchful waiting group (-5.4 vs. -3.6 points, P < 0.001). | Efficacy and safety analysis was conducted in intent-to-treat population basis. Estimating of sample size were assumed in a normal distribution and mean variable of IPSS improvement from baseline 1.6, a standard deviation (SD) of 6 were computerized. Improvement of IPSS, BII, and IPSS QoL score from baseline were analyzed in LOCF method. The *t*-test was used in comparison of mean score across groups. Log-rank test was also used to compare the first occurrence of disease progression among groups with defined statistical significance of P ≤ 0.05. | 1) Lifestyle advice about caffeine and alcohol avoidance, fluid management and bladder retraining may be considered as a part of management for moderate BPH. 2) The safety of fixed-dose combination therapy was consistent with tamsulosin 0.4 mg and dutasteride 0.5 mg monotherapy and when administered concomitantly in free combination. |
| Once daily dose |
| Lifestyle advice about caffeine, alcohol avoidance, fluid management and bladder retraining | Secondary outcomes included BPH clinical progression, impact of QoL and safety: 1) In fixed-dose combination therapy, the risk of BPH progression was reduced by 43.1% (P < 0.001); 2) 29% and 8% of men in the watchful waiting and fixed-dose combination therapy groups had clinical progression, respectively; 3) Improvement in QoL were seen in both groups but were significantly greater with fixed-dose combination therapy group (P < 0.001). |
| Chung et al, 2018 [e4] | Multicenter, double-blind, randomized controlled trail (RCT) | Tamsulosin 0.4 mg monotherapy vs. tamsulosin 0.2 mg monotherapy vs. placebo treatment | Tamsulosin 0.4 mg (n = 162). Tamsulosin 0.2 mg (n = 165). Placebo treatment (n = 167). Patients aged ≥ 45 years old. | 1) Asian men aged 45 years old and older with diagnosed BPH; 2) IPSS ≥ 13; 3) Qmax 4 - 15 mL/s with a voided urine volume ≥ 100 mL; 4) PVRU < 300 mL | Primary outcome: total IPSS was improved in the 0.4 mg and 0.2 mg group, however, the extent of improvement was greater in 0.4 mg than 0.2 mg (P < 0.0001). | Efficacy and safety analysis was conducted in intent-to-treat population basis. Comparison of persistence of difference across all groups was analyzed in analysis of variance (ANOVA) approach. Efficacy and safety were compared with all groups by using analysis of covariance (ANCOVA) approach. Chi-squared test and fisher’s exact teste were used in analysis of categorical variables. SAS software v.9.3 was used for overall statistical analysis with a defined statistical significance P ≤ 0.05. | 1) Tamsulosin 0.4 mg was safe to administer for Asian men as it showed a better symptoms improvement than 0.2 mg without significant adverse events. 2) Safety profile was similar in tamsulosin 0.4 mg and 0.2 mg, but urination symptoms were improved greater in tamsulosin 0.4 mg. |
| Medication taken once daily every evening after meal |
| Secondary outcome: 1) IPSS voiding and storage symptoms sub score were improved more in both groups than placebo, however, there was no statistical difference between 0.4 mg and 0.2 mg group. 2) Qmax and PVRU were improved in both groups. |
| Safety outcomes: 1) TEAEs were 20.65% in tamsulosin 0.4 mg, 15.24% in tamsulosin 0.2 mg; 2) AEs were 7.10% in tamsulosin 0.4 mg, 2.44% in tamsulosin 0.2 mg. |
| Haque et al, 2018 [e5] | 4 weeks single-blind placebo followed by 2 years multicenter, double-blind, parallel-group, randomized controlled trail (RCT) | Free combination of tamsulosin 0.2 mg + dutasteride 0.5 mg vs. tamsulosin 0.2 mg monotherapy + dutasteride matched placebo | Tamsulosin 0.2 mg + dutasteride 0.5 mg combination therapy group (n = 305) | 1) Asian men ≥ 50 years old with diagnosed moderate-to-severe LUTS/BPH; 2) IPSS ≥ 12; 3) PV ≥ 30 mL; 4) Total serum PSA ≥ 1.5 and ≤ 10 ng/mL; 5) Qmax > 5 and ≤ 15 mL/s; 6) Minimum voided volume ≥ 125 mL | Primary outcome: significant improvement of IPSS in combination therapy compared with tamsulosin monotherapy at 2 years (P = 0.004). | Efficacy and safety analysis was conducted in intent-to-treat population basis. Primary analysis of IPSS improvement from baseline to 2nd year was conducted by using LOCF. PV change form baseline was compared using general linear model: log (post-baseline PV/baseline PV) = log (baseline PV) + treatment + country. The Mantel-Haenszel test was used in analysis of the first occurrence of AUR & BPH-related surgery. Fisher’s exact test analyzed difference of AEs within groups defined statistical significance of P ≤ 0.05. | 1) Most of these drug-related AEs were reported within the first 6 - 12 months; ≥50% were in combination therapy group and remained unresolved throughout entire 2 years. 2) Sexual relevant problems had mostly happened to combination therapy; however, the rate of sexual AEs was lower than previous CombAT study (tamsulosin 0.4 mg + dutasteride 0.5 mg). 3) Cardiovascular AEs rate was similar to CombAT study. |
| Free combination: drugs administered concomitantly | Tamsulosin 0.2 mg monotherapy + placebo (n = 302) |
| Once daily dose | Asian men aged ≥ 50 years old | Secondary outcome: 1) IPSS improvements were greater in combination therapy than tamsulosin monotherapy (P < 0.05); 2) Qmax improvement was significant higher in combination therapy (P < 0.001); 3) At 2 years, significant reduced risks of AUR by 85% in combination therapy (P = 0.012); 4) Safety and tolerability were similar in two groups, but AEs were more frequent in combination therapy and primarily were sexual dysfunction related. |

RCTs: randomized controlled trials; LUTS/BPH: lower urinary tract symptoms secondary to benign prostatic hyperplasia; IPSS: international prostate symptom score; PV: prostate volume; PSA: prostate specific antigen; Qmax: maximum urinary flow rate; BII: benign prostatic hyperplasia impact index; 5AR: 5-alpha reductase; QoL: quality of life; LUTS: lower urinary tract symptoms; LOCF: last observation carried forward; BPH: benign prostatic hyperplasia; SD: standard deviation; PVRU: post-void residual urine; TEAEs: treatment emergent adverse events; AEs: adverse events; ANOVA: analysis of variance; ANCOVA: analysis of covariance; SAS: statistical analysis system; AUR: acute urinary retention; CombAT: combination of Avodart and tamsulosin.

**References**

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