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Combination therapy with Tamsulosin plus Dutasteride Versus Tamsulosin in Benign Prostatic Hyperplasia: a Systematic review & Meta-analysis

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ABSTRACT

Background: This study aims to compare the efficacy and safety of combination therapy with tamsulosin plus dutasteride versus tamsulosin in benign prostatic hyperplasia.

Methods: An online search was conducted in PubMed, Cochrane Library, Embase, Scopus, and Web of Science to identify the relevant published studies up to July 2021. The reference list of the key review articles was searched as well. The Cochrane risk of bias was used to assess the quality of studies. Meta-analysis was performed using the RevMan software v.5.3.

Results: Six studies, including 6647 patients were included. A significant improvement was observed in combination therapy group compared to tamsulosin group in terms of international prostate symptom score (mean difference [MD]=-2.59, %95 confidence interval [CI]: -4.20 to -0.99; P=0.002), prostate volume (MD=-10.13, %95 CI: -12.38 to -7.88; P<0.05), maximum urine flow rate (MD=1.05, %95 CI: 0.82 to 1.29; P<0.05), transitional zone volume (MD=-3.18, %95 CI: -3.57 to -2.79; P<0.05), and prostate-specific antigen (MD=-0.54, %95 CI: -0.80 to -0.29, P<0.05). The result of the subgroup showed that tamsulosin 0.2 mg in combination therapy was not effective in terms of international prostate symptom score (MD=-2.97; 95% CI: -7.49 to 1.56; P=0.20). Adverse events were more in combination therapy

in terms of erectile dysfunction, retrograde ejaculation, decreased libido, ejaculation failure, any adverse events, and any drug-related adverse event (P<0.05). However, there was no significant difference between the two groups in terms of dizziness and any serious adverse event (P>0.05).

Conclusion: This meta-analysis showed that combination therapy has greater efficacy in treating patients with benign prostatic hyperplasia; however, it is associated with higher adverse events.

Keywords: Benign prostatic hyperplasia, Tamsulosin, Dutasteride, combination therapy.

Introduction

Benign prostatic hyperplasia (BPH) is one of the most common chronic diseases (1) in men older than 50 years, and its prevalence rises markedly with increased age (2). The prevalence of BPH is 50 to 60 percent at age 50 and 90 percent for men over 80 years(3, 4). Moreover, it is associated with severe morbidities such as an increased risk of falls, depression, poor health-related quality of life, and billions of dollars in annual healthcare costs (5, 6). As the world population ages, the incidence and prevalence of BPH and urinary tract obstruction (LUTS) have increased rapidly (7). Enlargement of the prostate due to BPH may lead to bladder outflow obstruction, which is the main cause of LUTS (8). BPH's consequences include: Bladder stones, urinary tract infections, bladder failure, incontinence, obstructive uropathy, hematuria, acute urinary retention (AUR), and erectile dysfunction (9, 10).

Currently, among prescription drugs, 5-alpha reductase inhibitors (5-ARIs) and Alpha-blockers (ABs) are used for treating BPH (11-13). ABs have been the first-line treatment in men with BPH (14). Many ABs have benefits such as long-term efficacy, low adverse events, availability, and single daily dose (15). Furthermore, relaxing the prostate and bladder muscles improves relatively quickly in controlling symptoms such as increased urine flow rate_and improved quality of life in patients with BPH (16). Tamsulosin is the most common ABs prescribed in patients (17, 18).

5-ARIs are widely used in treating patients with BPH (19). 5-ARIs can inhibit the conversion of testosterone to dihydrotestosterone, reducing PV, increasing urinary flow rates, and improving symptoms (20). Dutasteride is the complete 5-ARIs because it blocks both type I and type II receptors (21) and is currently widely used in treating BPH (22). The complementary effects of 5-ARIs and ABs, which control the symptoms of ABs and reduce the long-term risk of progression of 5-ARIs, make them suitable components of combination therapy to improve faster, better, and more stable in preventing disease progression in patients with BPH (23). combination therapy is a first-line option recommended for treating moderate to severe urinary tract symptoms in men with hyperplasia at risk of developing the disease (24). Clinical trials have shown that fixed-dose combination therapy with Tamsulosin and dutasteride is significantly more effective than either component in reducing symptoms and decreasing AUR and surgery associated with BPH (25, 26). This study aimed to examine the efficacy and safety of Tamsulosin plus dutasteride versus Tamsulosin in patients with BPH.

Method

We have registered the protocol of this systematic meta-analysis with the number CRD42019119156. We prepared our report based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (27).

Search strategy

An electronic search was conducted on major databases, including PubMed, Cochrane Library, Embase, Scopus, and Web of science, for identifying published relevant studies up to July 2021. To find further evidence, the reference list of review studies and studies related to the subject and key journals in this field were manually searched. Keywords and Mesh terms were used: “benign prostatic hyperplasia," “prostatic hypertrophy," “Dutasteride," “Tamsulosin," and “combination therapy”. Studies included if they were published in the English language.

Study selection

The inclusion criteria were as follows:

1) Population: BPH
2) Intervention: Tamsulosin plus Dutasteride
3) Comparator: Tamsulosin
4) Outcomes: International Prostate Symptom Score (IPSS), Prostate volume (PV), Maximum urine flow rate (Qmax), transitional zone volume (TZV), Prostate-specific antigen (PSA), and Adverse Events (erectile dysfunction, retrograde ejaculation, decreased libido, ejaculation failure, dizziness, any adverse event, any drug-related adverse event, and any serious adverse event)
5) Study design: randomized controlled trial (RCT).

The exclusion criteria were the studies conducted on BPH prostate cancer and other illnesses,

unrelated outcomes, cohort and retrospective studies, case reports, and letters to the editor.

Quality assessment

After removing duplicates, the two researchers (BA & BA) independently reviewed the titles and abstracts based on the criteria. Discrepancies were resolved through discussions between the two authors. In disagreement, a third person (MD) entered the discussion. The quality of randomized clinical trials was evaluated using the Cochrane Collaboration's tools.

Data extraction

Two authors (BA & BA) separately extracted data using a constructed data extraction form. The extracted data included the characteristics of the study (design, duration, and follow-up duration), characteristics of the participants (mean or medium age and number of patients), interventions (numbers, doses, and duration of the treatment with intervention), measured outcomes, and AEs. After completing the data extraction forms, the three authors discussed and finalized the differences (BA, BA, MD). Eventually, the efficacy and safety outcomes were analyzed.

Statistical analyses and meta-analysis

The efficacy and safety outcomes, including IPSS, PV, Qmax, TZV, PSA, and AEs, were analyzed using Review Manager software version 5.3. The mean difference (MD) and risk ratio (RR) were used for continuous and dichotomous variables with a 95% confidence interval (CI), respectively. Statistical heterogeneity has been evaluated using the I-square and chi-square tests. The random and fixed effects models were used based on heterogeneity.

Findings

Characteristics of included studies

Figure 1 shows the search process, exclusion of duplicates, and screening based on the title, abstract, and full text. After deleting duplicates, 423 articles were independently reviewed based on title, abstract, and full text by the two authors. Disagreements between authors were resolved through discussion. A total of 22 studies were eligible for full-text review. However, after reviewing the selected full texts, six studies (28-33) were eligible for final inclusion and selected for data synthesis. The studies were published between 2010 and 2018 and included 6647 patients. The follow-up duration ranged from 12 to 48 months. The characteristics of the studies are demonstrated in (Table 1). The studies assessment using the Cochrane Collaboration tool is presented (Figure 2).

Efficacy

The combination therapy demonstrated better efficacy compared to Tamsulosin in terms of IPSS (MD= -2.59, %95 CI: -4.20 to -0.99; P=0.002), PV (MD= -10.13, %95 CI: -12.38 to -7.88; P<0.00001), Qmax (MD= 1.05, %95 CI: 0.82 to 1.29; P<0.05), TZV (MD= -3.18, %95 CI: -3.57 to -2.79; P<0.05), and PSA (MD= -0.54, %95 CI: -0.80 to -0.29; P<0.05) (Figure 3).

Subgroup Analysis

A subgroup analysis was performed based on the dose of received Tamsulosin between groups for efficacy outcomes. The result demonstrated that Tamsulosin 0.2 mg in combination therapy was ineffective in terms of IPSS (MD= -2.97; 95% CI: -7.49 to 1.56; P=0.20) (Figure 4).

Safety

The result showed that there was a significant difference between combination therapy and Tamsulosin in terms of erectile dysfunction (OR= 3.03; 95% CI: 1.28 to 7.17; P=0.01), retrograde ejaculation (OR= 2.30; 95% CI: 1.08 to 4.93; P=0.03), decreased libido (OR= 2.29; 95% CI: 1.57 to 3.36; P<0.05), ejaculation failure (OR= 3.75; 95% CI: 2.22 to 6.34; P<0.05), any adverse event (OR= 1.74; 95% CI: 1.15 to 2.63; P=0.009), and any drug-related adverse event (OR= 3.04; 95% CI: 1.27 to 7.24; P=0.01). However, there was no significant difference between combination therapy and Tamsulosin in terms of dizzies (OR= 1.23; 95% CI: 0.81 to 1.87; P=0.34), and any serious adverse event (OR= 1.14; 95% CI: 0.74 to 1.77; P=0.55) (Figure 5).

Discussion

This study aimed to examine the efficacy and safety of combined Tamsulosin plus Dutasteride compared with Tamsulosin in BPH. The results showed that combined therapy, compared with Tamsulosin in patients with BPH, improved the IPSS, PV, Qmax, TZV, and PSA indexes. These findings were consistent with the results of the study done by Zhou et al. (34). Several studies have shown that combination therapy with 5alpha-reductase inhibitors and ABs are used in the treatment of BPH, which relieves symptoms, and contributed to delaying and reducing the progression of BPH (35-37), and avoiding the need for surgical intervention (38). It is reported that long-term combination therapy with α-blocker and 5-ARI reduced the progression of BPH (39) and AUR or BPH-related surgery, compared with α-blocker-only treatment (40). However, combination therapy is much more effective for managing BPH (41). However, a retrospective study's results showed no statistically significant

differences between combination therapy and Tamsulosin in IPSS, PV, and PSA (42).

The network meta-analysis (43) results showed no difference between Tamsulosin 0.4 mg and 0.2 mg in terms of IPSS, which is inconsistent with our findings. This difference is due to placebo controls in network meta-analysis.

A systematic review showed that combination therapy with 5-ARIs and ABs also benefits patients when medical treatment is intended for more than one year (44). It should be noted that 5-ARIs have a permanent role in reducing PV (45). Adding Dutasteride to ABs reduces PV (46). Evidence has suggested that among the drugs used to treat BPH, only 5-ARIs decrease the size and volume of the prostate (47). Because dihydrotestosterone (DHT) is primarily responsible for prostate androgen growth (48), it plays an essential role in prostate growth (49). 5-ARIs have reduced the production of DHT, reducing PV (48) ,increasing Qmax, and improving symptom scores (50).

The meta-analysis that Qmax was higher in combination therapy versus Tamsulosin. This result is consistent with Wang and colleagues' study that combination therapy with 5-ARIs plus ABs had the most excellent effect on Qmax (51). Adding dutasteride to ABs improves the Qmax (46). The meta-analysis showed that TZV was higher in the urine of those receiving combination therapy than Tamsulosin.

In our study, PSA was higher in combination therapy versus Tamsulosin. ABs, including Tamsulosin, are a safe and effective treatment in improving LUTS and quality of life in patients with BPH (52). The meta-analysis showed that erectile dysfunction, decreased libido, ejaculation failure, and dizziness were more in combination therapy. Other studies showed that combined treatment with ABs and 5-ARIs is associated with a higher risk of erectile dysfunction than monotherapy (53, 54). The evidence showed that 5-ARIs significantly increased the risk of erectile dysfunction, ejaculatory dysfunction, and decreased libido (55). However, the result of a study showed that Tamsulosin did not have any significant impact on sexual function or any negative impact on ejaculatory function (56).

In Zhou's study, dizziness was the same in the two groups. However, another study showed that the use of 5-ARIs did not significantly increase the risk of erectile dysfunction, and the risk of erectile dysfunction increased with prolonged BPH (57). Although AEs of combination therapy are higher than a single treatment, it is better if used long-term (more than 12 months) (58). The rationale behind the combined use of an AB and a 5-ARIs is the potential synergistic effect of these two pharmaceutical agents due to their different modes of action (58). Our study also had some limitations, including heterogeneity between studies, a wide range of sample sizes, and different doses used in the methodology.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the ethical committee of the Tehran University of Medical Sciences (TUMS). All the participants accepted enrollment in the study orally and all of the data that were gathered was considered confidential.

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Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declare no conflict of interest.

Table 1. Characteristics of included RCTs

Study	Country	Study design	Sample size			Mean age	T+D (dosage)	Tamsulosin (dosage)	Follow-up (Month)
			Total	T+D	T				
Hong 2010	South Korea	RCT	120	37	37	NR	0.2 + 0.5mg	0.2 mg	12
Joo 2012	South Korea	RCT	216	98	95	≥40	0.2 + 0.5mg	0.2 mg	12
Roehrborn 2014	USA	RCT	4844	1610	1611	≥50	0.4 + 0.5mg	0.4 mg	48
Roehrborn 2015	International	RCT	742	369	373	≥50	0.4 + 0.5mg	0.4 mg	24
Choi 2016	South Korea	RCT	118	59	59	≥40	0.2 + 0.5mg	0.2 mg	12
Haque 2018	China, Japan, South Korea, Taiwan	RCT	607	305	302	≥50	0.2 + 0.5mg	0.2 mg	24

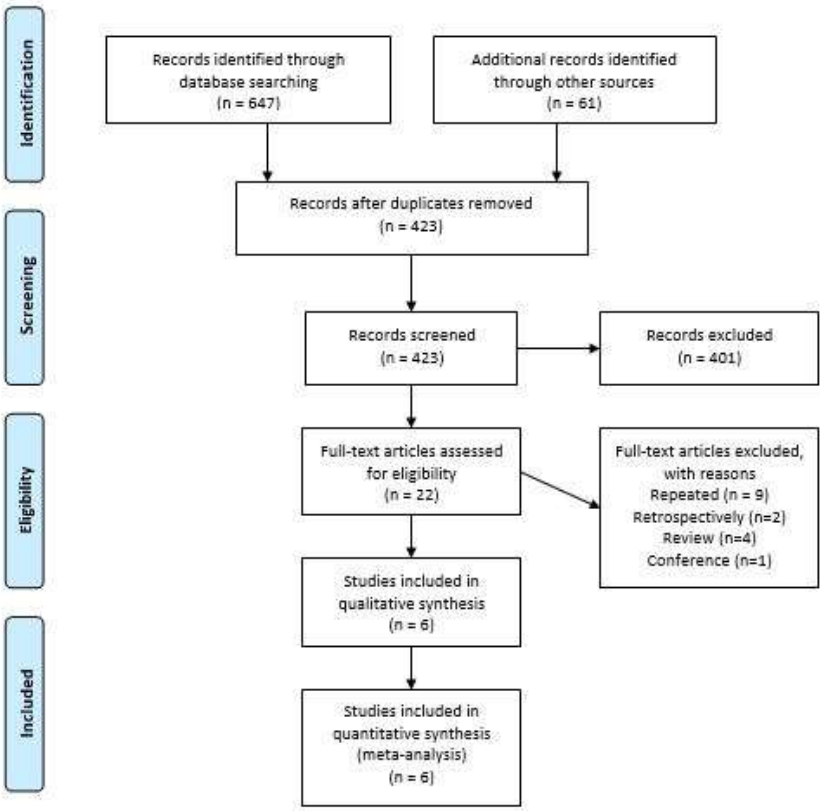


Figure 1. Flow diagram of the study selection process

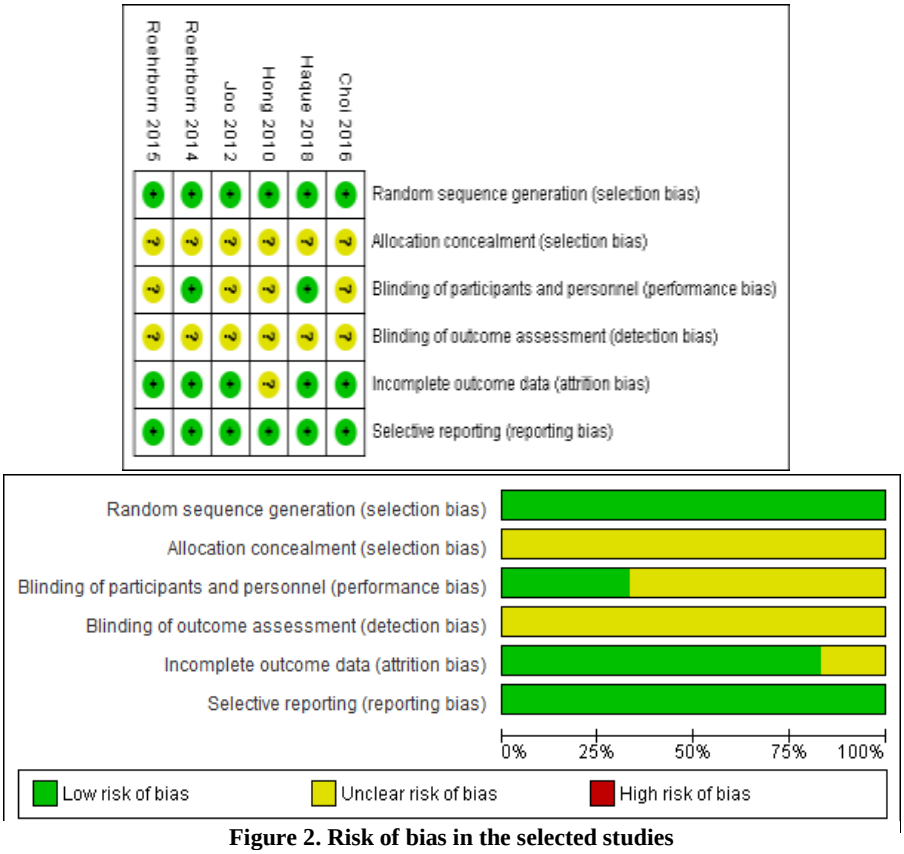
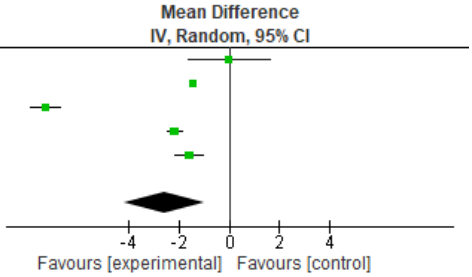


Figure 2. Risk of bias in the selected studies

A.

Study or Subgroup	Combination Mean	SD	Total	Tamsulosin Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Choi 2016	-6	4.62	59	-6	4.6	59	17.2%	0.00 [-1.66, 1.66]
Haque 2018	-4.96	0.39	305	-3.53	0.39	302	21.0%	-1.43 [-1.49, -1.37]
Joo 2012	-7.42	2.91	98	-0.06	0.22	95	20.5%	-7.36 [-7.94, -6.78]
Roehrborn 2014	-6.34	4.43	1610	-4.15	4.07	1611	20.9%	-2.19 [-2.48, -1.90]
Roehrborn 2015	-5.2	4.06	369	-3.6	3.95	373	20.5%	-1.60 [-2.18, -1.02]
Total (95% CI)			**2441**			**2440**	**100.0%**	**-2.59 [-4.20, -0.99]**

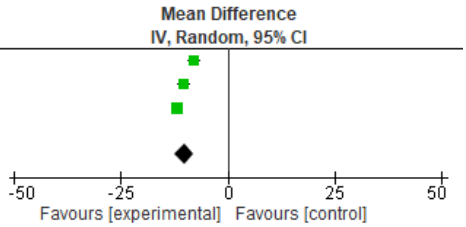
Heterogeneity: Tau² = 3.20; Chi² = 423.69, df = 4 (P < 0.00001); I² = 99%
Test for overall effect: Z = 3.16 (P = 0.002)



B.

Study or Subgroup	Combination Mean	SD	Total	Tamsulosin Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Choi 2016	-8	4.56	59	0	2.43	59	32.0%	-8.00 [-9.32, -6.68]
Joo 2012	-10.04	6.14	98	0.38	2.1	95	32.2%	-10.42 [-11.71, -9.13]
Roehrborn 2014	-11.25	5.87	1610	0.52	3.18	1611	35.7%	-11.77 [-12.10, -11.44]
Total (95% CI)			**1767**			**1765**	**100.0%**	**-10.13 [-12.38, -7.88]**

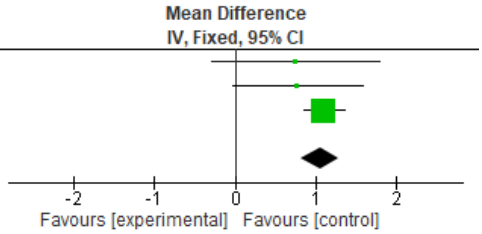
Heterogeneity: Tau² = 3.66; Chi² = 32.40, df = 2 (P < 0.00001); I² = 94%
Test for overall effect: Z = 8.82 (P < 0.00001)



C.

Study or Subgroup	Combination Mean	SD	Total	Tamsulosin Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Choi 2016	4.25	3.29	59	3.5	2.38	59	5.1%	0.75 [-0.29, 1.79]
Joo 2012	3.46	2.07	98	2.69	3.45	95	8.4%	0.77 [-0.04, 1.58]
Roehrborn 2014	2	3.61	1610	0.9	3.66	1611	86.5%	1.10 [0.85, 1.35]
Total (95% CI)			**1767**			**1765**	**100.0%**	**1.05 [0.82, 1.29]**

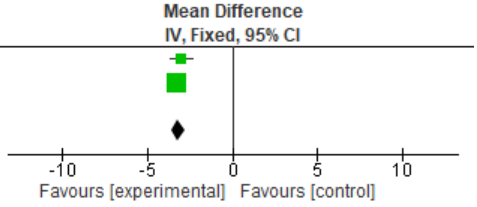
Heterogeneity: Chi² = 0.94, df = 2 (P = 0.63); I² = 0%
Test for overall effect: Z = 8.85 (P < 0.00001)



D.

Study or Subgroup	Combination Mean	SD	Total	Tamsulosin Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Choi 2016	-3	2.33	59	0	1.26	59	33.4%	-3.00 [-3.68, -2.32]
Joo 2012	-3.03	2.32	98	0.24	0.66	95	66.6%	-3.27 [-3.75, -2.79]
Total (95% CI)			**157**			**154**	**100.0%**	**-3.18 [-3.57, -2.79]**

Heterogeneity: Chi² = 0.41, df = 1 (P = 0.52); I² = 0%
Test for overall effect: Z = 15.97 (P < 0.00001)



E.

Study or Subgroup	Combination Mean	SD	Total	Tamsulosin Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Choi 2016	-0.24	0.55	59	0.17	0.19	59	49.6%	-0.41 [-0.56, -0.26]
Joo 2012	-0.73	0.68	98	-0.06	0.22	95	50.4%	-0.67 [-0.81, -0.53]
Total (95% CI)			**157**			**154**	**100.0%**	**-0.54 [-0.80, -0.29]**

Heterogeneity: Tau² = 0.03; Chi² = 6.16, df = 1 (P = 0.01); I² = 84%
Test for overall effect: Z = 4.16 (P < 0.0001)

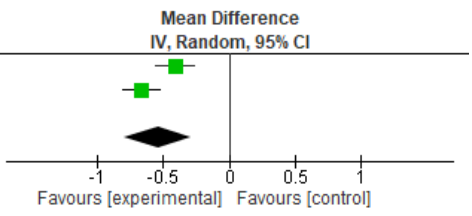


Figure 3. Forest plot of combination therapy vs. Tamsulosin for outcomes of IPSS (A), PV (B), Qmax (C), TZV (D), and PSA (E).

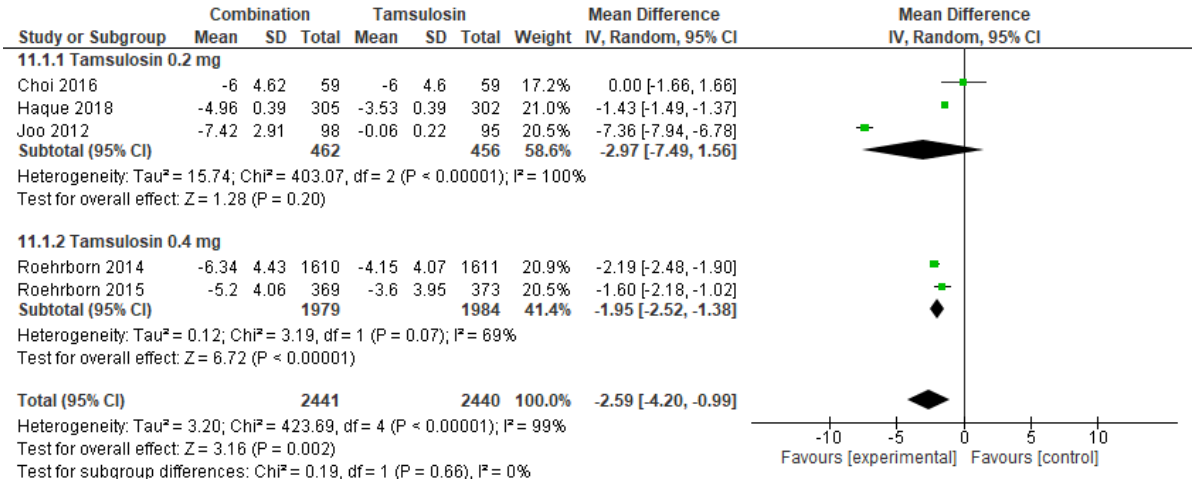


Figure 4. Forest plot of combination therapy vs. Tamsulosin based on dosage for outcomes of IPSS

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