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# A Randomized, Open-Label, Comparative Study of Efficacy and Safety of Tolterodine Combined with Tamsulosin or Doxazosin in Patients with Benign Prostatic Hyperplasia

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**Background:** Benign prostatic hyperplasia (BPH), a common disease in men over age 50 years, often causes bladder outlet obstruction and lower urinary tract symptoms (LUTS). Alpha blockers in combination with muscarinic receptor antagonists may have the potential to improve symptoms. This study aimed to assess the efficacy and safety of doxazosin or tamsulosin combined with tolterodine extend release (ER) in patients with BPH and LUTS.





**Material/Methods:** In a prospective, randomized, open-label study (ChiCTR-IPR-15005763), 220 consecutive men with BPH and LUTS were allocated to receive doxazosin 4 mg and tolterodine ER 4 mg per day (doxazosin group) or tamsulosin 0.2 mg and tolterodine ER 4 mg per day (tamsulosin group). Treatment lasted 12 weeks. The primary endpoint was the international prostatic symptom score (IPSS). Secondary endpoints were quality of life (QoL) and maximum flow rate ( $Q_{max}$ ), which were evaluated at 0, 6, and 12 weeks, and urodynamic parameters assessed at 0 and 12 weeks.

**Results:** A total of 192 patients completed the trial. Baseline measurements showed no differences between the groups. After 6 weeks, IPSS improved in both groups and QoL was significantly better in the doxazosin group ( $P=0.01$ ). After 12 weeks,  $Q_{max}$ , IPSS, QoL, intravesical pressure (Pves), and bladder compliance (BC) in the doxazosin group were significantly better than in the tamsulosin group ( $P=0.03$ ,  $P<0.001$ ,  $P<0.001$ ,  $P=0.027$ , and  $P=0.044$ , respectively).

**Conclusions:** Administration of alpha blockers combined with muscarinic receptor blocker for 12 weeks improved LUTS in men with BPH.

**MeSH Keywords:** **Doxazosin • Lower Urinary Tract Symptoms • Prostatic Hyperplasia**

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## Background

Benign prostatic hyperplasia (BPH) is a common disease that is mostly experienced by men over age 50 years and it progresses with age. The resulting enlarged prostate often causes bladder outlet obstruction (BOO) and results in lower urinary tract symptoms (LUTS). LUTS associated with BPH include urinary frequency, urgency, nocturia, a weak stream and incomplete emptying, dribbling, and hesitancy [1].

The treatment options for BPH depend upon the severity of symptoms and the impact they have upon the patient's quality of life (QoL) [2]. LUTS can be divided into storage (filling symptoms) and voiding (emptying symptoms). Surgical resection of the prostate often provides permanent relief, but  $\alpha$ -adrenergic receptor antagonists or 5  $\alpha$ -reductase inhibitors are commonly used in clinical practice as a first-line drug to relieve voiding LUTS [3].  $\alpha$ -blockers may improve symptoms quickly, while 5- $\alpha$  reductase inhibitors may decrease prostate size and alter the disease course but act more slowly [2]. However, a certain number of BPH patients may not respond to  $\alpha$ -adrenergic receptor antagonists and are not improved after treatment with finasteride, a 5  $\alpha$ -reductase inhibitor [4,5]. These data indicate that many patients with LUTS associated with BPH still suffer from the symptoms even after receiving  $\alpha$ -blockers or 5  $\alpha$ -reductase inhibitors.

Muscarinic receptor antagonists reduce contraction of the bladder by inhibiting smooth muscle tone and central nervous system action. Muscarinic receptor antagonists such as tolterodine are widely used to treat overactive bladder (OAB) symptoms [6], and they have been introduced as a potential treatment for storage LUTS secondary to BPH [7]. The combined use of  $\alpha$ 1-adrenergic receptor antagonist and tolterodine improved LUTS compared to using a single drug [8,9]. The combination of these drugs provides treatment of storage symptoms and voiding symptoms, resulting in decrease of urgency, frequency, and nocturia and improvements in weak stream and incomplete emptying. The European Association of Urology (EAU, 2015) guidelines for LUTS management [10] say muscarinic receptor antagonists may be used in men with moderate-to-severe LUTS who mainly have bladder storage symptoms, but they advise caution for men with BOO. They also say that combination treatment of  $\alpha$ 1-blocker and muscarinic receptor antagonist may be used in patients with bothersome moderate-to-severe LUTS if relief of storage symptoms has been insufficient with the monotherapy of either drug. Short-term treatment with antimuscarinic drugs in men with BPH is safe. The American Urological Association (AUA, 2014) guideline [11] states that anticholinergic agents are recommended for LUTS secondary to BPH, with caution of post-void residual urine volume (PVR) greater than 250–300 mL. Clinically, an anticholinergic agent such as tolterodine is cautiously added

to therapy of men with prostatic obstruction only if there is no therapeutic effect of  $\alpha$ -blockers after several months. Therefore, around 6–7% of men with storage LUTS receive antimuscarinics [12]. Recently, a multicenter, multinational, double-blind study with a large case number demonstrated that tolterodine was safe and tolerable in men with BOO [13]. There is no evidence of clinically meaningful changes in voiding pressure and PVR or urinary retention [14,15]. Treatment with tolterodine extended release (ER) plus tamsulosin for 12 weeks resulted in statistically significant treatment benefit for men with moderate-to-severe LUTS, although no statistically significant improvement was observed in the international prostatic symptom score (IPSS) and QoL compared to tamsulosin alone [16].

While previous studies suggest some benefit in using antimuscarinic drugs in combination with  $\alpha$ -blockers in a select population of patients with LUTS secondary to BPH, it is unclear whether different  $\alpha$ -blockers will have different efficacy and safety in combination therapy. In this study, we compared the efficacy and safety of 2  $\alpha$ -blockers, doxazosin and tamsulosin, combined with tolterodine ER in patients with LUTS associated with BPH.

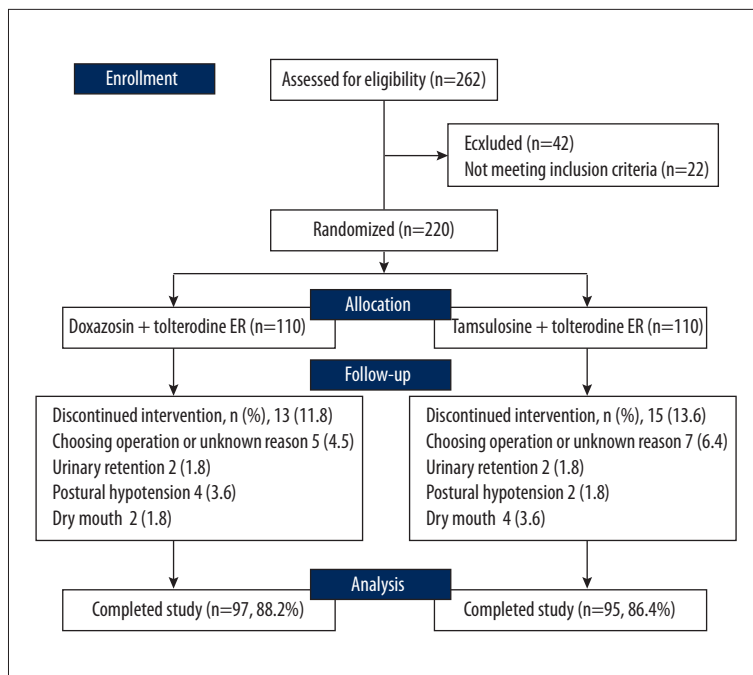
## Material and Methods

### Patients

In this prospective, open-label study (ChiCTR-IPR-15005763) from March 2012 to March 2013, 220 consecutive men aged 50–80 years with newly diagnosed symptoms of BPH (frequent daytime urination, nocturia, a sensation of incomplete bladder emptying, and an intermittent urinary stream) who met the inclusion/exclusion criteria were selected. Inclusion criteria were normal urine analysis, a benign digital rectal examination (DRE), IPSS  $\geq 12$ , and QoL  $\geq 3$ , and frequency of urination  $\geq 8$  per day.

Furthermore, all symptoms of BOO lasted at least 3 months. Exclusion criteria were prostate-specific antigen (PSA) level of  $>4$  ng/mL, PVR  $>100$  mL, maximum flow rate ( $Q_{max}$ )  $\leq 5$  mL, previous urological surgery or current pharmacological therapy including an  $\alpha$ -blocker or antimuscarinic agents in 1 month, and long-term use of 5  $\alpha$ -reductase inhibitors. In addition, men with neurological diseases (stroke, diabetes, Parkinson's disease) and BOO due to any reason other than BPH were also excluded.

Initial screening evaluation was performed at Qingdao University affiliated hospital, urological institution. All participants assigned informed consent and the project was approved by the Chinese Qingdao University Affiliated Hospital Ethics Committee (2012031).



**Figure 1.** Flowchart of the study enrollment and allocation into groups.

## Study design

Figure 1 shows the enrollment of the study subjects and their allocation into groups. All enrolled patients were randomized into 2 groups using a computer-generated table. The doxazosin group (n=110, 50%) received doxazosin 4 mg per day and tolterodine extend release (ER) 4 mg per day at bedtime. The tamsulosin group (110, 50%) received tamsulosin 0.2 mg per day and tolterodine ER 4 mg per day at bedtime. All patients received treatment for 12 weeks according to their allocated regimen.

## Clinical diagnosis

BPH was characterized by a proliferation of prostatic gland and stromal cells, leading to enlargement of the prostate and subsequent urinary outlet obstruction and LUTS; the LUTS included frequent daytime urination, nocturia, a sensation of incomplete bladder emptying, and an intermittent urinary stream [17].

## Data collection

The primary endpoint efficacy assessment was IPSS. The questionnaire is a commonly used Chinese form with good reliability and validity [18] and was completed by 4 specialized urologists. Urological history was collected and DRE was performed during the initial screening visit. Routine laboratory samples were taken, including those for creatinine, PSA, and urinary analysis. The primary endpoint IPSS was evaluated at the 6<sup>th</sup> and 12<sup>th</sup> weeks and the difference was compared to the baseline data.

Secondary endpoints of QoL and  $Q_{max}$  were also recorded at the 6<sup>th</sup> and 12<sup>th</sup> weeks and compared to baseline data. QoL is affected by benign prostatic hyperplasia due to the appearance of voiding symptoms, such as nocturia, urinary frequency, urgency, dysuria, urine dribbling, and incontinence. The International Coordinating Committee recommended a questionnaire to assess quality of life. The score was rated by the patients according to their own assessment at 7 levels from 0 to 6, from the best to the worst feeling, so a low score represented a high QoL. Scoring was 0 “That’s good”; 1 “Great”; 2 “Most satisfied”; 3 “Half satisfied and dissatisfied”; 4 “Most unsatisfactory”; 5 “Unhappy”; and 6 “Very painful”. The questionnaire is a commonly used Chinese form with good reliability and validity [18] and was completed by 4 specialized urologists.

Prostate volume was assessed by transabdominal ultrasound examination and  $Q_{max}$  was recorded by uroflowmetry. Men received urodynamic evaluation. PVR, maximum cystometric bladder capacity (MCBC), intravesical pressure at the time of the end of filling (Pves) [19], and bladder compliance (BC) were recorded. Its normal range was from 31 to 42 cmH<sub>2</sub>O.

PVR, MCBC, Pves at the time of  $Q_{max}$ , and BC as urodynamic parameters were assessed at the 12<sup>th</sup> week in patients who initially underwent urodynamics testing.

Adverse events were recorded throughout the trial and were reported to evaluate the safety of the 2 treatment regimens. All adverse effects were followed at the 6<sup>th</sup> and 12<sup>th</sup> weeks, such as dry mouth, headache or dizziness, urinary retention, nausea, and blurred vision. They were all rated according to the

**Table 1.** Baseline LUTS characteristics of the two groups of patients.

Baseline parameters	Doxazosin + tolterodine ER (N=110)	Tamsulosin + tolterodine ER (N=110)	P value
n	97	95	
Age (mean)	61.4±8.7	60.5±9.1	0.52
BMI	25.6±5.7	26.1±6.4	0.89
Gland volume (ml)	54.2±14.5	56.1±16.4	0.38
PSA (ng/ml)	2.50±1.0	2.45±1.20	0.69
IPSS	22.90±3.8	22.7±4.5	0.69
QoL	4.3±1.1	4.2±0.8	0.49
Q <sub>max</sub> (ml/s)	10.3±1.8	10.1±2.0	0.38
PVR (ml)	68.84±20.35	68.04±15.26	0.88
MCBC (ml)	227.96±48.92	216.76±39.53	0.38
Pves (cm H <sub>2</sub> O)	101.76±21.84	91.88±23.23	0.13
BC (ml/cm H <sub>2</sub> O)	16.40±3.33	17.32±4.03	0.38

LUTS – lower urinary tract symptoms; BMI – body mass index; PSA – prostatic special antigen; IPSS – international prostatic symptom score; QoL – quality of life; Q<sub>max</sub> – maximum flow rate; PVR – post void residual volume; MCBC – maximum cystometric bladder capacity; Pves – intravesical pressure; BC – bladder compliance.

degree of seriousness, with *mild* indicating not needing treatment with no real adverse effect, *moderate* indicating the patient felt discomfort but it did not require drug treatment, and *severe* indicating the effects were serious enough that the patient did not continue treatment and withdrew from the trial.

### Statistical analysis

The sample size of the study was calculated assuming a type 1 error of 0.05 and a type 2 error of 20% to detect a difference in the primary endpoint IPSS score of 2 points from baseline to the 6<sup>th</sup> week and a 20% loss to follow-up. The minimum sample size to detect statistically significant differences was 97 patients in each group.

Results were assessed statistically using SPSS 17.0 statistical software (SPSS Inc., Chicago, IL, USA) with Student's *t* test and values are presented as the mean. *P*<0.05 was considered to indicate significant differences.

## Results

### Patient characteristics

From the 220 patients enrolled, 192 (87%) patients completed the study (Figure 1). Twelve (5%) patients discontinued because they opted to undergo an operation or for unknown

reasons. Severe adverse effects caused 16 (8%) patients to withdraw from the trial. No significant difference was observed between the 2 groups with regard to baseline parameters (Table 1, *P*>0.05). Urodynamic evaluation was done in 192 patients. Table 1 shows there was no difference between the 2 groups with regard to dynamic parameters (*P*>0.05).

### Primary endpoint: assessment of IPSS

After 6 weeks of treatment, LUTS were improved in both groups, as seen by the change in IPSS from baseline (Tables 1, 2). There was no significant difference between groups in terms of total IPSS (*P*=0.86, Table 2). At 12 weeks, greater improvement of total IPSS was observed in the doxazosin group (14.0±4.3) than in the tamsulosin group (17.3±4.0; *P*<0.001).

### Secondary endpoints: Assessment of Q<sub>max</sub>, QoL

After 6 weeks treatment there was no significant difference between the groups in Q<sub>max</sub> (*P*=0.19; Table 2). However, QoL was significantly improved in the doxazosin group compared to the tamsulosin group (*P*=0.01; Table 2). At 12 weeks Q<sub>max</sub> showed greater improvement in the doxazosin group (14.1±1.6 mL/s) than in the tamsulosin group (13.5±2.1 mL/s, *P*=0.03). In addition, QoL (2.5±0.67) of the doxazosin group was much better.

Dynamic parameters were analyzed at the 12<sup>th</sup> week. No significant difference was observed between the 2 groups in

**Table 2.** Changes in IPSS,  $Q_{max}$  and QoL and comparison between groups at 6<sup>th</sup> week and 12<sup>th</sup> week.

Parameters	6 <sup>th</sup> week		P	12 <sup>th</sup> week		P
	Doxazosin + tolterodine ER (N=110)	Tamsulosin + tolterodine ER (n=110)		Doxazosin + tolterodine ER (n=97)	Tamsulosin + tolterodine ER (n=95)	
IPSS	18.6±4.6	18.7±4.0	0.86	14.0±4.3	17.3±4.0	<0.001
$Q_{max}$ (mL/s)	12.4±1.8	12.1±2.1	0.19	14.1±1.6	13.5±2.1	0.03
QoL	3.3±0.7	3.5±0.6	0.01	2.5±0.67	3.1±0.7	<0.001

IPSS – international prostatic symptom score; QoL – quality of life;  $Q_{max}$  – maximum flow rate.

**Table 3.** Dynamic parameters in both groups after 12-weeks of treatment.

Parameters	Doxazosin + tolterodine ER (n=97)		Tamsulosin + tolterodine ER (n=95)		P value
	Baseline	12-week	Baseline	12-week	
PVR (ml)	68.8±20.4	49.7±10.8	68.0±15.3	50.7±11.7	0.251
MCBC (ml)	228.0±48.9	219.1±67.3	216.8±39.5	231.9±41.9	0.787
Pves (cm H <sub>2</sub> O)	101.8±21.8	48.7±16.0	91.9±23.23	61±17.1	0.027
BC (ml/cm H <sub>2</sub> O)	16.4±3.3	24.4±4.3	17.3±4.0	20.0±7.2	0.044

PVR – post void residual volume; MCBC – maximum cystometric bladder capacity; Pves – intravesical pressure; BC – bladder compliance.

PVR ( $P=0.251$ ) or MCBC ( $P=0.787$ ; Table 3). However, the Pves ( $P=0.027$ ) and BC ( $P=0.044$ ) were much better in the doxazosin group than in the tamsulosin group (Table 3).

### Adverse events

The adverse events experienced by both groups of patients are shown in Table 4 and were similar between the 2 groups. The most common adverse event was dry mouth, which was experienced by 12 (18.2%) and 10 (10.3%) patients in the doxazosin group at 6 and 12 weeks, respectively, and 13 (11.8%) and 9 (9.5%) patients in the tamsulosin group at 6 and 12 weeks, respectively. It was found to be severe at 6 weeks for 2 (1.8%) patients in the doxazosin group and 4 (3.6%) patients in the tamsulosin group. The second most common adverse event was headache or dizziness, which was found in 10 (9.1%) patients in the doxazosin group at 6 weeks and was severe in 4 (3.6%) of them; at 12 weeks it was found in 4 (4.1%) but all cases were mild. In the tamsulosin group 9 (8.2%) patients suffered headache or dizziness at 6 weeks with 2 (1.8%) classed as severe; at 12 weeks it was found in 7 (7.3%) patients but all cases were mild. There were no significant differences between the 2 groups in all adverse events ( $P>0.05$ ).

Adverse events that led to discontinuations are listed in Table 5. In total, 16 (8%) patients discontinued because of adverse

events – 8 from each group. In both groups the discontinuations all occurred by the 6<sup>th</sup> week; these included urinary retention 4 (2%), postural hypotension 6 (3%), and dry mouth 6 (3%). There was no significant difference between the 2 groups regarding the proportion of discontinuations ( $P=0.84$  at the 6<sup>th</sup> week).

One death due to heart shock (myocardial infarction) occurred during the study; this was a patient in the tamsulosin group.

### Discussion

The aim of this investigation was to compare the efficacy and safety of 2  $\alpha$ -blockers, doxazosin and tamsulosin, in combination with tolterodine ER for LUTS secondary to BPH. The results show that both treatment regimens improved LUTS after 6 weeks in terms of IPSS. At 12 weeks the doxazosin combination treatment showed greater improvement of IPSS than the tamsulosin combination treatment. In addition, QoL was significantly higher in the doxazosin group at 6 weeks. After 12 weeks,  $Q_{max}$  and QoL and changes in Pves and BC in the doxazosin group were also significantly better than in the tamsulosin group. There were some severe adverse events in both groups, including dry mouth and headache or dizziness, and some patients withdrew from the trial because of

**Table 4.** Adverse events during the treatment.

Adverse event	Doxazosin + tolterodine ER (doxazosin group)		Tamsulosin + tolterodine ER (tamsulosin group)		P value	
	N		N			
Observation time	110	97	110	95		
	6 <sup>th</sup> week	12 <sup>th</sup> week	6 <sup>th</sup> week	12 <sup>th</sup> week	P (6 <sup>th</sup> week)	P (12 <sup>th</sup> week)
Dry mouth	12 (18.2)	10 (10.3)	13 (11.8)	9 (9.5)	1	1
Mild	8 (7.3)	10 (10.3)	9 (8.2)	8 (8.4)	1	0.81
Moderate	2 (1.8)	0	0	1 (1.0)	0.49	1
Severe	2 (1.8)	0	4 (3.6)	0	0.68	0.12
Headache or dizzy	10 (9.1)	4 (4.1)	9 (8.2)	1 (1.1)	1	0.37
Mild	5 (4.5)	4 (4.1)	7 (6.4)	7 (7.3)	0.77	0.37
Moderate	1 (0.9)	0	0	0	1	–
Severe	4 (3.6)	0	2 (1.8)	0	0.68	–
Constipation	0	1 (1.0)	0	0	–	1
Nausea	0	2 (2.0)	1 (0.9)	1 (1.1)	1	1
Urinary retention	2 (1.8)	0	2 (1.8)	0	1	–
Blurred vision	0	0	1 (0.9)	2 (2.1)	1	0.24

**Table 5.** Reasons for discontinuations from the trial.

Adverse event	Doxazosin + tolterodine ER (doxazosin group)		Tamsulosin + tolterodine ER (doxazosin group)		P (6 week)
	N		N		
Observation time	110	97	110	95	
	6 <sup>th</sup> week	12 <sup>th</sup> week	6 <sup>th</sup> week	12 <sup>th</sup> week	
Discontinuations	13 (11.8)	0	15 (13.6)	0	0.84
Adverse events	8 (7.3)	0	8 (7.3)	0	1
Dry mouth	2 (1.8)	0	4 (3.6)	0	0.68
Headache or dizzy	4 (3.6)	0	2 (1.8)	0	0.68
Urinary retention	2 (1.8)	0	2 (1.8)	0	1
Voluntary withdraw	4 (3.6)	0	5 (4.5)	0	1
Others	9 (8.2)	0	9 (8.2)	0	1
Death	0	0	1 (0.9)	0	1

adverse events, including urinary retention and postural hypotension. These adverse events and withdrawals were similar in both groups.

Selective  $\alpha$  1-adrenoceptor antagonists are considered as the first-line drugs to treat male BPH/LUTS because of their rapid onset of action and good efficacy [20]. Currently, the common  $\alpha$ 1-adrenoceptors used in the clinic are doxazosin and tamsulosin, which can interrupt sympathetic motor neuron responses, reducing urethral pressure and inhibiting smooth

muscle tone in the prostate and lower urinary tract [21,22]. However, there are still some men with no response to  $\alpha$  blockers [3,20,23]. Many patients with BPH /LUTS still suffer from symptoms even after receiving  $\alpha$ -blockers or 5  $\alpha$ -reductase inhibitors systematically.

The methodology of this clinical trial has some points worth discussing, because it took place in China. There is no clear standard PVR when using of antimuscarinics in BPH. According to trails from Asian medical centers, when PVR is 50 to 100 mL

it is believed to be safe to use antimuscarinics in BPH patients [5,24]. However, in the USA and Europe, antimuscarinics are still considered for use in patients with PVR 200 to 250 mL [25]. As this was an Asian study, in order to make sure that patients did not have severe emptying dysfunction, those with PVR greater than 100 mL were excluded from our trial. We used 0.2 mg/d of tamsulosin in our study because, compared to 0.4–0.8 mg/d in the USA or Europe, a low dosage of tamsulosin has favorable efficacy and tolerability for Asians [5,24]. We used the standard dose of doxazosin; however, there is no suggestion that a lower dose is effective in an Asian population. This may have biased the results of the study. No placebo was given to patients because doxazosin and tamsulosin are confirmed to improve LUTS.

After treatment, LUTS were improved significantly at 6 or 12 weeks in both groups compared to the baseline. The data showed that both combination medical therapies had similar clinical efficacy after 6-week treatment. There was no significant difference between the 2 groups in IPSS or  $Q_{max}$  at the 6<sup>th</sup> week. However, QoL was better in patients with doxazosin and tolterodine ER ( $P=0.01$ ). At the end of 12 weeks, we found greater improvement of IPSS ( $P<0.001$ ),  $Q_{max}$  ( $P=0.03$ ), and QoL ( $P<0.001$ ) in the doxazosin group than in the tamsulosin group; therefore, we conclude that doxazosin plus tolterodine ER showed better therapeutic efficacy in treatment of LUTS. It is difficult to understand why these differences between groups were only evident at 12 weeks; the study by Kaplan et al. [16] evaluating tamsulosin and tolterodine therapy at 6 and 12 weeks found the 12-week IPSS improvement in symptoms during treatment was significantly higher than those at the 6<sup>th</sup> week. This suggests that the therapeutic effect of the treatment becomes more stable with time, but further study is needed to understand this fully. When urodynamic parameters were evaluated at the 12<sup>th</sup> week, no significant difference was found between the 2 groups in the PVR and MCBC. However, Pves ( $P=0.027$ ) and BC ( $P=0.044$ ) results were much better in the doxazosin group than in the tamsulosin group. The improvement of Pves and BC indicated a lower outlet pressure and more stable bladder contraction. Monitoring PVR may allow for identification of patients at risk of acute urinary retention. Our results show that tolterodine ER did not increase PVR in either group. Only 4 (2%) patients discontinued because of urinary retention during the whole trial. A few patients (8%) suffered from unacceptable adverse effects due to drugs in both groups; this was slightly higher than in another study that evaluated the safety of tolterodine ER and  $\alpha$ -blocker use in patients with overactive bladder symptoms, in which 3.1% withdrew because of adverse events [26]. Both the previous study and these results suggest that tolterodine and  $\alpha$  blocker are generally safe and tolerable. However, the influence of these adverse effects on patients should be carefully considered, particularly in older men [27].

To date, 4 unique  $\alpha$ 1-AR subtypes ( $\alpha$ 1A,  $\alpha$ 1B,  $\alpha$ 1D, and  $\alpha$ 1L) have been identified [28,29].  $\alpha$ 1 A-AR subtypes are predominant in human prostate and urethra. Distribution ratios of the  $\alpha$ 1A-AR and  $\alpha$ 1D-AR subtypes are 69.3% and 27.3% in the urethra and 85% and 15% in prostatic tissue, respectively [30,31]. The  $\alpha$  1D-AR subtype is mainly expressed in the detrusor muscle of the bladder and the sacral region of the spinal cord, and blockade of the  $\alpha$  1D-AR subtype can relieve irritative symptoms [32]. We presume the differences in Pves and BC might be because tamsulosin mainly targets the  $\alpha$ 1A receptor, while doxazosin mainly targets the A and D receptor.

Doxazosin is a long-acting selective  $\alpha$  1-adrenoceptor antagonist that has been shown to be effective and well tolerated in the treatment of patients with BPH [33]. Another  $\alpha$ 1-adrenoceptor antagonist, tamsulosin, is selective for the  $\alpha$ 1A-adrenoceptor. Because 70% of the  $\alpha$ 1-adrenoceptors in the prostate are of the  $\alpha$  1A subtype [34,35], the action of tamsulosin may be concentrated in the prostate with little involvement of the central nervous system. It has been suggested that the  $\alpha$  1A subtype-specific action of tamsulosin may result in incomplete relief of BPH symptoms [36]. However, data from many trials showed that all  $\alpha$ 1 blockers have a similar efficacy in appropriate doses [37]. Our results show that IPSS,  $Q_{max}$ , QoL, Pves, and BC were improved more in the doxazosin group than in the tamsulosin group, and this difference was statistically significant. This could be due to the pharmacological characteristics of doxazosin.

The limitations of this study are in part due to the design of an open-label study, and because commercial medicine was used the patients and clinicians could not be blinded to the allocated drug regimen. This may have introduced some bias into the study, but the endpoints investigated should be fairly resistant to bias. Recently it has been shown that the level of inflammation in BPH may be related to the level of symptoms experienced by patients [38]. This suggests that measuring levels of factors such as heat shock protein 27 might provide alternative methods of monitoring the success of treatment. More randomized multi-center studies should be carried out to add weight to these results in the future.

## Conclusions

In conclusion, combined therapy improves symptoms in patients with BPH with a significant presence of irritative symptoms. The good tolerability and improved symptoms resulting from combined treatment may provide improvement in LUTS for patients without bladder obstruction symptoms.

## Conflict of interest

The authors declare that they have no conflicts of interest.

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