

Tamsulosin and Dutasteride Combination Therapy for Asian Men With Moderate-to-Severe Lower Urinary Tract Symptoms Secondary to Benign Prostatic Hyperplasia: A Systematic Review of Clinical Considerations That Influence the Prescription

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Abstract

The goal of combination therapy for moderate-to-severe lower urinary tract symptoms secondary to benign prostatic hyperplasia (LUTS/BPH) is to ease both the dynamic and static symptoms by using agents that have complementary mechanisms of action. Similar to prescribing other drugs, LUTS/BPH combination therapy has been affected by multiple factors. Previous qualitative research discussed the individual perspectives that influenced combination therapy administration. Yet, until recently, there has been limited interest in clinical reasons that physicians have to consider before prescribing LUTS/BPH combination treatment. This systematic review aimed to identify the clinical considerations that influence the decision to prescribe combination therapy of tamsulosin 0.4 mg + dutasteride 0.5 mg for Asian men with LUTS/BPH. This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A systematic search was performed in databases Medline, CINAHL, the Cochrane Library, and Embase from inception until January 2024 using Medical Subject Headings (MeSH) terms and keywords with truncation for alternative acronyms. A citation search was performed to gather works of literature on LUTS/BPH combination treatment in addition to the “PICO” framework for search terms. Five English-language primary randomized controlled trials (RCTs) were included in the narrative analysis using the Critical Appraisal Skills Program (CASP) checklist after critical appraisal. Several dosages of tamsulosin (0.2 mg and 0.4 mg) have been administered in LUTS/BPH combination treatment over the last few decades despite 0.2 mg tamsulosin being standardized as an effective regime in Asian countries. A remarkable correlation between prostate volume (PV) and prostate-specific antigen (PSA) was found in Asian

men, which requires higher PSA secretion to enlarge each prostate unit and causes an increased risk of moderate-to-severe LUTS. Additionally, BPH baseline variables may lead to a different response to combination therapy, especially the PV and PSA differences. In conclusion, compared with Caucasian men, a significantly higher risk of moderate-to-severe LUTS was found in Asian men. Initiation of combination therapy, especially dutasteride, depends on a larger PV (≥ 30 mL); it is possible, therefore, that earlier PV and PSA examinations and baseline variables assessments ought to be performed by physicians before the combination therapy prescription. Alternative treatment options may be considered for a patient who prefers an active pattern of sexual activity during their BPH combined pharmacotherapy. These clinical considerations may influence the prescription of tamsulosin 0.4 mg + dutasteride 0.5 mg combination therapy for Asian men with moderate-to-severe LUTS/BPH. This study was registered on PROSPERO (CRD42024575528).

Keywords: Clinical consideration; Combination therapy; Prescription; Lower urinary tract symptoms; Benign prostatic hyperplasia; Systematic review

Introduction

The presence of lower urinary tract symptoms secondary to benign prostatic hyperplasia (LUTS/BPH) is a classic clinical problem in males aged 45 years and above worldwide [1]. LUTS/BPH is indicated by a range of lower urinary tract dysfunction characterized by storage, voiding, and post-urination symptoms, which usually result in poor quality of life (QoL) [1, 2]. Prevalence of significant LUTS is often associated with aging, and typically owing to BPH begins around the 60s, while periurethral prostate enlargement could be as early as age 45 [3]. Some fundamental research mentions that approximately one in five men over the age of 45 suffer from a certain degree of BPH with an international prostate symptom score (IPSS) greater than or equal to 7 [4-6].

Investigating LUTS/BPH treatment is a continuing concern of its clinical management, which varies from watchful

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waiting to conservative therapy, minor procedures, and endoscopic or open surgery [7]. Men with unpleasant LUTS without complications from BPH, such as urinary retention, impaired kidney function, etc., are generally ideal candidates for medication treatment. Nevertheless, the clinical decisions for medication prescribing have been affected by multiple factors. Globally, there are few European countries' practice guidelines, and the urological clinical handbook of Asian countries recommends that highly urological selective alpha-1a adrenergic receptor antagonists (alfuzosin 5 mg, doxazosin 4 or 8 mg, terazosin 10 mg, tamsulosin 0.2 mg or 0.4 mg) and dual 5-alpha-reductase inhibitors (dutasteride 0.5 mg, finasteride 5 mg) are most commonly prescribed for men with moderate-to-severe LUTS/BPH in monotherapy and combination therapy [8-11].

However, in recent years, novel combination therapy of tamsulosin 0.4 mg + dutasteride 0.5 mg has been emphasized for its efficacy and safety in several randomized controlled trials (RCTs). Yet, its extensive administration was reported in those studies [12-16]. Previous qualitative studies have indicated that individual factors such as healthcare-seeking behaviors, previous experience with treatment, personal preferences and perspectives are all different. Those personal circumstances could influence the prescription of varied dosages of combination therapy [17-21]. In contrast, clinical considerations that affected the prescription of combination therapy for Asian men were not previously described [22].

Background

Benign prostatic hyperplasia (BPH), an exceptionally prevalent condition in older adults, is caused by the prostate smooth muscle and epithelial cells' abnormal proliferation in the transition zone (TZ) of the gland [7, 11, 23, 24]. On histopathology, the unnatural anatomy change of BPH has been described as prostate adenoma. By measuring the intravesical prostatic protrusion (IPP) and prostate volume (PV) under a transabdominal ultrasound, prostate adenoma can be diagnosed [11, 25-27]. When the prostate weighs less than 20 g and the maximum urinary flow rate (Q_{max}) is greater than 20 mL/s in a healthy man, the bladder neck is inverted; whereas in a man with clinical BPH, the bladder neck is deformed by prostate adenoma, and location of adenoma determines the shape of the bladder neck. In early detection of prostate enlargement, the physician may perform a digital rectal examination. Still, a more accurate measurement of the prostate is scanned by ultrasound. In transabdominal ultrasound, the PV is measured as an irregular round shape, which represents the prostate's clinical size, and abnormal enlargement can be detected here. Meanwhile, the prostatic protrusion is graded based on the millimeter IPP scores [11, 27]. Grade 3 IPP is always present with prostatic obstruction and less void when compared with grade 1; it can, therefore, be assumed that IPP is correlated to Q_{max}, which is measured through urination into an electronic uroflowmetry detector [11, 27, 28].

In clinical BPH, prostate gland enlargement usually first appears at age 45, but symptoms typically do not present until

about 20 years later [3]. Over time, as the progression of BPH manifests, there are varied degrees of LUTS [3]. Inappropriate urination is the emblematic symptom of LUTS, which is not considered a disease but may cause the following symptoms: storage (nocturia, frequency, urgency), voiding (poor urinary stream, hesitancy), and post-micturition (incomplete voiding) [10, 29-31]. Symptoms frequency and prostate hyperplasia worsen with age, leading to a decreased urine flow, an increased urinary tract infection (UTI), acute urinary retention (AUR), and the need for surgical treatment. These have negatively impacted male healthcare and QoL [20, 32].

Prevalence and management approaches of LUTS/BPH

In Asia, studies claim that the prevalence of moderate-to-severe LUTS/BPH has constantly risen over the past decade in males aged 45 years and above. A multiracial society with a large aging population has challenged the healthcare system [1]. It is paramount to address the suitability of LUTS/BPH treatment for Asian men. Thus, it gained massive attention in public health and urged the management of LUTS/BPH to become increasingly concretized, specific, and integrated. Based on the BPH progression and LUTS severity, management approaches range from observation to conservative treatment and endoscopic and invasive surgery. IPSS assessment has been used in primary care when general practitioners investigate the severity of a patient's BPH and QoL. In secondary care, a specialist consultation with urologists is needed if the condition changes rapidly and severely [7]. The three leading causes of LUTS/BPH have been proven to be dynamic, static, and compensatory. Consequently, the prevalent option is relieving the condition's dynamic and static components in combination therapy [2].

Rationale of alpha-1 blockers and 5-alpha reductase inhibitors (5ARIs)

Current evidence supports that alpha-1 adrenergic receptor antagonists or alpha-1 blockers block the alpha-1 adrenergic receptors (A1ARs: A1aAR, A1bAR and A1dAR), resulting in a relaxing of the smooth muscle tone, then alleviate the dynamic component of BPH. In addition, A1aAR comprises approximately 70% of A1ARs within the fibromuscular stromal cells of the prostate [3, 33]. Historically, urology selective and non-selective alpha-1a blockers were commonly prescribed for males with BPH [7, 11, 34, 35]. It has been noted that long-term studies state those agents have shown rapid onset of symptom relief and few severe adverse events [36, 37]. A slow-release alpha-1a blocker, tamsulosin, is now mainly prescribed for the treatment of BPH, and it has a relatively higher receptor selectivity to alpha-1a receptors, clinically demonstrating its efficiency and safety. Alpha-1a blockers work as a symptom reliever. However, they cannot inhibit the prostate's progressive growth while considering a long-term treatment.

Regarding the static symptoms of BPH, 5ARIs (finasteride and dutasteride) prevent the conversion of testoster-

one to dihydrotestosterone (DHT), and DHT is the essential hormone that promotes prostatic gland proliferation [38-40]. Thus, urological association guidelines in different countries highly recommend dutasteride and finasteride. They are both effective in inhibiting DHT, with dutasteride inhibiting type I and II enzymes over 90% of serum and intraprostatic DHT, and finasteride inhibiting type I enzyme around 70% of serum DHT and 85% of intraprostatic DHT [11, 41]. Additionally, dutasteride has a longer serum half-life of 5 weeks than finasteride's half-life of less than 1 day [38].

Tamsulosin 0.4 mg plus dutasteride 0.5 mg combination therapy

The goal of combination therapy for LUTS/BPH is to ease both the dynamic and static symptoms by using agents that have complementary mechanisms of action. Tamsulosin and dutasteride combination therapy is often prescribed to males with moderate-to-severe LUTS/BPH, who are at risk of disease progression, with dutasteride specifically recommended for individuals with larger prostates ($PV \geq 30$ mL) in a long-term treatment due to its slow onset of action [11, 35, 42-45]. Several necessary clinical trials have recently provided evidence that using tamsulosin 0.4 mg + dutasteride 0.5 mg combination therapy is effective and safe for males with moderate-to-severe LUTS/BPH at risk of disease progression [46-48]. Moreover, combination therapy is more efficient than using either agent alone in long-term treatment [10, 46-48].

In the scope of evidence-based practice, clinical considerations refer to the essential attention which physicians must be aware of or cautious about before making the critical decisions in their daily practice. A previous systematic review by Emberton [12] investigated patient factors that affect general medical treatment for LUTS/BPH. Besides, relevant Asian clinical guidelines have emphasized clinical considerations for LUTS/BPH monotherapy, but there has been no detailed analysis of prescribing combination therapy (A1aARAs and 5ARIs). Thus, this systematic review intends to explore further the clinical considerations that influence the prescription of tamsulosin 0.4 mg + dutasteride 0.5 mg combination therapy for treating moderate-to-severe LUTS/BPH in the background of the Asian population.

Methods

Study design

RCTs are prospective studies designed to evaluate the effectiveness of a new intervention or treatment. Randomization reduces bias and provides a rigorous method for examining cause-and-effect relationships between an intervention and its outcome [49]. This systematic review of clinical considerations for combination therapy prescription primarily reveals those utmost important considerations from available RCTs. Primarily, it allows a comprehensive analysis of the effectiveness of tamsulosin 0.4 mg + dutasteride 0.5 mg combination

therapy in comparison with varied doses of tamsulosin and dutasteride monotherapy. Secondly, within the Asian region, whether there are specific clinical reasons that physicians have to be aware of when this combination therapy is prescribed for Asian men needs to be addressed. Then, a systematic review of RCTs was performed using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [50-52]. This systematic review has been registered on PROSPERO (CRD42024575528).

Search strategy

Following the PRISMA guidelines, a systematic search was conducted in databases Medline (OVID), CINAHL, the Cochrane Library, and Embase (OVID) to identify eligible studies that were published up to January 2024. Overall, Medical Subject Headings (MeSH) and keywords related to lower urinary tract symptoms, BPH, combination therapy, alpha-1 blockers, 5ARIs, monotherapy with truncation for alternative acronyms were utilized in the search strategy (Supplementary Material 1, www.jocmr.org). Firstly, the search formula followed the "PICO" framework by indicating the "population" as Asian men who were diagnosed with moderate-to-severe LUTS/BPH, "intervention" as tamsulosin 0.4 mg + dutasteride 0.5 mg combination therapy, "comparator" as tamsulosin and dutasteride monotherapy, and "outcome" as clinical considerations [53]. Many studies regarding various combination therapies were retrieved while using terms "alpha-1 blockers" and "5-alpha reductase inhibitors" during the initial search process. Consequently, additional terms "tamsulosin" and "dutasteride" were added separately, as the current review focused on tamsulosin 0.4 mg + dutasteride 0.5 mg combination therapy. Secondly, the Boolean operators "OR" and "AND" were applied to combine each facet of search terms. Lastly, a citation search was performed with other sources to gather additional literature on LUTS/BPH combination treatment. The retrieval process was conducted by two reviewers independently, and disagreements were resolved by discussion among two reviewers.

Study selection criteria

Inclusion criteria were: 1) The research population is strictly restricted to Asian men aged 45 years and above with diagnosed moderate-to-severe LUTS/BPH [54-56]; 2) Additional criteria for IPSS scores of 8 and greater were included because of the extensive use of IPSS in assessing BPH globally; 3) In order to have a broad spectrum retrieve on relevant research, there were no limitation of the publication year of the study; 4) Conversely, the duration of the study in terms of the treatment cycle was restricted to at least 1 year because medication trials required an extended period for generating evidence regarding efficacy and safety [57]; 5) Most recent (≤ 12 years) RCTs were expected and preferable for review.

Exclusion criteria were: 1) Eliminated all other combination pharmacotherapy and monotherapy except tamsulosin 0.4 mg + dutasteride 0.5 mg, tamsulosin 0.2 mg + dutasteride

Table 1. Selection Criteria

Inclusion criteria	Exclusion criteria
Asian men who aged 45 years and above	Other non-tamsulosin + dutasteride combination therapy and either monotherapy
Moderate-to-severe LUTS/BPH	Diagnosed with other prostate condition simultaneously (prostatitis, prostate cancer, UTI) and other conditions that may lead to dysuria (neurogenic bladder, urethral stricture, etc.)
Diagnosed BPH with IPSS \geq 8	History of any current or prior relevant BPH treatments
Tamsulosin + dutasteride combination therapy treatment and either tamsulosin or dutasteride monotherapy	Non-English language studies
Long-term intervention for at least 1 year	
RCTs that conducted \leq 12 years ago	

LUTS/BPH: lower urinary tract symptoms secondary to benign prostatic hyperplasia; IPSS: international prostate symptom score; RCTs: randomized controlled trials; UTI: urinary tract infection.

0.4 mg and either tamsulosin 0.2/0.4 mg or dutasteride 0.5 mg monotherapy; 2) Presenting with other prostate issues (prostatitis, prostate cancer, UTI) and conditions that may lead to dysuria (neurogenic bladder, urethral stricture) simultaneously in the study were not considered; 3) History of any current or previous relevant administration of either monotherapy or combination therapy was excluded as this would interrupt the combination therapy cycle, validity of outcome, and rigorosity of study; 4) Studies that were published in non-English language were not included. The above selection criteria were summarized in Table 1 [54-57].

Screening and data collection

The electronic search yielded 84 studies, considering the inclusion and exclusion criteria. Two independent reviewers carefully screened the retrieved articles for initial eligibility for inclusion. The article selection and elimination process are illustrated in Figure 1, a mapping of the PRISMA flow diagram [50-52]. Data extraction was performed by two reviewers using standardized data collection sheet: 1) Author and publication year; 2) Study design; 3) Study intervention and control group; 4) Sample size and age profile; 5) Sample inclusion criteria; 6) Clinical outcomes; 7) Statistical analysis used; and 8) Clinical considerations summarized from study.

Quality and bias assessment

The quality of included seven RCTs has been appraised by two independent reviewers using the CASP checklist (Supplementary Material 2, www.jocmr.org) for RCTs that covers 11 questions, and the appraisal results are summarized in Table 2 [58, 59, 64-68]. Disagreements were solved with assistance from the third reviewer. Each question is answered with “yes”, “no”, or “cannot tell”. Two out of seven studies were excluded in the final data synthesis because of high bias, with a total score of “4” and “5”, respectively. A high attrition rate of 20.4% was noted in the RCT by Lee et al [58], which negatively impacted

the study’s validity. In contrast, Ngu et al [59] conducted an RCT with a lack of validity in the measurement of study intervention and a loss of comprehensive comparison between the intervention and control group, which caused an insignificant clinical meaning [60].

Data synthesis and analysis

Five studies were enrolled in the data analysis, which involved a narrative summary of the extracted data based on the effectiveness of relevant pharmacotherapy, and its specific clinical reasons. Attrition bias was assessed by two independent reviewers, who found only a lower drop-out rate of less than 5% in these five studies, as evidenced by CASP question 3 scoring “yes” for them [61]. Randomized allocation and fair treatment were strongly emphasized in all five studies. However, blinding is not always possible, as double-blinded, single-blinded, and open-label were designed in different studies, but they were fit in each study. They had no performance, selection, or detection bias [62]. Also, all five studies’ outcomes or findings were reported verily without bias [63]. Discussion and consultation were carried out with a third researcher to solve the discrepancies.

Results

This systematic review aims to explore the clinical considerations that impact the prescription of combination therapy for LUTS/BPH. Eventually, five RCTs are included in the data extraction, as consolidated in Supplementary Material 3 (www.jocmr.org). From the selected five RCTs, clinical considerations seek to conclude those specific precautions by evaluating the prevalence and tendency of prescribing tamsulosin 0.4 mg + dutasteride 0.5 mg combination therapy, and discovering its adverse events and side effects via comparing it with various dosages of available drug formulations worldwide. Besides, baseline variables that affect the change of IPSS in combination therapy were found in one of those RCTs. Hence, a nar-

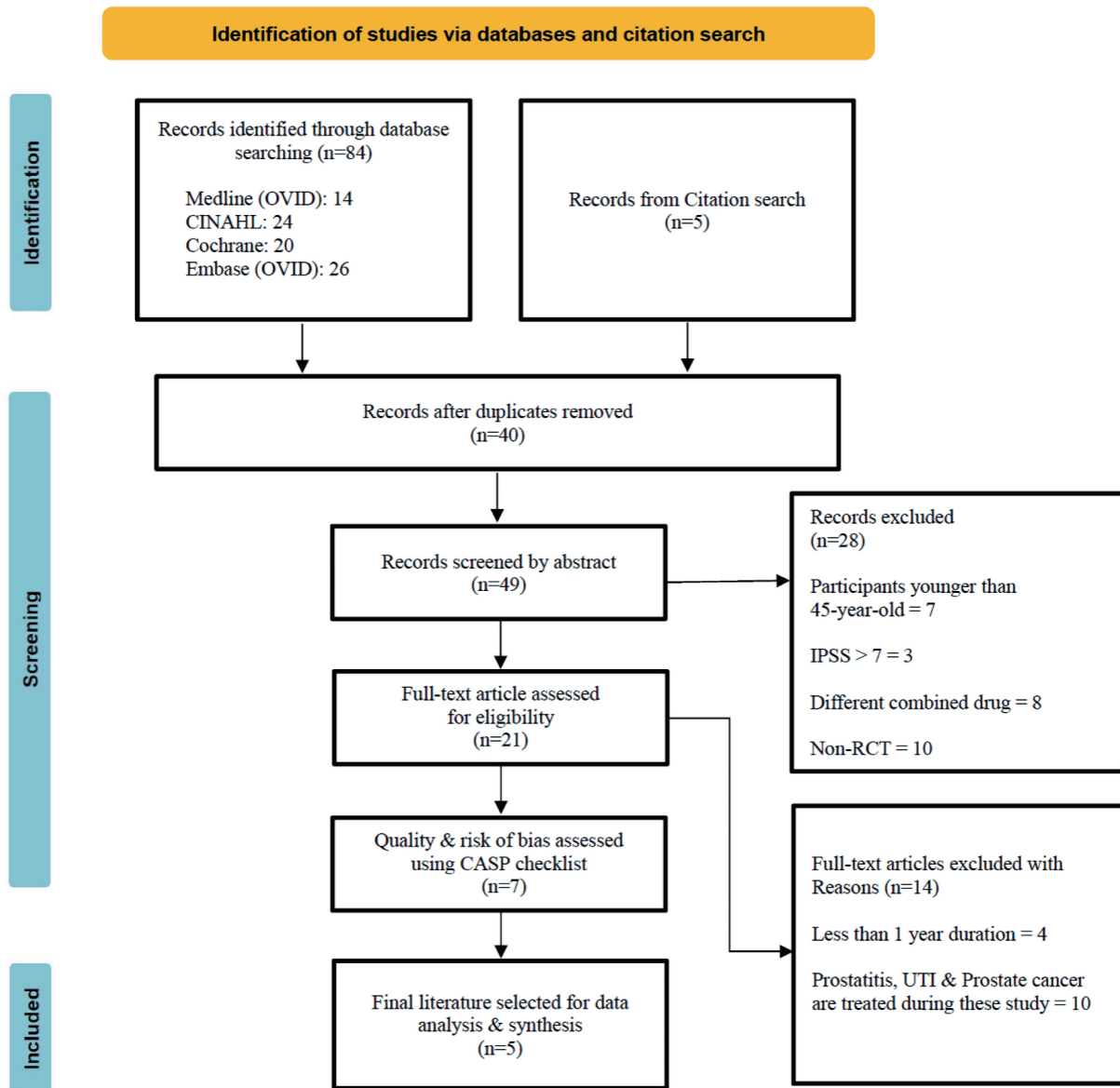


Figure 1. PRISMA flow diagram. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses. IPSS: international prostate symptom score; CASP: Critical Appraisal Skills Program; UTI: urinary tract infection; RCT: randomized controlled trial.

Table 2. Quality Assessment of RCTs Using CASP Checklist

Authors, year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	TS
Lee et al, 2012, [58]	Y	Y	N	N	Y	Y	N	CT	N	CT	CT	4
Chung et al, 2012 [64]	Y	Y	Y	Y	Y	Y	Y	CT	N	CT	Y	8
Roehrborn et al, 2014, [65]	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	10
Roehrborn et al, 2015, [66]	Y	Y	Y	N	Y	Y	Y	Y	N	CT	Y	8
Chung et al, 2018 [67]	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	10
Haque et al, 2018 [68]	Y	Y	Y	Y	Y	Y	Y	CT	N	Y	Y	9
Ngu et al, 2022 [59]	Y	Y	Y	N	Y	Y	N	CT	N	CT	CT	5

RCTs: randomized controlled trials; Q: question; CASP: Critical Appraisal Skills Program; Y: yes; N: no; CT: cannot tell; TS: total score.

rative analysis approach was subsequently used in the data synthesis process.

Comparison of clinical response to tamsulosin 0.4 mg + dutasteride 0.5 mg combination therapy between Asian and Caucasian population

Clinical findings suggested that BPH risk may vary by race and ethnicity. A post-hoc analysis of the combination of Avodart and tamsulosin (CombAT) study by Chung et al [64] compared the response to free combination (i.e., medications administered concomitantly) of tamsulosin 0.4 mg + dutasteride 0.5 mg between 325 Asian and 4,259 Caucasian men. Primary outcomes measured the incident percentage of AUR and BPH-related surgery in the second year. The results revealed that differences were not statistically significant between combination therapy (6.5%) and either monotherapy (tamsulosin 0.4 mg, $P = 0.27$, 10.7% and dutasteride 0.5 mg, $P = 0.092$, 4.9%) in the Asian subgroup. However, in the Caucasian subgroup, there was significantly lower incidence rate in combination therapy (4.1%) versus tamsulosin 0.4 mg monotherapy ($P < 0.001$, 12%); there was no statistically significant difference when compared with dutasteride 0.5 mg ($P = 0.074$, 5.5%). In the fourth year, secondary outcomes measured the clinical progression incident, IPSS change, Qmax increase, PV decrease, and QoL improvement. Overall, there was a significantly lower incidence rate of BPH clinical progression in combination therapy versus tamsulosin 0.4 mg monotherapy, which was observed in Asian (18.7% vs. 33%, $P < 0.05$) and Caucasian men (12.1% vs. 20.4%, $P < 0.05$). Also, a lower incidence rate of BPH clinical progression was noted in combination therapy versus dutasteride 0.5 mg monotherapy in Caucasian men (12.1% vs. 17.7%, $P < 0.05$), but not in Asian men (18.7% vs. 17.9%, $P = 0.072$). Besides, more remarkable improvements in IPSS, Qmax, and QoL and a more significant reduction in PV were found in combination therapy compared with tamsulosin 0.4 mg monotherapy in Asian and Caucasian men ($P < 0.05$). Similarly, greater improvements in IPSS, Qmax, and QoL were noted in combination therapy versus dutasteride 0.5 mg in Caucasian men, but there was no significant difference in Asian men. However, reduction of PV did not differ significantly between combination therapy and dutasteride 0.5 mg monotherapy in Asian and Caucasian men.

Comparison of clinical response to tamsulosin 0.4 mg + dutasteride 0.5 mg combination therapy among subgroups with varied baselines

The 4-year results of the CombAT study were examined by Roehrborn et al [65]. They attempted to examine the influence of baseline variables on changes in IPSS, Qmax, and QoL in patients with moderate-to-severe LUTS/BPH after free combination of tamsulosin 0.4 mg + dutasteride 0.5 mg or monotherapy of tamsulosin 0.4 mg and dutasteride 0.5 mg, respectively. Totally, 4,844 patients were enrolled in this RCT. Eight baseline subgroups were developed by authors based on

baseline variables of age, body mass index (BMI), BPH impact index (BII), PV, PSA, QoL, Qmax, and IPSS. Combination therapy reported a more remarkable constant improvement in IPSS, Qmax, and QoL than tamsulosin 0.4 mg monotherapy among all eight baseline subgroups at 48 months. In contrast, differences between combination therapy and dutasteride 0.5 mg monotherapy were varied in the PV and PSA subgroups compared with the other six subgroups, which observed that combination therapy has a better benefit over dutasteride 0.5 mg monotherapy in lower baseline of PV (< 60 mL) and PSA (< 4 ng/mL), but combination therapy and dutasteride 0.5 mg monotherapy provided similar benefits in higher baseline of PV (≥ 60 mL) and PSA (≥ 4 ng/mL) concerning improvements in IPSS, Qmax, and QoL.

At 48 months, combination therapy demonstrated a significant improvement in QoL. It was higher than the improvement seen in dutasteride 0.5 mg monotherapy with a lower baseline of PV (< 60 mL) and PSA (< 4 ng/mL), as well as higher than tamsulosin 0.4 mg monotherapy with PV baseline subgroup ≥ 40 mL and all PSA subgroups ($P \leq 0.01$). Overall, IPSS, Qmax, and QoL improved synchronously in combination therapy, whereas Qmax was significantly greater compared to tamsulosin 0.4 mg monotherapy, but not compared to dutasteride 0.5 mg monotherapy.

Evaluate the effectiveness of fixed-dose combination of tamsulosin 0.4 mg + dutasteride 0.5 mg

Differently, fixed-dose combination therapy was used by Roehrborn et al [66]. Two years of follow-up with 742 participants allowed researchers to evaluate the effectiveness of the fixed-dose combination of tamsulosin 0.4 mg + dutasteride 0.5 mg along with lifestyle advice in the intervention group, whereas watchful waiting with same lifestyle advice was applied in the control group. Symptomatic change of IPSS (73%, $P < 0.001$), reduction of BPH progression (43.1%), and overall improvement of QoL ($P < 0.001$) were statistically more significant in combination therapy. The safety of fixed-dose combination is comparable to known profiles of either monotherapy. This study also revealed that lifestyle advice about caffeine and alcohol avoidance, fluid management, and bladder retraining may be considered part of managing BPH.

Comparison of clinical effectiveness between tamsulosin 0.2 mg and 0.4 mg in monotherapy and combination therapy

Two studies by Chung et al [67] and Haque et al [68] focused on the comparison of efficacy and safety between different dosages of tamsulosin (0.2 vs. 0.4 mg) in monotherapy and combination therapy for Asian men. The former study by Chung et al [67] prescribed tamsulosin 0.4 mg monotherapy ($n = 162$) and 0.2 mg monotherapy ($n = 165$) in two intervention groups, while a placebo treatment was given to ($n = 167$) the control group for Asian men. Among the three groups, baseline characteristics were similar in the beginning. At 12 weeks of

study, primary efficacy analyzed the change in total IPSS. The outcome stated that the reduction in IPSS was greater in tamsulosin 0.4 mg monotherapy group than in both tamsulosin 0.2 mg monotherapy and placebo groups ($P < 0.0001$). Secondary efficacy measured the change in IPSS voiding and storage symptoms sub-score, Qmax, post-void residual (PVR), and QoL. The uroflowmetry test measured Qmax and PVR, which showed improvement in the tamsulosin 0.2 mg and 0.4 mg monotherapy groups. However, the two intervention groups had no statistical difference in the change in IPSS sub-scores, Qmax, PVR, and QoL ($P = 0.001$, $P = 0.9423$, $P = 0.6137$, and $P = 0.0009$). The safety of three treatment groups was investigated through the adverse events and treatment-emergent adverse events (TEAEs) rate. A total TEAE rate of 15.35% was calculated among three groups, but no statistical difference was observed ($P = 0.411$).

The latter study by Haque et al [68] divided 607 Asian men into two groups. A free combination of tamsulosin 0.2 mg + dutasteride 0.5 mg was given in the intervention group ($n = 305$) and tamsulosin 0.2 mg + placebo in the control group ($n = 302$). IPSS was significantly reduced at 24 months ($P < 0.05$), and greater improvements in Qmax were found at every measurement ($P \leq 0.006$), along with a statistically significant reduction in PV at 12 and 24 months ($P < 0.001$) in the combination group. In conclusion, the risk of AUR and BPH-related surgery was significantly reduced in the combination group ($P = 0.012$), with a primary reduction in the AUR risk ($P = 0.005$). Safety and tolerability reported in the present study data showed that sexual adverse events of ejaculation, libido, and impotence problems were more frequently seen in the combination therapy (7.2%) versus tamsulosin 0.2 mg monotherapy (3.3%). Likewise, these problems were started at the early stage of therapy and remained unsolved by the end of the study. Interestingly, the incidence rate of sexual adverse events in this study was lower than that observed in the CombAT study by Roehrborn et al [65], but cardiovascular adverse events were similar to that observed in the CombAT study. However, tamsulosin 0.4 mg was administered in the CombAT study [64, 65].

Overall, these five RCTs demonstrated that drug therapy accounted for the majority of LUTS/BPH treatments (98.77%), and the number of patients followed an upward trend in the use of combination therapy worldwide [64-68].

Discussion

This systematic review was designed to determine the clinical considerations influencing the prescription of tamsulosin 0.4 mg + dutasteride 0.5 mg combination therapy for treating moderate-to-severe LUTS/BPH in an Asian population. Five RCTs were reviewed for the data analysis, which reported statistically significant clinical meaning in LUTS/BPH combination therapy.

Clinical considerations from selected RCTs

In reviewing the literature, data were found on the associa-

tion between drug dosage and ethnicity on the dimension of clinical considerations that require physicians to be aware of. Asian men have been found to have decreased 5-alpha reductase (5AR) enzyme activity and variable 5AR type 2 gene expression, according to Chung et al [64]. Meanwhile, Asian ethnicity has lower levels of PSA and PV. Still, the amount of PSA released in each volume unit of the prostate gland is greater, which demonstrates a different relationship between PSA and PV compared with Caucasian men [64, 69, 70]. This unique relationship between PV and PSA in Asian men results in a higher risk of experiencing moderate-to-severe LUTS than Caucasian men [71, 72]. Another interesting finding is that Asian and Caucasian men have similar responses to tamsulosin 0.4 mg + dutasteride 0.5 mg combination therapy despite the dissimilarity of the correlation between PV and PSA [64].

In contrast to Western countries, tamsulosin 0.2 mg is recommended as the standard administration regimen in Asia [73]. Therefore, with regards to the efficacy and safety of various doses of tamsulosin (0.2 mg vs. 0.4 mg) in monotherapy and different combination formulations (tamsulosin 0.2 mg + dutasteride 0.5 mg vs. tamsulosin 0.4 mg + dutasteride 0.5 mg), another four RCTs had been reviewed. Tamsulosin 0.2 and 0.4 mg were used in double-blind RCT by Chung et al [67]. Results showed that tamsulosin 0.4 mg is safe to prescribe for Asian men as a greater improvement in IPSS, Qmax, and QoL over tamsulosin 0.2 mg was found and without significant adverse events [67]. Additionally, numerous clinical patients do not respond well to tamsulosin 0.2 mg; the dosage is often raised to 0.4 mg; and tamsulosin 0.4 mg is safe and more efficacious than 0.2 mg dose in Asian men [74]. It was surprising that tamsulosin 0.8 mg was used a decade ago, and study concluded that tamsulosin 0.4 and 0.8 mg were safe and efficient in treating LUTS/BPH. However, tamsulosin 0.8 mg was associated with a significantly higher incidence of adverse events [75].

Tamsulosin 0.4 mg + dutasteride 0.5 mg combination therapy vs. tamsulosin 0.4 mg monotherapy and dutasteride 0.5 mg monotherapy and tamsulosin 0.2 mg + dutasteride 0.5 mg combination therapy vs. tamsulosin 0.2 mg monotherapy were conducted in a double-blind RCT by Roehrborn et al [65] and a single-blind RCT by Haque et al [68], respectively. Former study investigated the baseline variables on change in IPSS, Qmax, and QoL among eight subgroups. Outcomes reported that the combination of tamsulosin 0.4 mg + dutasteride 0.5 mg was significantly superior in improving LUTS. Patients with high PV value ≥ 30 mL and high PSA level ≥ 1.5 ng/mL should considered long-term combination therapy. Patients with higher PV ≥ 60 mL and PSA ≥ 4 ng/mL showed similar responses to combination therapy and dutasteride 0.5 mg monotherapy, whereas limited benefit was determined in the PV < 60 mL or PSA < 4 ng/mL subgroups compared with dutasteride 0.5 mg monotherapy [65]. The latter RCT took Korean and Japanese urological association guideline recommendations into account, and tamsulosin 0.2 mg was used in combination therapy with dutasteride 0.5 mg. A persistent improvement in Qmax and PV was observed from 6 months onwards and throughout the 2 years in the combination therapy group. Overall, drug-related adverse events were mild and occurred within the first 6 to 12

months of the study; more than half of adverse events were reported in combination treatment. Sexual-related problems more frequently happened in combination therapy. However, the incident rate of sexual adverse events was lower than that in the previous CombAT study, and cardiovascular adverse events were similar to those in the CombAT study [64, 65].

Relevant correlations from additional literatures

Tamsulosin 0.4 mg + dutasteride 0.5 mg combination therapy is often administered to males with moderate-to-severe LUTS/BPH who are at risk of the condition worsening, with dutasteride specifically recommended for individuals with larger prostates (PV \geq 30 mL) in a long-term treatment [11, 35, 42-45]. However, over 50% of males with moderate-to-severe LUTS have a prostate size that is rather modest, measuring 30 mL or less [76, 77]. Furthermore, the possibility of experiencing sexual dysfunction while using dutasteride in combination therapy may limit its use in clinical settings, despite reported satisfaction with the treatment [77] and demonstrated effectiveness in reducing symptoms, disease progression, and the need for surgery [78, 79].

Numerous studies provide evidence for a negative correlation between the size of BPH and the occurrence of prostate cancer (PCa) [80-82]. The prostate consists of three different zones: the central zone (CZ), TZ, and peripheral zone (PZ) [82]. Research confirms that approximately 80% of PCa initiates in the prostate's PZ [82, 83], while the enlargement of the TZ is widely recognized as the primary cause of aging and enlarging BPH prostate [81, 84]. The growth of the TZ in BPH leads to significant alterations in both the volume and glandular density of the PZ, as well as changes in the prostate capsule. The disease mechanisms described in recent studies revealed that the expanding TZ adds pressure on the PZ, leading to glandular tissue atrophy and fibrosis in the PZ [81, 83, 85].

Recommendation

An open-label, prospective, randomized pilot study conducted in Korea by Lee et al [58] and an RCT conducted by Barkin et al [86] in Europe examined the effect of discontinuing tamsulosin in patients with LUTS/BPH, who had been receiving combination therapy of tamsulosin 0.4 mg + dutasteride 0.5 mg. Still, there has been a vacancy of research that examines the broader Asia population: Can tamsulosin be discontinued from long-term combination therapy for Asian men? Whether an earlier initiation of BPH treatment for Asian men is advisable due to the high risk of moderate-to-severe LUTS? Can fixed-dose combination therapy result in better compliance compared with co-administer of tamsulosin and dutasteride?

Research proves that using shared-decision making (SDM) results in individuals making high-quality decisions, experiencing greater satisfaction, adhering better to medication regimens, and achieving improved clinical outcomes [87-79]. Discussing the options with the patient and acknowledging the optimized and individualized treatment is necessary. It enables

healthcare professionals to make informed decisions based on the patient's circumstances and context [90, 91]. Thus, SDM is highly recommended when the physician is prescribing combination therapy for Asian men with moderate-to-severe LUTS/BPH [92, 93].

Strengths and limitations

This systematic review comprehensively searched RCTs relevant to tamsulosin 0.4 mg + dutasteride 0.5 mg combination therapy. Its efficacy and safety had been reported in several previous published meta-analysis, which supported the benefits of the administration of combination therapy. Including relevant RCTs provides a significant clinical view and research validation on the recommended clinical considerations that physicians must be cautious with while prescribing combination treatment.

Although five RCTs were involved in narrative data analysis, the quality of those studies was high. Different tolerances and preferences for combination therapy, varied durations, and the subjectiveness of each RCT may introduce potential biases that affect the results of the present systematic review. Many other factors, such as personal belief, BPH progression, and delayed treatment, may still reduce the long-term benefits of combination therapy. Unfortunately, these factors are difficult to interpret in this review because much research needs to be involved.

Conclusions

Tamsulosin 0.4 mg + dutasteride 0.5 mg combination therapy has been extensively prescribed for men with moderate-to-severe LUTS/BPH in a long-term treatment. Asian ethnicities have similar responses to tamsulosin 0.4 mg but different sensitivity to dutasteride 0.5 mg in combination therapy compared with European races. A relatively higher risk of moderate-to-severe LUTS was found in Asian men. Besides, initiation of medical treatment and consideration of dutasteride relies on a larger PV (\geq 30 mL); it is possible, therefore, that earlier PV and PSA examinations and baseline variables assessments should be launched before combination therapy prescription. Alternative treatments may be considered to minimize the potential sexual adverse events of dutasteride during combination therapy if the patient prefers to maintain active sexual activity. These are factors correlated with clinical considerations that may influence the prescription of tamsulosin 0.4 mg + dutasteride 0.5 mg combination therapy for moderate-to-severe LUTS/BPH in Asian men.

Supplementary Material

Suppl 1. Search strategy for Medline (OVID).

Suppl 2. CASP checklist.

Suppl 3. Data extraction of selected RCTs for synthesis and analysis.

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Conflict of Interest

The authors declare that they do not have a conflict of interest.

Informed Consent

Not applicable.

Author Contributions

FY contributed to study conception and design, literature search, screening, risk of bias assessment, data extraction, analysis and interpretation of data, manuscript preparation and revision. RH contributed to conception and design of study, literature search, screening, risk of bias assessment, data extraction, analysis and interpretation of data. JP contributed to risk of bias assessment, analysis and interpretation of data. Each author participated sufficiently in review. All authors have been involved in preparation of the article prior to submission. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

Abbreviations

AUR: acute urinary retention; A1AR: alpha 1 adrenergic receptor; A1aAR: alpha 1a adrenergic receptor; A1bAR: alpha 1b adrenergic receptor; A1dAR: alpha 1d adrenergic receptor; A1aARA: alpha 1a adrenergic receptor antagonist; AEs: adverse events; ANOVA: analysis of variance; ANCOVA: analysis of covariance; 5AR: 5-alpha reductase; 5ARI: 5-alpha reductase inhibitor; BPH: benign prostatic hyperplasia; BMI: body mass index; BII: benign prostatic hyperplasia impact index; CASP: Critical Appraisal Skills Program; CombAT: Combination of Avodart and Tamsulosin; CZ: central zone; DHT: dihydrotestosterone; MeSH: Medical Subject Heading; IPP: intravesical prostatic protrusion; IPSS: international

prostate symptom score; LUTS: lower urinary tract symptoms; LOCF: last observation carried forward; PV: prostate volume; PVR: post-void residual; PVRU: post-void residual urine; PSA: prostate specific antigen; PROSPERO: International Prospective Register of Systematic Review; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PCa: prostate cancer; PZ: peripheral zone; QoL: quality of life; Qmax: maximum urinary flow rate; RCTs: randomized controlled trials; SD: standard deviation; SAS: statistical analysis system; SDM: shared decision-making; TEAEs: treatment emergent adverse events; TZ: transition zone; UTI: urinary tract infection

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