REVIEW PAPER

FUNCTIONAL UROLOGY

Comparative efficacy and safety of silodosin and tadalafil combination or monotherapy for treating lower urinary tract symptoms due to benign prostatic obstruction: A systematic review and meta-analysis

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Introduction Over the last few years, trends in managing benign prostatic hyperplasia (BPH) have improved, advancing from reliance on surgery to satisfactory medical therapies. However, the efficacy and safety of combination therapies, including silodosin and tadalafil, are not well established compared to monotherapy for treating lower urinary tract symptoms (LUTS) due to benign prostatic obstruction (BPO).

Material and methods A systematic search was conducted in PubMed, ScienceDirect, Cochrane Library, and Scopus up to April 1, 2024. The quality of the studies was assessed using The Cochrane Risk of Bias (RoB) Tools 2 and Risk of Bias in Non-randomized Studies of Exposures (ROBINS-E). Meta-analysis was conducted using RevMan 5.4.

Results A total of 1,300 records were screened, resulting in 7 final studies. Our meta-analyses showed that international prostate symptom score (IPSS), maximum urine flow rate (Q_{max}), and postvoid residual volume (PVR) led to considerably greater improvements with the combination of silodosin and tadalafil compared to using either as monotherapy. However, combination therapy notably exhibited higher rates of adverse events (AE). On the other hand, as monotherapy, silodosin demonstrated a statistically significant improvement in Q_{max} ($p = 0.006$) and PVR ($p = 0.02$) over tadalafil but with higher rates of total AE, discontinuation, and risk of retrograde ejaculation.

Conclusions Silodosin and tadalafil are effective for treating LUTS in men due to BPO, especially when used in combination. However, with concerns about safety, tadalafil as monotherapy offers an advantage for patients with fertility desires due to its favorable side effect profile.

Key Words: benign prostatic obstruction ‹› lower urinary tract symptoms ‹› meta-analysis ‹› silodosin ‹› tadalafil

INTRODUCTION

Urology deals with both benign and malignant illnesses of the urinary tract and the genital system. With increasing age, men often experience dissatisfactory changes in their urinary system, particularly related to the continuous growth of the prostate gland. The majority of individuals with urological problems experience a decline in quality of life (QoL), which eventually results in a financial burden [1]. Benign prostatic hyperplasia (BPH), a disorder characterized by the enlargement

of the prostate gland, is a prevalent diagnosis in urology, affecting over 80% of men as they age. Over the last few years, trends in the management of BPH have improved, advancing from reliance on surgery to satisfactory medical therapies [2].

The utilisation of α-androgenic receptor blockers remains a fundamental therapeutic strategy for managing urological disorders, with silodosin being the preferred choice among α-blockers for treating lower urinary tract symptoms (LUTS) due to benign prostatic obstruction (BPO) because of its strong 1A uroselectivity. A number of recent studies shows that silodosin is effective in treating a wide range of urological conditions [3].

On the other hand, tadalafil, a medication that inhibits the enzyme phosphodiesterase type 5 (PDE5i), has demonstrated its effectiveness in many controlled clinical trials involving LUTS due to BPO individuals with and without erectile dysfunction (ED) [4]. Given its demonstrated efficacy in treating both ED and BPH at the recommended dose of 5 mg per day, this medication offers significant therapeutic benefits for individuals seeking management for multiple urologic conditions [5]. The effectiveness of PDE5 inhibitors in combination with α-blockers for reducing LUTS has also been evaluated. Current research has demonstrated that this regimen offers advantageous additional benefits compared to a single therapy [6]. Therefore, the possibility of treating LUTS with or without ED using tadalafil alone or in combination with α-blockers may lead to the development of novel and more specific therapeutic approaches.

The effectiveness and safety of combined therapies like silodosin and tadalafil for treating LUTS due to BPO have yet to be widely recognized. To date, there is no published meta-analysis evaluating this combination treatment in BPH individuals. Thus, we aim to assess the effectiveness and safety of these combined therapies compared to monotherapy for managing LUTS associated with BPH.

MATERIAL AND METHODS

Search strategy

Two authors conducted a comprehensive search and analysis of all clinical studies (randomized controlled trials or observational studies) that examined the effectiveness and safety of combining silodosin and tadalafil, as well as their monotherapies. The search included databases such as PubMed, ScienceDirect, Scopus, and Cochrane Library, covering the period from the beginning until April 1st, 2024. The following keywords were employed by combining several terms including "Silodosin, Tadalafil, Benign Prostatic Hyperplasia (BPH) or Benign Prostatic Enlargement (BPE) or Benign Prostatic Obstruction (BPO) and LUTS". An additional database was utilized to conduct a comprehensive search for other studies. This study did not have any restrictions based on country or publication year. The protocol of this meta-analysis was registered in PROSPERO (CRD42024576429). This study also followed the guideline of Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA 2020 guidelines) [7].

Eligibility criteria

This systematic review and meta-analysis included studies which met the following criteria: (1) the study either randomized or non-randomized controlled trials; (2) the study evaluated a comparison of combination therapy with silodosin and tadalafil vs silodosin monotherapy or tadalafil monotherapy for treatment of LUTS in men due to BPO; (3) the study provided precise information, mostly consisting of the quantity of subjects and the valuable outcomes of indicators; (4) full-text content and related data can be obtained; and (5) article available in English language. Studies presented as abstracts, review articles, and case reports were excluded from the analysis.

Selection process

Duplicate studies were identified and excluded after the initial search. The titles and abstracts of the remaining literature were screened by at two independent reviewers to determine eligibility. Studies meeting the criteria were included, while those which were not were excluded. Conflicts in study classification were resolved through group discussion.

Data extraction

Each study was reviewed by independent reviewers, and the following information was gathered for each study: (1) first author name; (2) publication date; (3) the type of study design; (4) patients description; (5) therapies received by patients, including dosage and treatment duration; (5) The number of individuals in all groups; (6) age, and (7) Furthermore, data related to the total International Prostate Symptom Score (IPSS), maximum urine flow rate (Q_{max}), postvoid residual volume (PVR), International Index of Erectile Function (IIEF), any adverse event (AE) and incidences of discontinuation that occurred as a result of AE.

Quality assessment

Two authors conducted an independent assessment of all the inclusion studies that were identified. In case of any disagreement between the authors, a third reviewer was included to resolve the issue. The Cochrane Risk of Bias (RoB) Tools 2 were used to evaluate the RCT study investigation. Risk Of Bias in Non-randomized Studies of Exposures (ROBINS-E) was used in the assessment of retrospective/observational study. Risk-of-bias VISualization (robvis) was used for the visualization of risk of bias graph [8].

Statistical analysis

The data obtained were processed using Review Manager 5.4 (Cochrane Collaboration, UK). We utilized the differences in data between the baseline and the end-point measure to assess changes in the outcomes. Mean difference (MD) was used to analyze continuous data, whereas the odds ratio (OR) was used for dichotomous outcomes with the corresponding 95% confidence interval (CI). The heterogeneity of the statistical analysis was seen in the I^2 value. The fixed-effects model is used if $I^2 < 50\%$, while the random-effects model is used if $I^2 \geq 50\%$. The results will be presented in a forest plot, and the overall effect is considered significant if $p < 0.05$. Asymmetry tests, including Egger's test for assessing potential publication bias via funnel plots, were not performed due to their restricted reliability in meta-analyses comprising less than 10 studies [9]. Furthermore, because of small number of studies, subgroup analysis and sensitivity analysis were also not conducted [10].

RESULTS

Literature search, screening results and characteristic of studies

From various databases, 1.300 studies were initially identified using keywords. Furthermore, we discovered two additional studies outside of the databases that were relevant to the topic, resulting in a final total of 1,302 studies. After removing 168 duplicates, two reviewers conducted independent assessments of the remaining 1,132 study titles and abstracts. Based on the inclusion and exclusion criteria, we removed 1,284 articles. Following a detailed examination of the full article, we excluded seven articles because of insufficient data or failure to match the study criteria. Finally, seven studies [11–17] were included in our analysis, consisting of five RCTs [11, 14–17] and two observational studies [12, 13], with a total of 1.208 patients. Full details of the search and selection process are presented in the PRISMA flow diagram (Figure 1) and the characteristics of these studies are presented in (Table 1).

Quality assessment result

The Cochrane RoBTools 2 was used to evaluate the RCT study investigation. ROBINS-E was used in the assessment of retrospective/observational study. The Cochrane RoBTools 2 was used to evaluate 5 RCT studies consist of 5 domains [18] and ROBINS-E evaluated 2 observational studies consist of 7 domains [19]. Overall risk-of-bias judgement of these instruments was classified into 3 groups which low bias risk (If the study is determined to have a minimal risk of bias in all areas), some concerns (if there is any apprehension in at least one area) and high bias risk (if the study is determined to have a significant risk of bias in at least one area). Out of the RCT studies, four [11, 14–16] raised some concern, primarily due to the lack of blinding among personnel to the intervention in domain D2, which refers to the risk of bias due to deviations from the intended interventions. All of the observational studies were classified as low risk of bias. The detailed assessment of the risk of bias was shown in supplementary materials.

Statistical analysis

Total IPSS

Total IPSS from two studies comparing the efficacy of the combination group vs silodosin showed that the combination revealed a marked decline in total IPSS (MD = –1.51; 95% CI: from –2.18 to –0.84; $p < 0.00001$) compared with the silodosin group (Figure 2A). Furthermore, three studies comparing combination group vs tadalafil also exhibited a significant decline in the combination group (MD = –2.76; 95% CI: from –3.66 to –1.86; $p < 0.00001$) relative to the tadalafil group (Figure 3A). Furthermore, an analysis of five studies comparing the effectiveness of silodosin and tadalafil found no statistically significant disparity in the total International Prostate Symptom Score (IPSS) between these monotherapies (MD = –0.89; 95% CI: from –1.85 to –0.06; $p = 0.07$; Figure 4A).

Q_{max}

Two trials comparing the combination group with silodosin monotherapy showed that the combination

Table 1. *Characteristics of included study*

No	Study (author, ref.)	Study design	Population	Intervention			Treatment duration	Mean age (years)	Total sample (each group)	Outcome assesments				Adverse event
				Combination	Silodosin monotherapy	Tadalafil monotherapy				IPSS Total	Q_{max} [ml/s]	PVR [ml]	IIEF Score	
1	Yoshida et al. 2017 [11]	RCT	Men ≥60 years old with LUTS due to BPO and IPSS ≥13	-	Silodoson 8 mg/day	Tadalafil 5 mg/day	8 weeks	70.1	Total sample: 181 (89 silodosin /92 tadalafil)	✓	✓	✓	–	Headache, orthostatic hypotension, retrograde ejaculation, etc.
2	Yoshida et al. 2017 [12]	Retrospective study	Men ≥50 years of age with a history of LUTS secondary to BPO and IPSS >8	Silodosin 8 mg/day plus Tadalafil 5 mg/day	Silodoson 8 mg/day	-	8 weeks	76	Total sample: 101 (50 silodosin plus tadalafil /51 silodosin)	–	–	–	–	Headache, palpitation, dyspepsia, etc.
3	Singh et al. 2018 [13]	Prospective observational study	Men >45 years old with LUTS due to BPO	Silodosin 8 mg/day plus Tadalafil 5 mg/day	Silodoson 8 mg/day	Tadalafil 5 mg/day	12 weeks	60.33	Total sample: 45 (15 combination /15 silodosin /15 tadalafil)	✓	✓	✓	–	Orthostatic hypotension
4	Vajpeyi and Chipde 2019 [14]	RCT	All men patients with LUTS due to BPO	-	Silodoson 8 mg/day	Tadalafil 5 mg/day	4 weeks	NR	Total sample: 100 (50 silodosin /50 tadalafil)	✓	–	–	–	NR
5	Abdelrazek et al. 2021 [15]	RCT	All men patients with LUTS due to BPO and ED	Silodosin 8 mg/day plus Tadalafil 5 mg/day	Silodoson 8 mg/day	Tadalafil 5 mg/day	12 weeks	62.4	Total sample: 308 (105 combination /102 silodosin /101 tadalafil)	✓	✓	✓	✓	Headache, orthostatic hypotension, retrograde ejaculation, etc.
6	Abdallah et al. 2023 [16]	RCT	Men ≥45 years old with LUTS due to BPO with or without ED and IPSS ≥13	-	Silodosin 8 mg/day	Tadalafil 5 mg/day	12 weeks	58.7	Total sample: 97 (50 silodosin /47 tadalafil)	✓	✓	–	✓	Headache, orthostatic hypotension, retrograde ejaculation, back pain, etc.
7	Avinash et al. 2024 [17]	DBRCT	All men patients with LUTS due to BPO with IPSS ≥13 and ED with IIEF-EF ≤25	Silodosin 8 mg/day plus Tadalafil 5 mg/day	-	Tadalafil 5 mg/day	12 weeks	NR	Total sample: 376 (186 combination /196 tadalafil)	✓	–	–	–	NR

BPO – benign prostatic obstruction; CI – confidence interval; DBRCT – double blind randomized controlled study; ED – erectile dysfunction; IIEF-EF – International Index of Erectile Function-Erectile Function; IPSS – International Prostate Symptom Score; LUTS – lower urinary tract symptoms; NR – not reported; PVR – post-void residual urine; Qmax – maximum urine flow rate; RCT – randomized controlled trial

group had a significantly higher Q_{max} compared to silodosin used alone (MD = 0.68; 95% CI: 0.11–1.24; p = 0.02; Figure 3A). In the combination group vs tadalafil, two studies also exhibited that the combination group was superiorly related to tadalafil (MD = 1.50; 95% CI: 0.97–2.04; p <0.00001; Figure 3B). In addition, Q_{max} from three studies that compared monotherapy between silodosin vs tadalafil revealed that there was a significant difference in Q_{max} in the silodosin group in compare to tadalafil (MD = 1.40; 95% CI: 0.40–2.40; p = 0.006; Figure 4B).

PVR

Two studies revealed that patients who received combination intervention had a significantly reduced PVR compared to the silodosin (MD = –2.19; 95% CI: from –3.93 to –0.45; p = 0.01; Figure 2C), as well as two studies compared to the tadalafil (MD = –4.40; 95% CI: from –6.24 to –2.57; p < 0.00001; Figure 3C). In addition, PVR from three studies that compared silodosin vs tadalafil revealed that silodosin is suggested to have more benefit at reducing PVR than tadalafil (MD = –2.14; 95% CI: from –3.97 to –0.31; p = 0.02; Figure 4C).

IIEF

There were only two studies that assessed the IIEF score and it is only in the silodosin vs tadalafil group. The random effects model showed that there was no significant difference in IIEF score changes between these monotherapy groups (MD = –0.04; 95% CI: from –1.38 to –1.30; p = 0.96; Figure 4D).

Safety: total adverse events, discontinuation due to adverse events and retrograde ejaculation

Three studies in the combination vs silodosin group, two studies in combination vs tadalafil group and four studies in silodosin vs tadalafil group assessed the number of total AE. Tadalafil monotherapy demonstrated a lower frequency of AE compared to the combination therapy (OR = 3.09, 95% CI: 1.57–6.09, p = 0.001; Figure 2D), but did not meet statistical significance compared to silodosin (OR = 1.22, 95% CI: 0.70, 2.10, p = 0.48; Figure 3D).

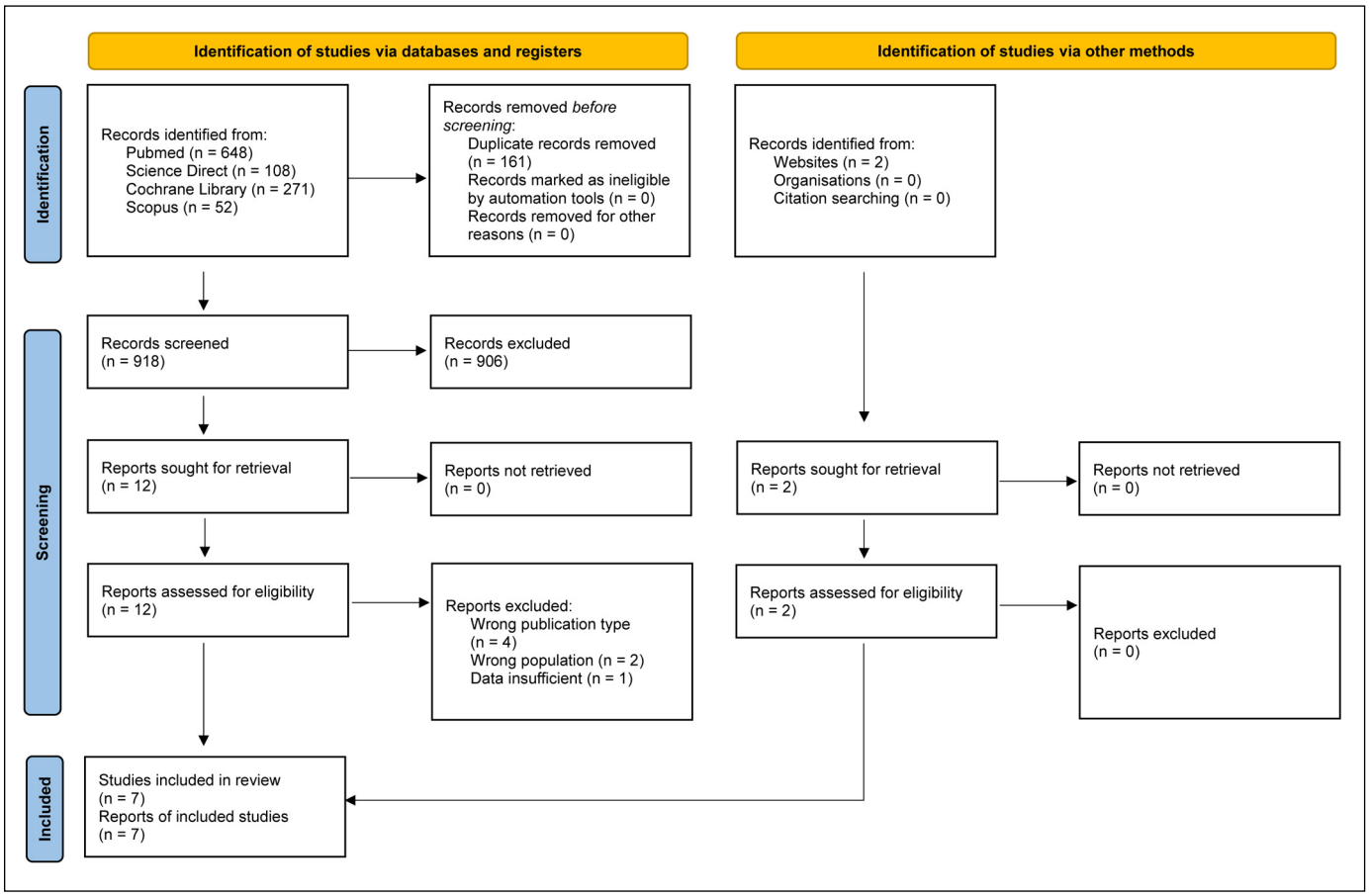


Figure 1. *Preferred reporting items for systematic reviews and meta-analyses flow chart.*

When comparing the monotherapy to total AEs, it was found that silodosin produced a higher incidence of AE compared to tadalafil (OR = 2.34, 95% CI: 1.49–3.68, p = 0.0002; Figure 4E). Regarding the events of discontinuation due to AE, all studies in combination vs silodosin (OR = 1.74,

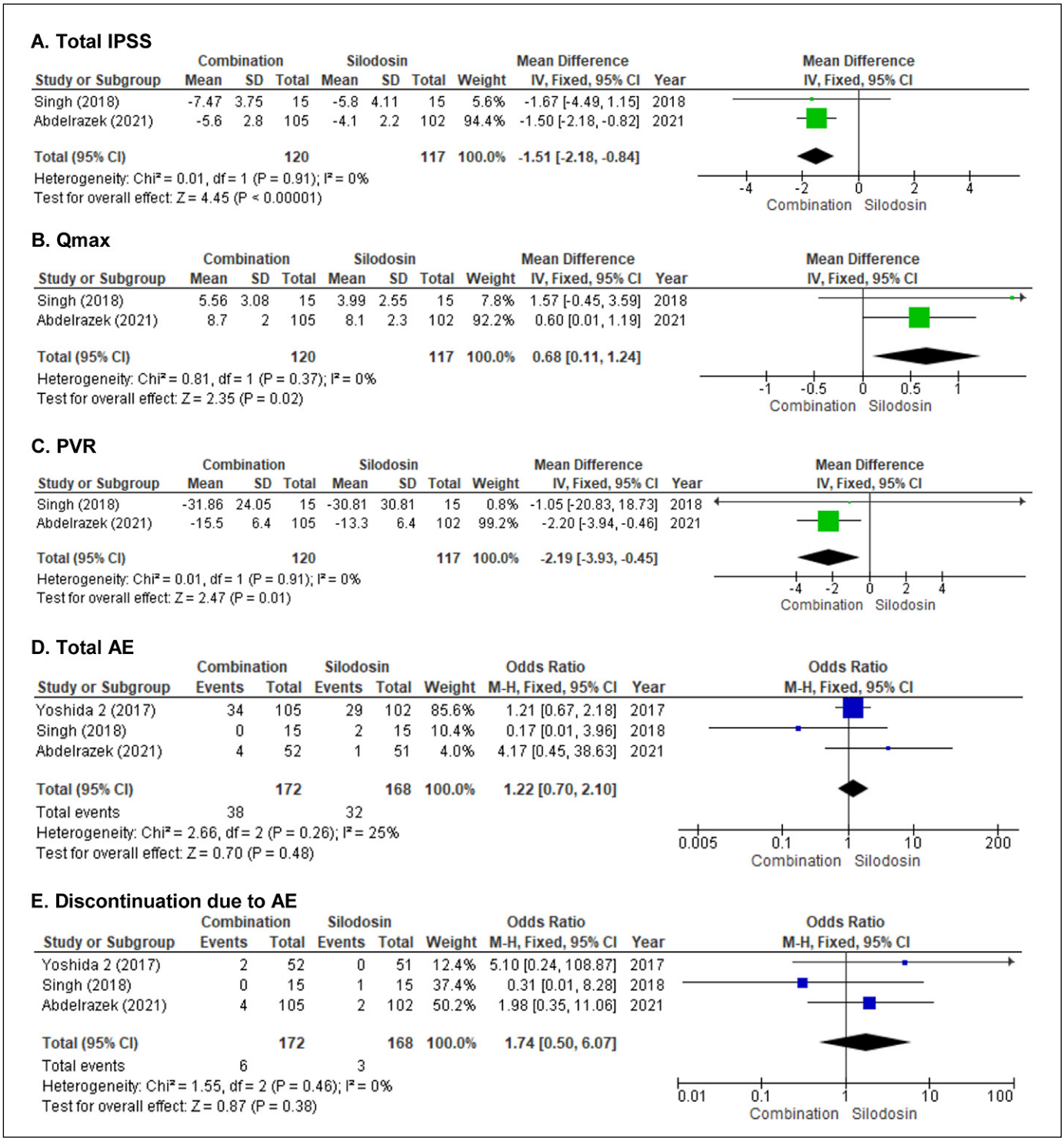


Figure 2. *Forest plot comparing the change between combination therapy versus silodosin monotherapy:* **A)** *total IPSS;* **B)** *Q_{max};* **C)** *PVR,* **D)** *total AE; and* **E)** *discontinuation due to AE.*

AE – adverse events; CI – confidence interval; IPSS – International Prostate Symptom Score; IV – inverse variance; Q_{max} – maximum urine flow rate; PVR – post-void residual; SD – standard deviation

95% CI: 0.50–6.07, p = 0.38; Figure 2E), combination vs tadalafil (OR = 6.21, 95% CI: 0.72–53.28, p = 0.10; Figure 3E), and silodosin vs tadalafil (OR = 4.16, 95% CI: 0.45–38.46, p = 0.21; Figure 4G) did not meet statistical significance. In addition, we also assessed the rate of retrograde ejaculation

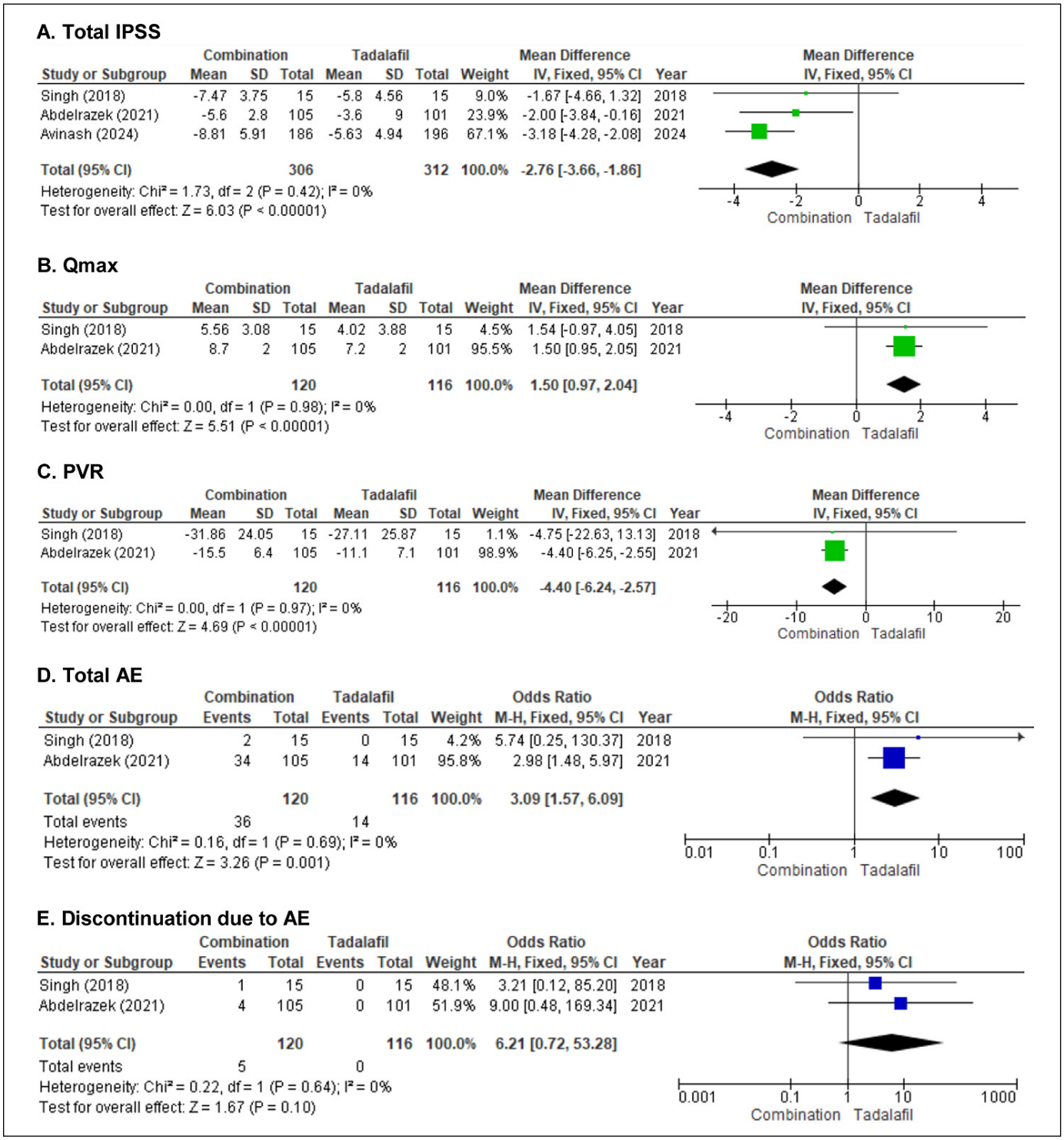


Figure 3. *Forest plot comparing the change between combination therapy versus tadalafil monotherapy:* **A)** *total IPSS;* **B)** *Q_{max};* **C)** *PVR;* **D)** *total AE; and* **E)** *discontinuation due to AE.*

AE – adverse events; CI – confidence interval; IPSS – International Prostate Symptom Score; IV – inverse variance; Q_{max} – maximum urine flow rate; PVR – post-void residual; SD – standard deviation

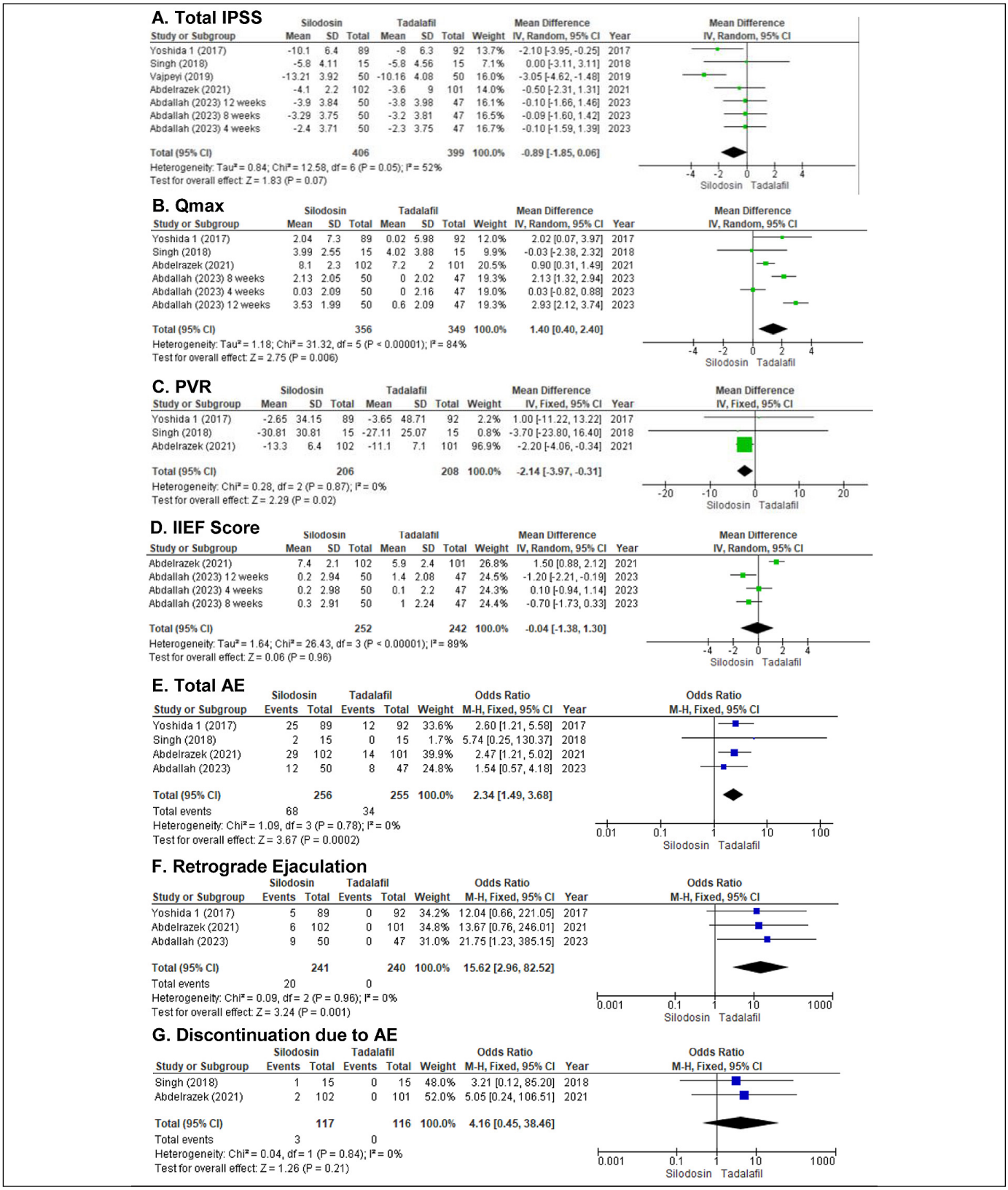


Figure 4. *Forest plot comparing the change between silodosin versus tadalafil monotherapy:* **A)** *total IPSS;* **B)** *Q_{max};* **C)** *PVR;* **D)** *IIEF score;* **E)** *total AE;* **F)** *retrograde ejaculation; and* **G)** *discontinuation due to AE.*

AE – adverse events; CI – confidence interval; IIEF – The International Index of Erectile Function; IPSS – International Prostate Symptom Score; IV – inverse variance; Q_{max} – maximum urine flow rate; PVR – post-void residual; SD – standard deviation

as a complication in the silodosin vs tadalafil group, which showed an absolutely higher incidence of retrograde ejaculation in the silodosin group compared to tadalafil (OR = 15.52, 95% CI: 2.96–82.52, p = 0.001; Figure 4F).

DISCUSSION

The results of this meta-analysis demonstrated that the combination therapy of silodosin and tadalafil provided greater improvement in LUTS due to BPO compared to either silodosin or tadalafil monotherapy as more significant reduction in both IPSS and PVR values as well as improvement in Q_{max} in the combination group. Generally, LUTS among patients are attributed to both static and dynamic components [20]. Static obstruction results from the direct effect of an enlarged prostate, causing periurethral compression and obstruction of the bladder outlet. The enlarged prostate distorts the bladder outlet causing urinary obstruction, while the periurethral compression result in increased pressure during urination to overcome the resistance to urine flow [21] Moreover, the dynamic component is caused by a decrease in elasticity and collagen in the prostatic urethra in BPH patients, which causes tension in the smooth muscles of the prostate and urethra. This explains the reason why the size of the prostate is not a constant indicator of BPH [22].

Silodosin is an α adrenoreceptor antagonist that is highly selective for α1A, which has a dominant effect in regulating smooth muscle tone in the prostate and prostatic urethra. A study reported that the affinity of silodosin for the α1A receptor is 593 times greater than for the α1B receptor and 57 times greater than for the α1D receptor. This shows that silodosin has high uroselective and is effective for the treatment of LUTS due to BPO [23]. In addition, Tadalafil is one of the PDE5-i groups which is able to inhibit the degradation of cGMP thereby increasing the activation of protein kinase, triggering the relaxation of smooth muscle in the prostatic urethra [24]. Previous studies reported that PDE5-I can enhance the action of α blockers by increasing NO mediated relaxant in penile smooth muscle, prostate, and bladder neck. *In vitro* studies by Angulo et al. on human prostate cells also showed that administration of tadalafil alone did not have any effect on nerve-mediated contraction of human prostate, whereas when combined with silodosin there was an inhibitory effect on nerve-mediated contraction, this demonstrates that the concurrent use of silodosin and tadalafil produces an additional effect on reducing muscle tone through inhibition of sympathetic tone [24, 25]. The results of this meta-analysis are supported by evidence from previous studies which reported that the combination of silodosin and tadalafil has a superior effect compared to silodosin or tadalafil monotherapy in the treatment of LUTS due to BPO.

Findings from this meta-analysis also indicated that there is no statistically significant difference in IIEF scores between the consumption of silodosin and tadalafil in combination therapy. However, only one study reported a comparison of the effectiveness of combination therapy with monotherapy on IIEF scores. The study indicated that the combination of silodosin and tadalafil yielded significantly superior results combination approach in comparison to using silodosin or tadalafil monotherapy [26]. Further research on a larger scale is still needed to learn more about the effects of this combination therapy on erectile function in men.

The relationship between IPSS, which reflects patient-perceived symptoms, and objective parameters like Q_{max} and PVR is essential in evaluating the effectiveness of therapy for BPH. Several studies have shown that although alpha blockers significantly reduce LUTS as measured by IPSS, improvements in Q_{max} and PVR are less consistent [27, 28]. For instance, a meta-analysis by Guo et al. involving 22 studies found that α-blockers reduced IPSS significantly compared to placebo but showed no significant difference in Q_{max} improvement when compared to PDE5-inhibitors like tadalafil (SMD: –0.59, 95% CI: from –1.73 to 0.54; p = 0.30) [28]. Another study also indicated that although the combination of α-blockers and PDE5 inhibitors gave better results in terms of IPSS reduction, the improvements in Qmax and PVR were not always in line with patients' perception of their symptoms [27]. The α-blockers appear to be more effective in alleviating subjective symptoms than in improving objective parameters. Therefore, evaluating both subjective and objective outcomes is essential for a comprehensive assessment of therapy effectiveness in managing LUTS due to BPO. Our analysis showed that combining silodosin with tadalafil was more effective in improving both subjective and objective parameters compared to using monotherapy. This suggests that while alpha blockers like silodosin effectively improve patients' conditions, adding tadalafil may provide additional benefits. Nonetheless, tadalafil remains a good option for patients prioritizing the preservation of sexual function due to its favorable side effect profile.

In terms of safety and side effects, the results of this meta-analysis showed that there was no sig-

nificant difference in the total incidence of adverse events between combination therapy and silodosin monotherapy. However, a significant difference was found between the total incidence of adverse events in the combination group compared to the tadalafil group alone. These results indicate that combination therapy has a slightly higher risk of adverse events compared to tadalafil monotherapy. The most common adverse events are headache, retrograde ejaculation, and orthostatic hypotension. The very high affinity of silodosin for 1A makes silodosin work very focused on smooth muscle in the bladder neck and proximal urethra, which has been shown to be able to reduce LUTS in the dynamic aspect. However, weakness in the bladder neck and proximal urethra muscles will increase the likelihood of retrograde ejaculation [29]. In addition, with spesific affinity of silodosin which focuses on α1A, the risk of orthostatic hypotension is significantly low [30]. However, when silodosin is combined with tadalafil, the risk of orthostatic hypotension tends to increase due to the effect of tadalafil which causes systemic vasodilation, thereby reducing peripheral systemic resistance [31]. Overall, there were no fatal and dangerous adverse events reported in all included studies, even the results of other meta-analyses in this study showed that there was no significant difference in the number of patients who discontinued due to AE between the combination group with silodosin or tadalafil monotherapy. Although the risk of adverse events remains, considering its effectiveness, we consider that the combination of silodosin and tadalafil has a very positive effect and safe on improving LUTS due to BPO and also well tolerated in BPH patients with or without ED. Patients with special conditions such as a history of hypotension or heart failure need to get special considerations before receiving the combination therapy of silodosin and tadalafil.

Medical therapy is widely accepted as the first-line treatment for LUTS due to BPO. However, when medication fails to provide adequate symptom relief, invasive and minimally invasive treatment options may be considered [32]. Furthermore, minimally invasive methods such as botulinum toxin injections have recently demonstrated efficacy in managing patients with BPH and neurogenic detrusor overactivity (NDO) [33, 34].

We acknowledge that this study still has several limitations, including the limited number of included studies and the variability of outcomes assessing LUTS in BPH patients. To minimize these limitations, we reviewed all reported outcomes to produce a comprehensive analysis. Based on the findings of this meta-analysis, we recommend using a combination of silodosin and tadalafil as a treatment for individuals with LUTS due to BPO, especially in cases where monotherapy is ineffective. The synergistic effect of silodosin and tadalafil is expected to improve LUTS and thus improve the quality of life of BPH patients. However, we do not recommend this combination therapy for patients who want to have children because of the risk of retrograde ejaculation due to the effects of silodosin.

CONCLUSIONS

The combined therapy shown greater effectiveness in treating LUTS due to BPO compared to the individual treatments of silodosin or tadalafil. While combination therapy resulted in a higher occurrence of AE compared to monotherapies, these effects were well tolerated. However, tadalafil monotherapy is preferred for patients who want to retain fertility due to its favorable side effect profile.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

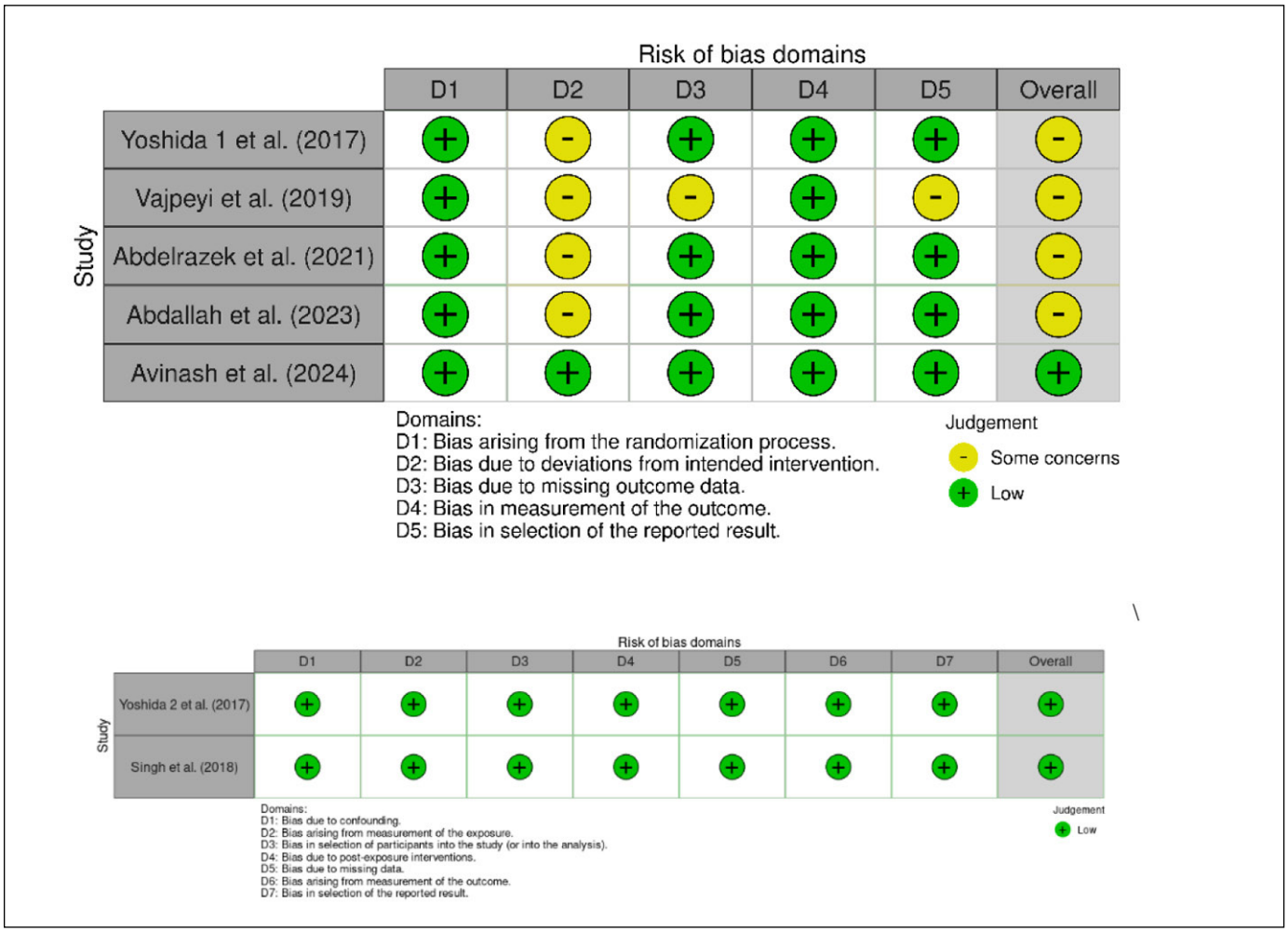
FUNDING

This research received no external funding.

ETHICS APPROVAL STATEMENT

The ethical approval was not required.

SUPPLEMENTARY MATERIALS



Suppl. Figure 1. *Risk of bias assessment using the Cochrane Risk of Bias (RoB) Tools-2 and the Risk of Bias in Non-randomized Studies of Exposures (ROBINS-E).*

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