Systematic Review and Meta-Analysis

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Efficacy and tolerability of doxazosin gastro-intestinal therapeutic system versus tamsulosin in patients with lower urinary tract symptoms associated with benign prostatic hyperplasia

A systematic review and meta-analysis

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Abstract

Background: Alpha1-adrenoceptor antagonists (α_1-blockers) are first-line drugs for the treatment of lower urinary tract symptoms associated with benign prostate hyperplasia (BPH). Doxazosin gastrointestinal therapeutic system (GITS) and tamsulosin belong to the 2 most frequently prescribed α_1-blockers. This systematic review and meta-analysis was performed to compare the efficacy and tolerability of these 2 α_1-blockers.

Methods: A systematic review of published randomized controlled trials in English or Chinese language was performed using the PubMed, EMBASE, Cochrane Library, CNKI, Wanfang, and Vip databases. After data extraction and quality assessment, the meta-analysis was performed to compare clinical parameters (International Prostate Symptom Score [IPSS] total [IPSS-T], storage [IPSS-S], voiding [IPSS-V], maximum urine flow [Q_{max}], and postvoid residual) and adverse events (AEs) that changed after first drug intake.

Results: After the screening, 8 eligible randomized controlled trials with 1316 patients were identified. Doxazosin-GITS showed a significantly higher efficacy compared with tamsulosin (IPSS-T $P < .001$, IPSS-S $P < .001$, and IPSS-V $P < .001$). There were no significant differences between the 2 drugs for changes in Q_{max} ($P = .477$) or postvoid residual ($P = .739$). The overall AEs were significantly lower in the doxazosin-GITS group (risk ratio: 0.77; 95% CI: 0.54–1.08; $P = .036$). However, dizziness ($P = .387$), headache ($P = .745$), asthenia ($P = .693$), postural hypotension ($P = .114$), and retrograde ejaculation ($P = .187$) were similar between the 2 groups.

Conclusions: This meta-analysis indicates that doxazosin-GITS has significantly higher efficacy and lower AEs than tamsulosin in patients with lower urinary tract symptoms/benign prostate hyperplasia.

Abbreviations: AEs = adverse events, BPH = benign prostate hyperplasia, FE = fixed-effects, GITS = gastrointestinal therapeutic system, IPSS-T = International Prostate Symptom Score questionnaire, LUTS = lower urinary tract symptoms, PVR = postvoid residual, QUORUM = quality of reporting of meta-analyses, RCTs = randomized controlled trials, RE = random effects, RR = risk ratio, WMD = weighted the mean difference.

Keywords: benign prostatic hyperplasia, doxazosin gastro-intestinal therapeutic system, lower urinary tract symptoms, meta-analysis, tamsulosin

1. Introduction

Lower urinary tract symptoms (LUTS) are one of the most common medical problems among men aged over 40 years worldwide.[1–3] LUTS can be caused by various conditions such as benign prostate hyperplasia (BPH), overactive bladder, urinary tract infection, tumors, stones, or functional disorders of the lower urinary tract.[4] In addition to neurological diseases in older men, LUTS are primarily considered to be associated with BPH, which may cause benign prostatic enlargement and/or bladder outlet obstruction, resulting in unspecific LUTS, such as hesitancy, poor urine stream, daytime frequency, or nocturia.[5–7] LUTS/BPH has a high prevalence of 70% among men aged over 80 years, which seriously affects the quality of life. Besides, these symptoms are associated with substantial personal and social problems.[7–9]

Management of LUTS/BPH includes conservative, pharmacological, and surgical treatment. Antagonists of a_1-adrenoceptors (α_1-blockers) have emerged as an effective and safe option for LUTS/BPH relief. Based on current guidelines, α_1-blockers including alfuzosin, doxazosin, silodosin, tamsulosin, and

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The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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terazosin are strongly recommended as first-line drug treatment for men with moderate to severe LUTS/BPH, especially in those with prostate volumes $< 40\,cm^3$.[10,11] Previous studies have suggested that all licensed α_1-blockers are significantly better than placebo and have similar efficacy in improving LUTS/BPH and urine flow[12–15] but differ in the prevalence and severity of adverse events (AEs). Only a few head-to-head studies published in the English literature are available to validate this statement. However, there are several studies in the non-English literature, which have not been analyzed.

Doxazosin gastrointestinal therapeutic system (GITS) has better pharmacokinetic profile and drug delivery rate and associated with lesser fluctuations in the serum concentration compared with the immediate-release doxazosin formulation. In addition, doxazosin-GITS has a lower serum peak-to-trough ratio. Therefore, there is no need for dose titration for doxazosin-GITS, which widens its clinical applications.[16] Based on previous placebo-controlled randomized trials (RCTs), doxazosin-GITS has a faster onset of action and better safety compared with the immediate-release doxazosin formulation.[17–19] Given the proven efficacy and tolerability of doxazosin-GITS and tamsulosin for LUTS/BPH treatment, these 2 specific α_1-blockers are widely being used in clinical practice. However, it still remains controversial whether these 2 most frequently α_1-blockers are comparable with regards to efficacy and tolerability,[20] with only a few published trials available to directly compare efficacy and safety.[21–28] Therefore, our study aimed to perform a systematic review and meta-analysis of study data published in the English and Asian literature to evaluate the efficacy and AEs of doxazosin-GITS vs. tamsulosin in patients with LUTS/BPH.

2. Materials and methods

2.1. Study selection

A systematic search of PubMed, EMBASE, Cochrane Library, CNKI, Wanfang, and Vip databases was performed to identify appropriate published trials from their inception up to March 2021 which directly compared doxazosin-GITS with tamsulosin. The following MESH search terms were used for the literature search: "randomized controlled trial," "doxazosin gastrointestinal therapeutic system," "tamsulosin," "benign prostate hyperplasia," and "lower urinary tract symptoms." The "related articles" function was used to broaden the search, and all abstracts, studies, and citations were reviewed. There were no restrictions on publication language and status. If a study was published in other languages, one author translated the full text of the article, and another author checked it. Any conflicts between these 2 authors were settled by group discussion until a consensus was reached.

2.2. Inclusion and exclusion criteria

Since this study is a meta-analysis, an approval by the Ethical Committee was not required. Trials were selected if they met the following criteria: RCTs; direct comparison of doxazosin-GITS with tamsulosin; patients with clinical BPH who suffered from LUTS; reports on at least 1 outcome of interest mentioned below or the possibility to extract or to calculate relevant data.

Trials were excluded if they were not an RCT; patients with other urological disorders than LUTS/BPH; patients who received concomitant therapy with antimuscarinics, cholinergic agents, other α_1-blockers, 5α-reductase inhibitors, or antiandrogens within the previous 6 months; no outcomes of interest (specified later) were reported or inability to calculate or extrapolate the necessary parameters; cohort, case-control or case series, reviews, or editorials.

2.3. Data extraction and outcomes of interest

Two reviewers independently extracted and analyzed the following data: the first author, publication year, sample size, study design, mean age, country, dosage and intake frequency of doxazosin-GITS or tamsulosin, follow-up time, and outcomes of interest. The following outcomes were extracted to compare doxazosin-GITS and tamsulosin for the treatment of LUTS/BPH: efficiency variables including the change from baseline to study end of the total International Prostate Symptom Score questionnaire (IPSS-T), IPSS voiding subscore (IPSS-V; i.e., IPSS questions 1, 3, 5, and 6), IPSS storage subscore (IPSS-S; i.e., IPSS questions 2, 4 and 7), maximum urine flow rate (Q_{max}), and postvoid residual (PVR). Safety and tolerability were evaluated by the incidence of adverse events (AEs), including asthenia, dizziness, headache, postural hypotension, retrograde or abnormal ejaculation, and flu symptoms. For the purpose of a more precise evaluation, we constructed subgroups according to the different dosages of doxazosin-GITS and tamsulosin. Any disagreements regarding RCT eligibility were resolved by discussion among all authors until consensus was reached.

2.4. Study quality

The selected RCTs' quality was evaluated using the Jadad scale[29] and Cochrane risk of bias based on the criteria published in the Cochrane Handbook for Systematic Reviews of Intervention.[30] The risk of bias consisting of selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective reporting), and other biases were assessed using the software RevMan 5.3 (Cochrane Library Software, Oxford, UK). Three potential bias judgments (low, high, or unclear risk) were determined for every single trial during the assessment. A judgment of low risk was made when all the 7 items met the criteria for "low risk," and a judgment of high risk of bias was made when at least 1 of the 7 items was assessed as "high risk." Two reviewers independently assessed the quality of the studies, and any disagreements were resolved by consensus.

The JADAD scale assesses 4 aspects: random sequence generation, randomized concealment, blinding method, and withdrawal/drop-out. Each one was judged as "appropriate," "unclear," and "not appropriate." An "appropriate" had a score of 2 points, and each "unclear" had a score of 1 point, while "not appropriate" had a score of zero. Trials with a total score of less than 3 were considered as "low" methodological quality.

2.5. Statistical analysis

The meta-analysis was performed based on the recommendations of the Cochrane Collaboration and the Quality of Reporting of Meta-analyses (QUORUM) guidelines.[31] All statistical analyses were performed using software STATS 12. For continuous variables weighted the mean difference (WMD) was used and for dichotomous parameters the risk ratio (RR) was used, both with

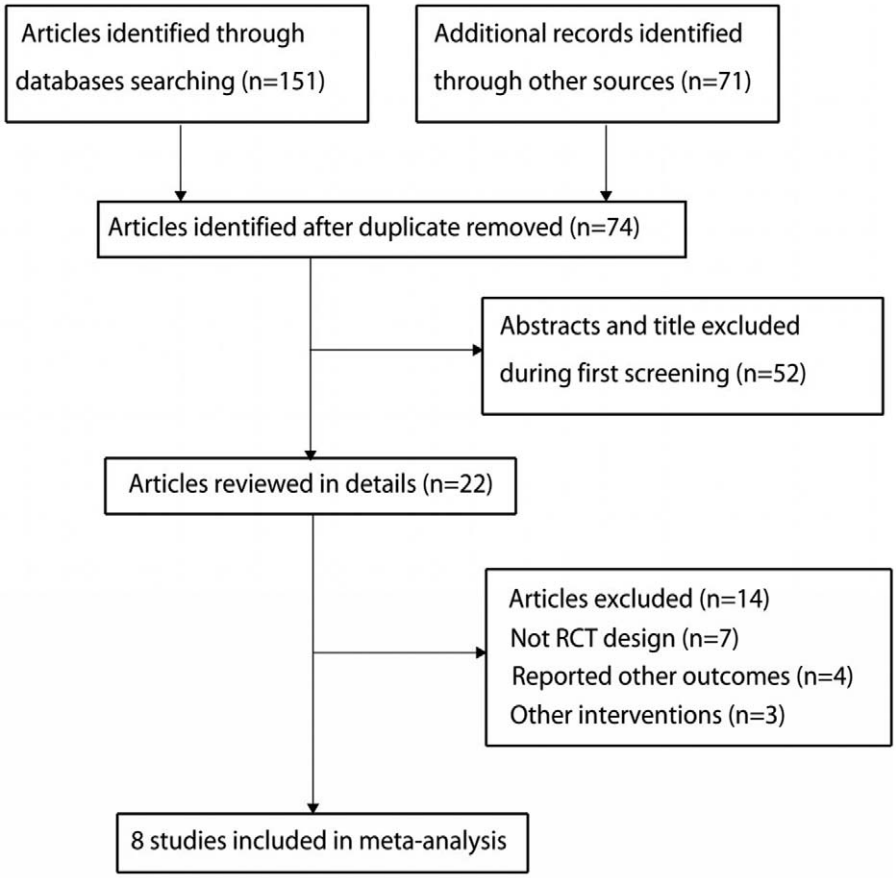

Figure 1. Flowchart showing the selection criteria of the studies for meta-analysis.

95% confidence intervals (CI). All the pooled effects were determined using the z test, and $P < .05$ was considered statistically significant. The quantity of heterogeneity among the included studies was assessed by the I2 test. When I2 < 50% and the evidence showed no heterogeneity, we used the fixed-effects (FE) model; otherwise, we used the random-effects (RE) model. Based on the different dosages of the agents, we also performed subanalyses, including "doxazosin-GITS 4 mg/8 mg vs. tamsulosin 0.4 mg/0.8 mg," "doxazosin-GITS 4 mg vs. tamsulosin 0.2 mg," and "doxazosin-GITS 4 mg vs. tamsulosin 0.4 mg," respectively. Sensitivity analyses were performed by omitting a trial each time during the analysis. Published bias was assessed by using funnel plots.

3. Results

3.1. Characteristics of the selected studies

In total, 222 studies were retrieved during the first database search. After removing duplicate publications, 74 records remained. Fifty-two articles were excluded. The remaining 22 studies were retrieved for further evaluations, and 14 studies were further excluded due to the following reasons: not RCT design (n = 7), reported other outcomes (n = 4), and patients received other interventions (n = 3). As a result, 8 RCTs[19–26] were selected for our meta-analysis (Fig. 1), which included a total number of 1,021 patients. The characteristics of these studies are shown in Table 1. The follow-up duration ranged from 8 to 20 weeks, while 52 to 207 individuals were included in each individual trial. Four trials were conducted in China, 2 in Korea, 1 in the UK, and the remaining 1 in Brazil.

3.2. Efficacy variables

All of the included studies reported the effect of doxazosin-GITS versus tamsulosin on IPSS-T, and the summary result indicated patients in the doxazosin-GITS group were associated with more significant improvement in IPSS-T than those in the tamsulosin group (WMD: −1.81; 95% CI: −2.95 to −0.67; $I^2 = 96.8\%$, $P_{\text{heterogeneity}} < .001$; (Fig. 2). Moreover, significant heterogeneity was detected across the included studies.

Five of the included studies reported the effect of doxazosin-GITS versus tamsulosin on IPSS-S. the summary WMD indicated no significant difference between doxazosin-GITS and tamsulosin (WMD: −0.84; 95% CI: −1.76 to 0.08; $I^2 = 98.5\%$, $P_{\text{heterogeneity}} < .001$; Fig. 3), and significant heterogeneity was detected among included studies.

Five of the included studies reported the effect of doxazosin-GITS versus tamsulosin on IPSS-V, and a significant improvement in IPSS-V was observed in patients who received doxazosin-GITS with significant heterogeneity (WMD: −1.32; 95% CI: −1.88 to −0.76; $I^2 = 92.0\%$, $P_{\text{heterogeneity}} < .001$; Fig. 4).

Five of the included studies reported the effect of doxazosin-GITS versus tamsulosin on Qmax, and the pooled WMD

Table 1

Characteristics of the selected RCTs.

	Author name	Year	Sample size	Study design	Age (year, mean ± SD)	Country	Dosage/frequency/cycle	Outcomes	Follow-up period
1	Kirby[19]	2003	52	Randomized, double-blind crossover study	65	UK	Doxazosin-GITS was started at 4 mg/d and tamsulosin at 0.4 mg/d, and then titrated to 8 mg/d and 0.8 mg/d, respectively, after 4 wks of therapy if the increase in Qmax was <3 mL/s or the reduction in total IPSS was < 30%.	IPSS-T, IPSS-V, IPSS-S, Q_{max}, AEs	20 wks
2	Tang et al[20]	2004	60	RCT	61.2 ± 8.1	China	Doxazosin 4 mg/d or tamsulosin (sustained release) 0.2 mg/d	IPSS-T, IPSS-V, IPSS-S, AEs	12 wks
3	Ma et al[21]	2005	124	RCT	64.2 ± 24.1	China	Doxazosin-GITS (group A) and tamsulosin (group B) were started at 4 mg/d and 0.4 mg/d. If the increase in Qmax was < 3 mL/s or the reduction in total IPSS was < 30% after 4 wks of therapy then the dose was titrated to 8 mg/d and 0.8 mg/d respectively.	IPSS-T, Q_{max}, AEs, QOL, PVR	16 wks
4	Pompeo et al[22]	2006	165	RCT	62.1 ± 7.2	Brazil	A 2-wk washout phase and a 12-wk active treatment phase Doxazosin 4 mg/d, tamsulosin 0.4 mg/d	IPSS-T, Q_{max}, QOL, AEs	12 wks
5	Xue et al[23]	2007	117	RCT	66.0 ± 7.1	China	2-wk placebo run-in phase, 4 mg/d doxazosin or 0.2 mg/d tamsulosin for 6 wks	IPSS-T, IPSS-V, IPSS-S, Q_{max}, PVR, AEs	8 wks
6	Hong et al[24]	2009	96	RCT	58.3 ± 6.1	Korea	0.2 mg of tamsulosin and 4 mg of doxazosin daily for a period of 3 mo	IPSS-T, QOL, AEs	12 wks
7	Chung et al[25]	2011	207	RCT	61.7 ± 0.9	Korea	A 12-wk daily treatment with doxazosin-GITS 4 mg or tamsulosin (sustained release) 0.2 mg	IPSS-T, IPSS-V, IPSS-S, QOL, AEs	12 wks
8	Zhang et al[26]	2011	200	RCT	68.6 ± 8.3	China	4 mg doxazosin-GITS or 0.2 mg tamsulosin for 8 wks.	IPSS-T, IPSS-V, IPSS-S, Q_{max}, PVR, QOL	8 wks

AEs = adverse events, IPSS-S = IPSS storage subscore, IPSS-T = total International Prostate Symptom Score, IPSS-V = IPSS voiding subscore, NR = not reported, PVR = postvoid residual, Q_{max} = maximum urine flow rate, QoL = quality of life, RCT = randomized controlled trial.

indicated a significant difference between doxazosin-GITS and tamsulosin (WMD: 0.89; 95% CI: 0.74–1.04; I^2 = 0.0%, $P_{heterogeneity}$ = .477; with no evidence of heterogeneity; Fig. 5).

Two of the included studies reported the effect of doxazosin-GITS versus tamsulosin on PVR, and the summary WMD indicated patients in the doxazosin-GITS group were associated with smaller changes than those in the tamsulosin group (WMD: −6.25; 95% CI: −12.18 to −0.32; I^2 = 0.0%, $P_{heterogeneity}$ = .739; with no evidence of heterogeneity; Fig. 6).

Two of the included studies reported the effect of doxazosin-GITS versus tamsulosin on quality of life, and the summary WMD indicated no significant difference between doxazosin-GITS and tamsulosin (WMD: −0.07; 95% CI: −0.76 to 0.61; I^2 = 88.5%, $P_{heterogeneity}$ = .003) (Fig. 7).

We additionally performed subanalyses to evaluate the efficacy and tolerability of different doxazosin-GITS and tamsulosin dosages. Except for doxazosin 4 mg/8 mg versus tamsulosin 0.4 mg/0.8 mg in IPSS-T (WMD: −1.60; 95% CI: −1.79 to −1.42; I^2 = 0.0%, $P_{heterogeneity}$ = .570), results indicated superior efficacy and tolerability of doxazosin-GITS similar to the previously seen results (Figs. 8–11).

3.3. Safety and tolerability variables

No significant difference was observed for the overall AEs between doxazosin-GITS and tamsulosin (RR: 0.77; 95% CI: 0.54–1.08; I^2 = 58.0%, $P_{heterogeneity}$ = .036) (Fig. 12) as well as in the doxazosin 4 mg/8 mg versus tamsulosin 0.4 mg/0.8 mg subanalyses (Fig. 13).

There were no significant differences in AEs for dizziness (RR: 0.83; 95% CI: 0.48–1.44; I^2 = 4.7%, $P_{heterogeneity}$ = .387), headache (RR: 0.94; 95% CI: 0.52–1.70; I^2 = 0.0%, $P_{heterogeneity}$ = .745), asthenia (RR: 0.75; 95% CI: 0.39–1.46; I^2 = 0.0%, $P_{heterogeneity}$ = .693), and postural hypotension (RR: 0.74; 95% CI: 0.33–1.65; I^2 = 49.6%, $P_{heterogeneity}$ = .114) between the 2 groups (Fig. 14). The incidence of ejaculation disorders and flu-like symptoms were also comparable (Table 2).

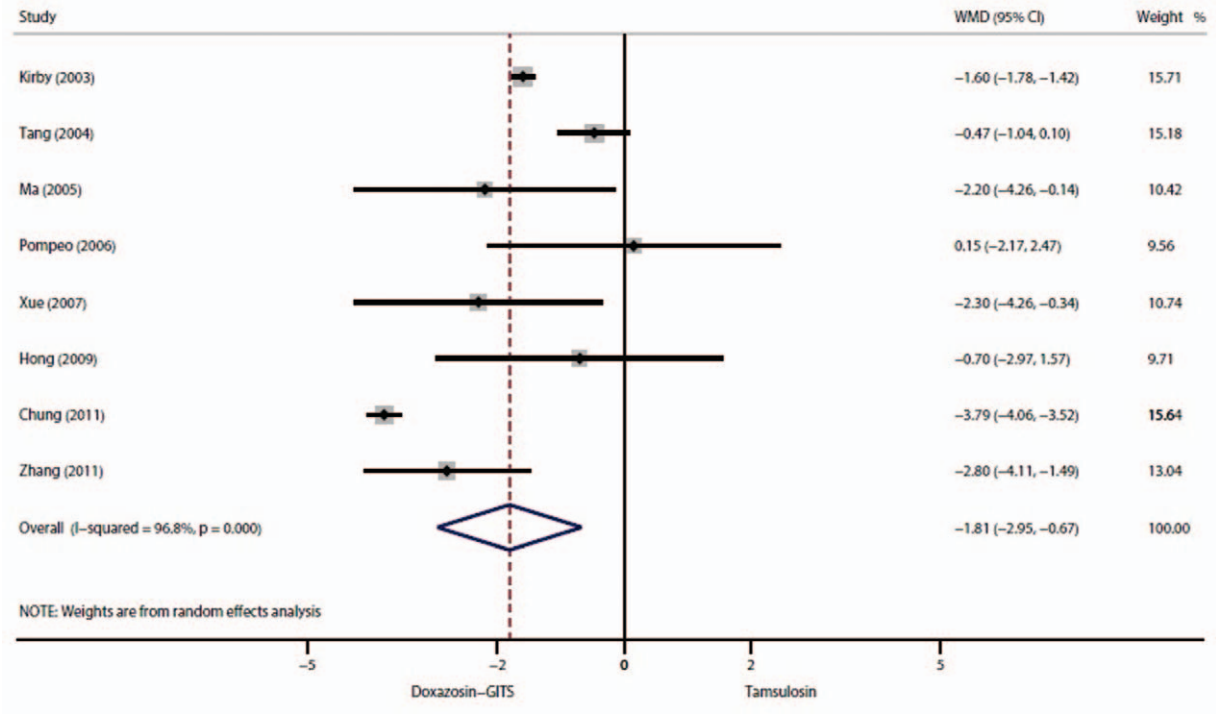

Figure 2. Forest plot and meta-analysis of total IPSS.

3.4. Sensitivity analysis and publication bias

Based on previously mentioned criteria, 4 RCTs were judged to have a high risk of bias (Figs. 15 and 16). The JADAD scores for each study are shown in Table 3. Two RCTs[24,26] had a JADAD score lower than 3, which indicated a poorer quality. These 2 studies counted for 296 patients (%).

Sensitivity analysis was carried out by omitting each of the selected trials one at a time from the overall analysis. Except for

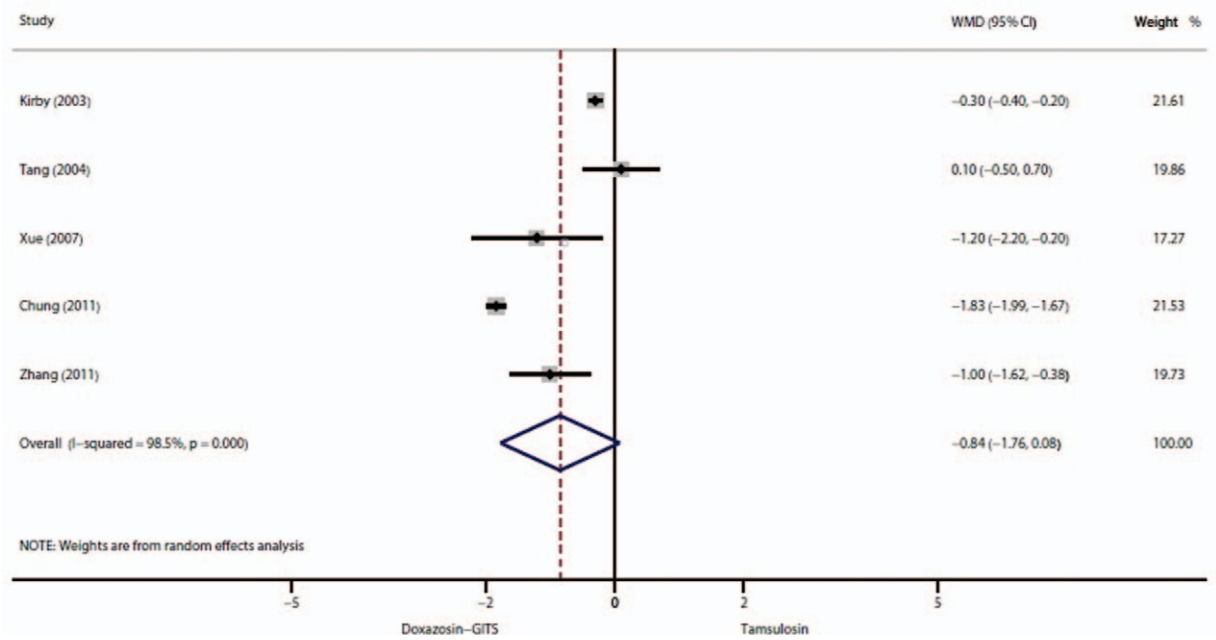

Figure 3. Forest plot and meta-analysis of storage IPSS.

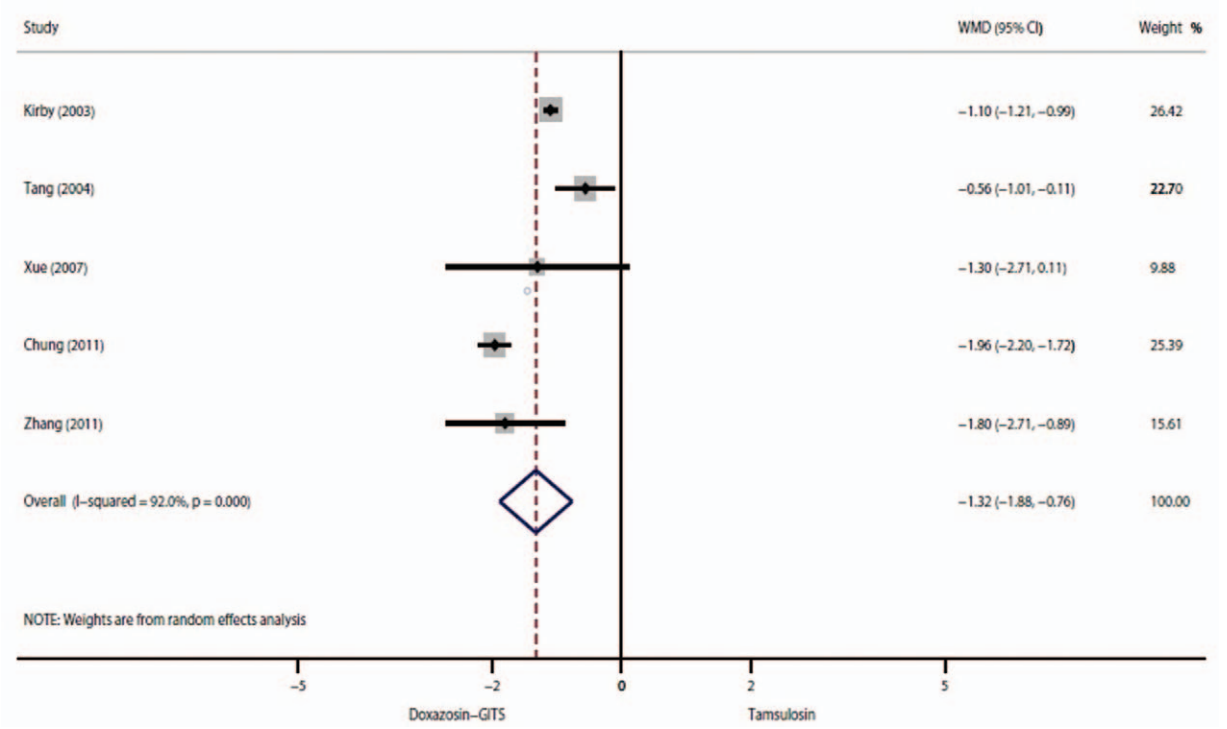

Figure 4. Forest plot and meta-analysis of voiding IPSS.

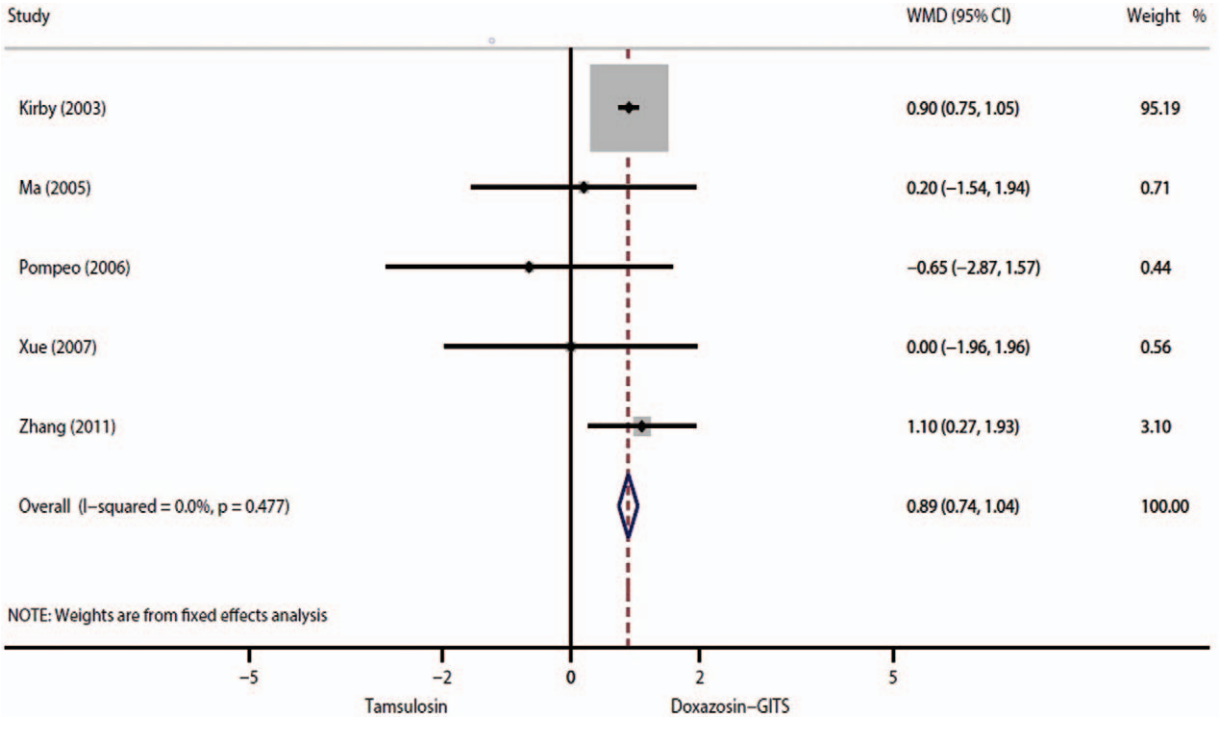

Figure 5. Forest plot and meta-analysis of maximum urine flow rate (Q_{max}).

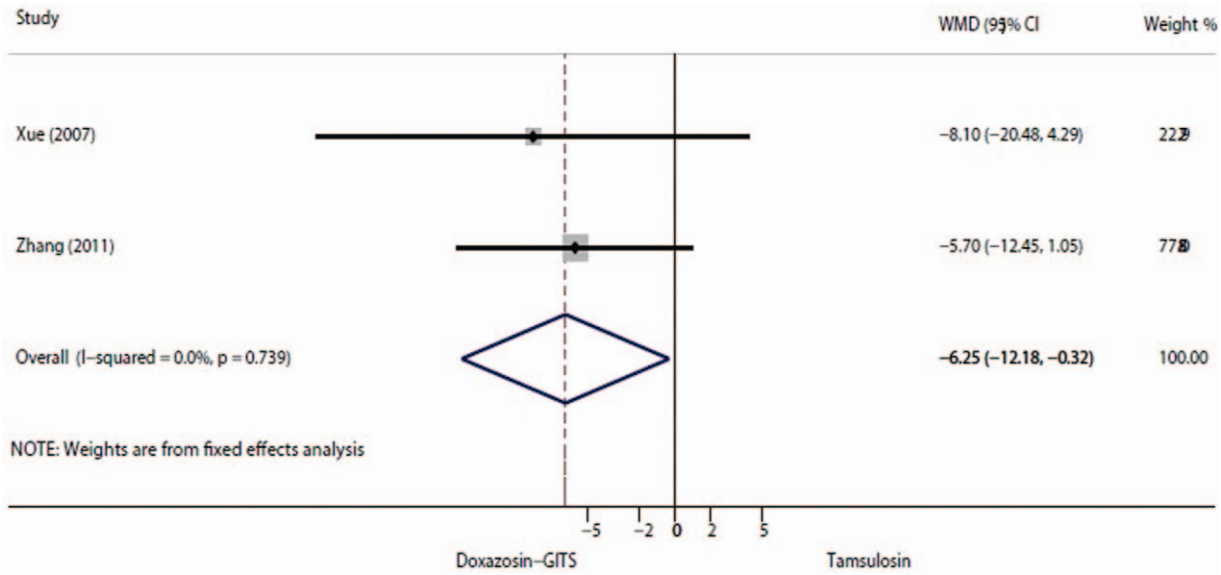

Figure 6. Forest plot and meta-analysis of postvoid residual (PVR).

omitting the Kirby trial,[14] Q_{max} changed significantly compared to the original analysis. However, omitting each trial one at a time did not influence the other results, indicating that the results of our meta-analysis were stable. Funnel plots were used to assess the publication bias of included studies, but no significant publication bias was found.

4. Discussion

Treatment modalities for LUTS/BPH in general and the number of drugs in particular have evolved extensively during the last 3 decades. For moderate-to-severe LUTS, pharmacological treatment with or without conservative management is the strongly recommended treatment option in all current LUTS/BPH guidelines.[11,32,33] Although prostate surgery's efficacy is still higher than pharmacological treatment and perioperative morbidity has dramatically reduced in the last decades, oral drugs are still favored by patients to avoid anesthesia, hospital admission, and severe AEs.

The currently available oral drugs for LUTS/BPH include α_1-blockers, 5α-reductase inhibitors, muscarinic receptor antagonists, phosphodiesterase type 5 inhibitors, and plant extracts,

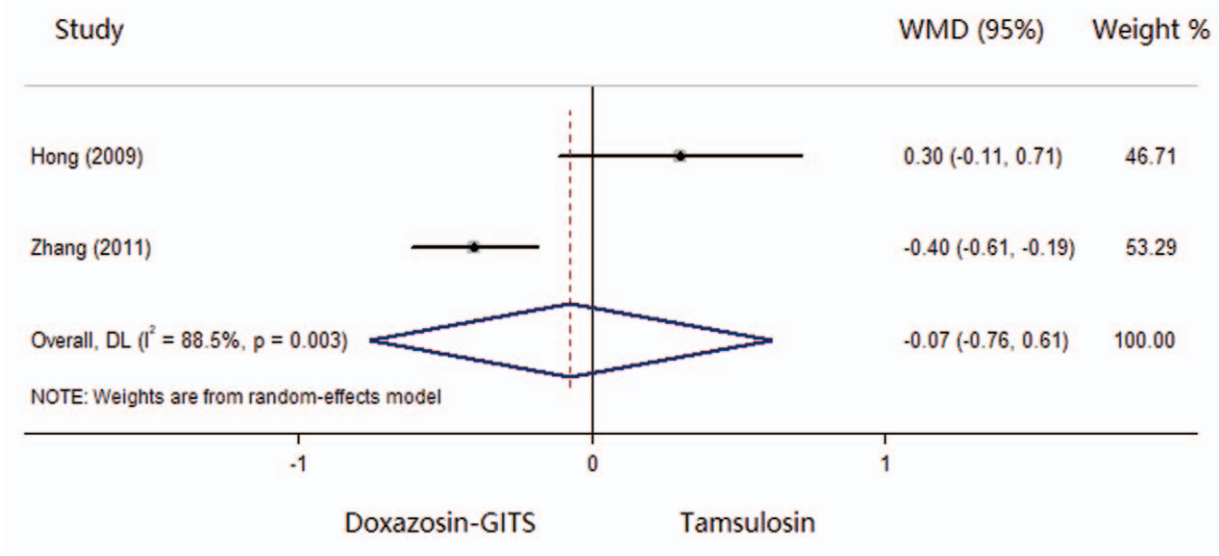

Figure 7. Forest plot and meta-analysis of the quality of life (QoL).

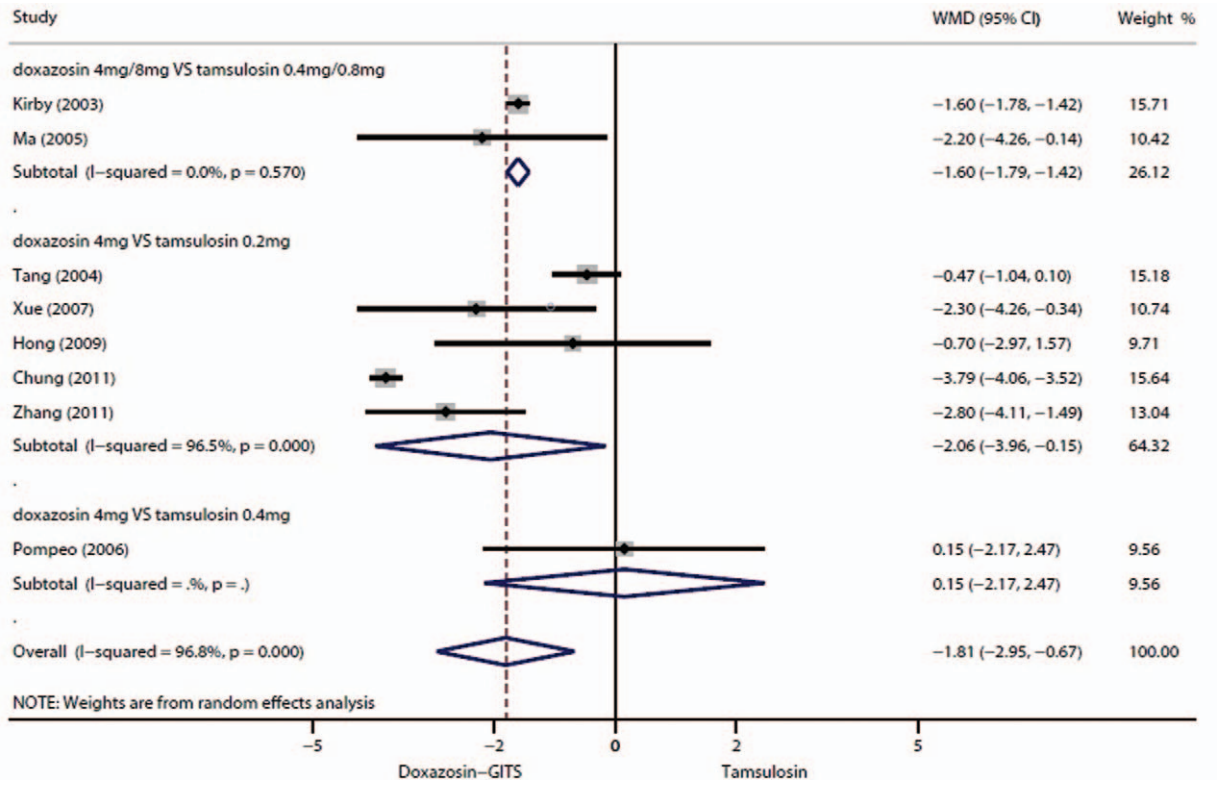

Figure 8. Forest plot and sub-meta-analysis of total IPSS when using different dosages.

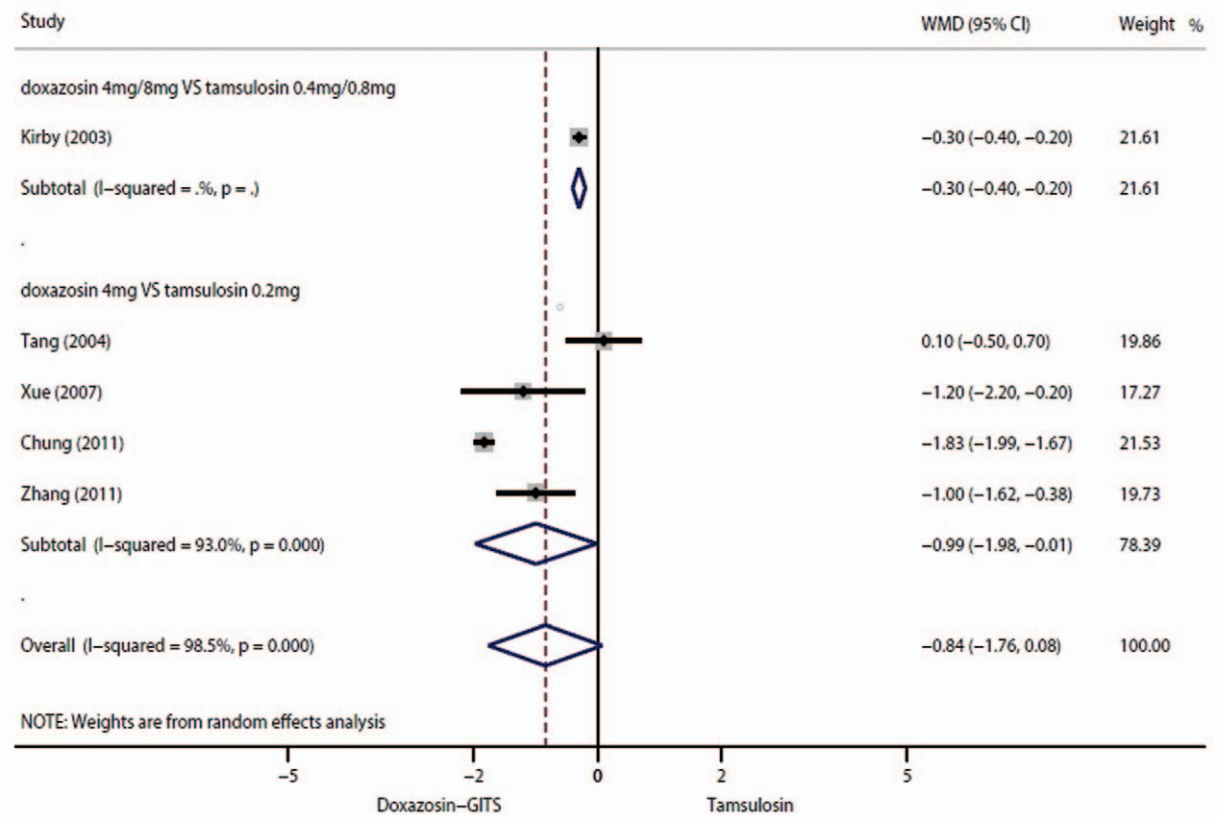

Figure 9. Forest plot and sub-meta-analysis of storage IPSS when using different dosages.

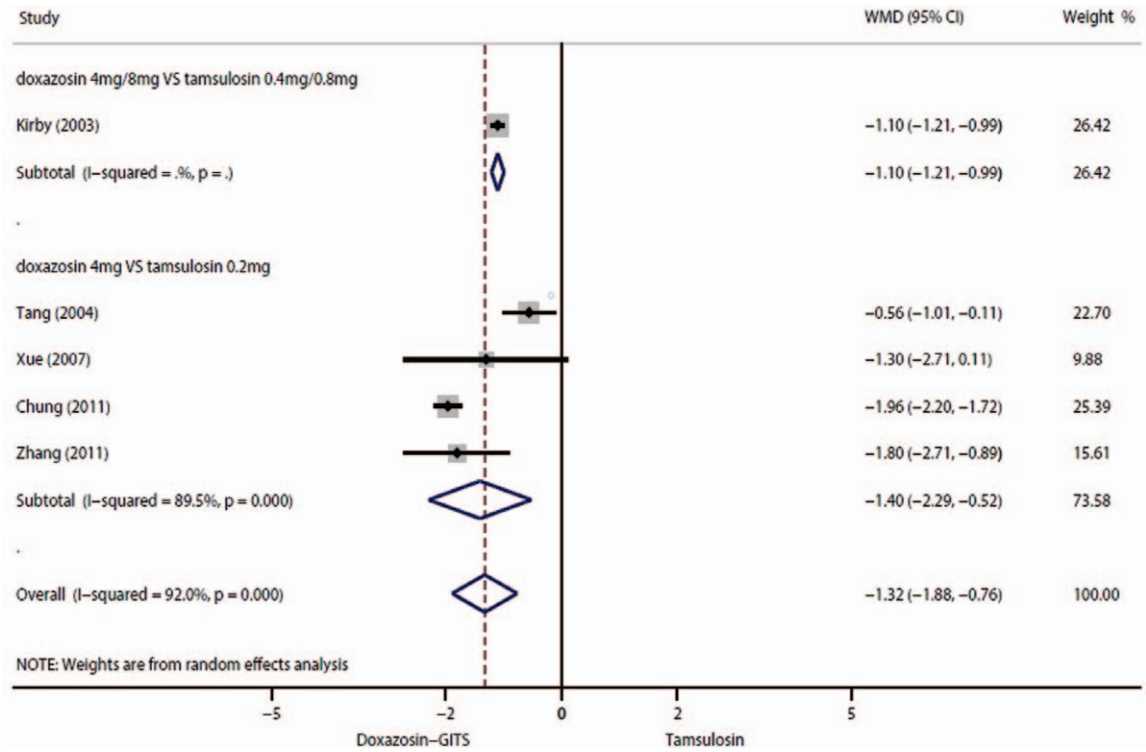

Figure 10. Forest plot and sub-meta-analysis of voiding IPSS based on different dosages.

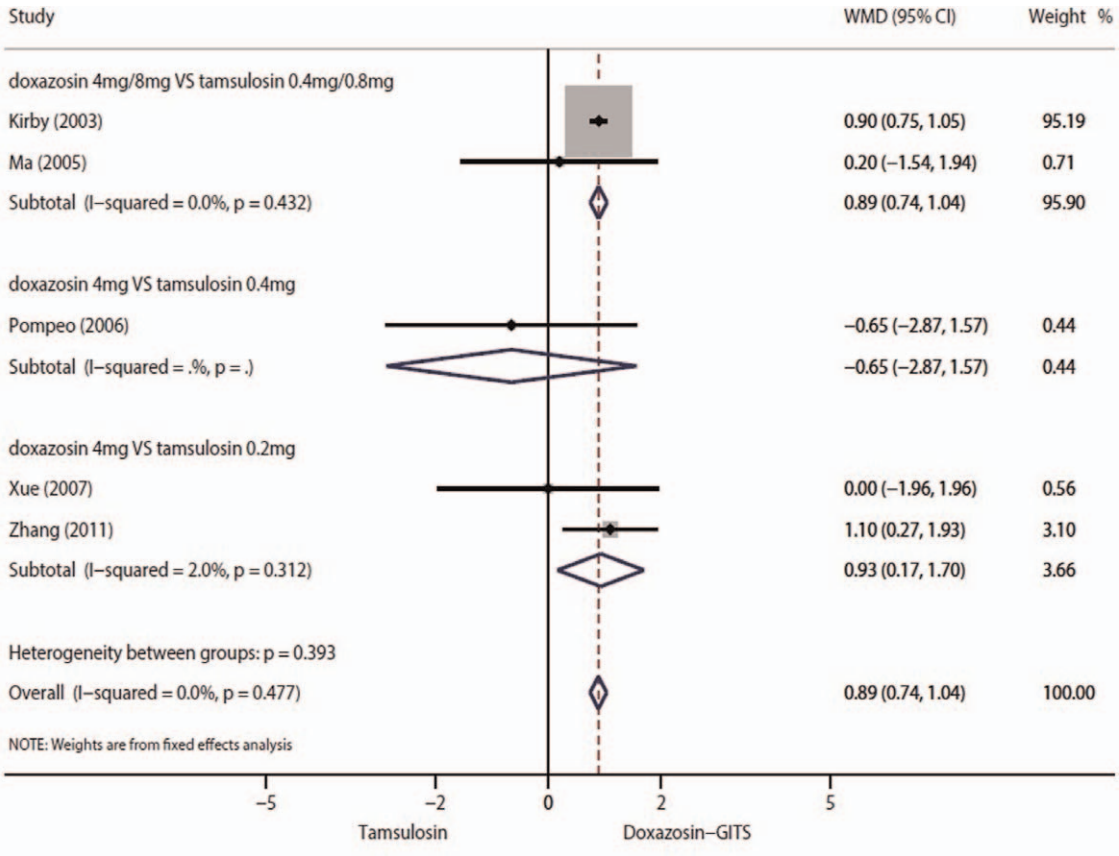

Figure 11. Forest plot and sub-meta-analysis of maximum urine flow rate (Q_{max}) when using different dosages.

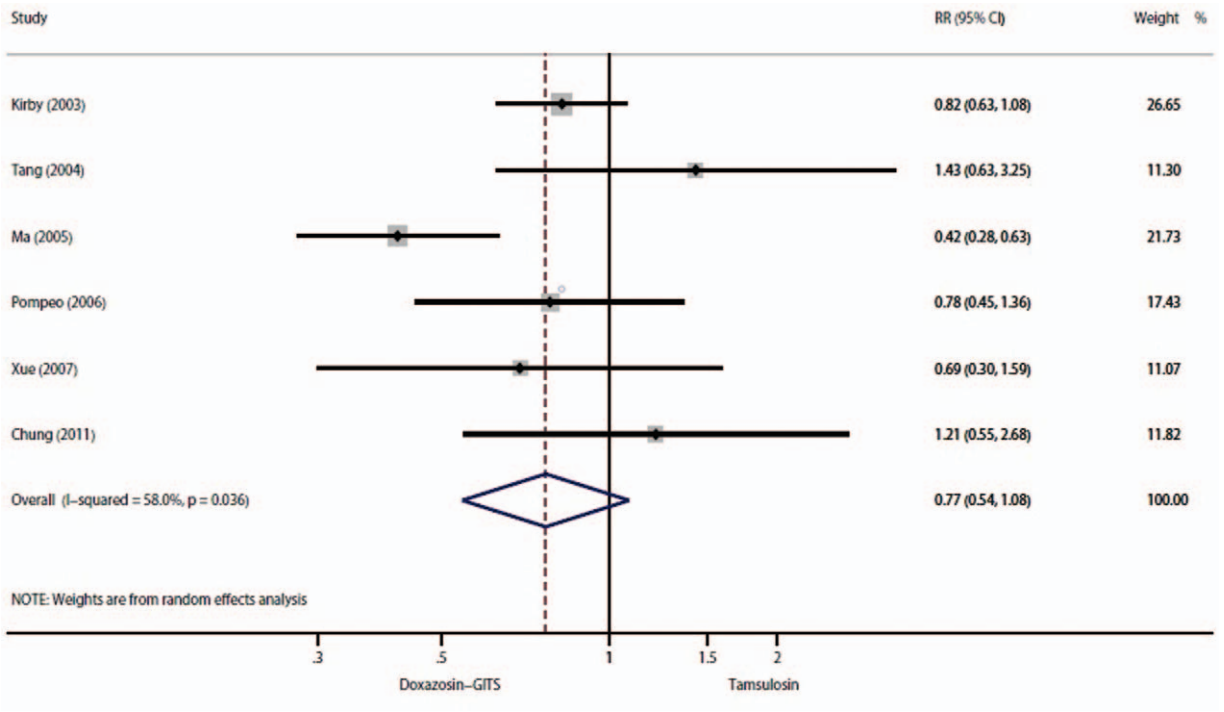

Figure 12. Forest plot and meta-analysis of overall adverse events (AEs).

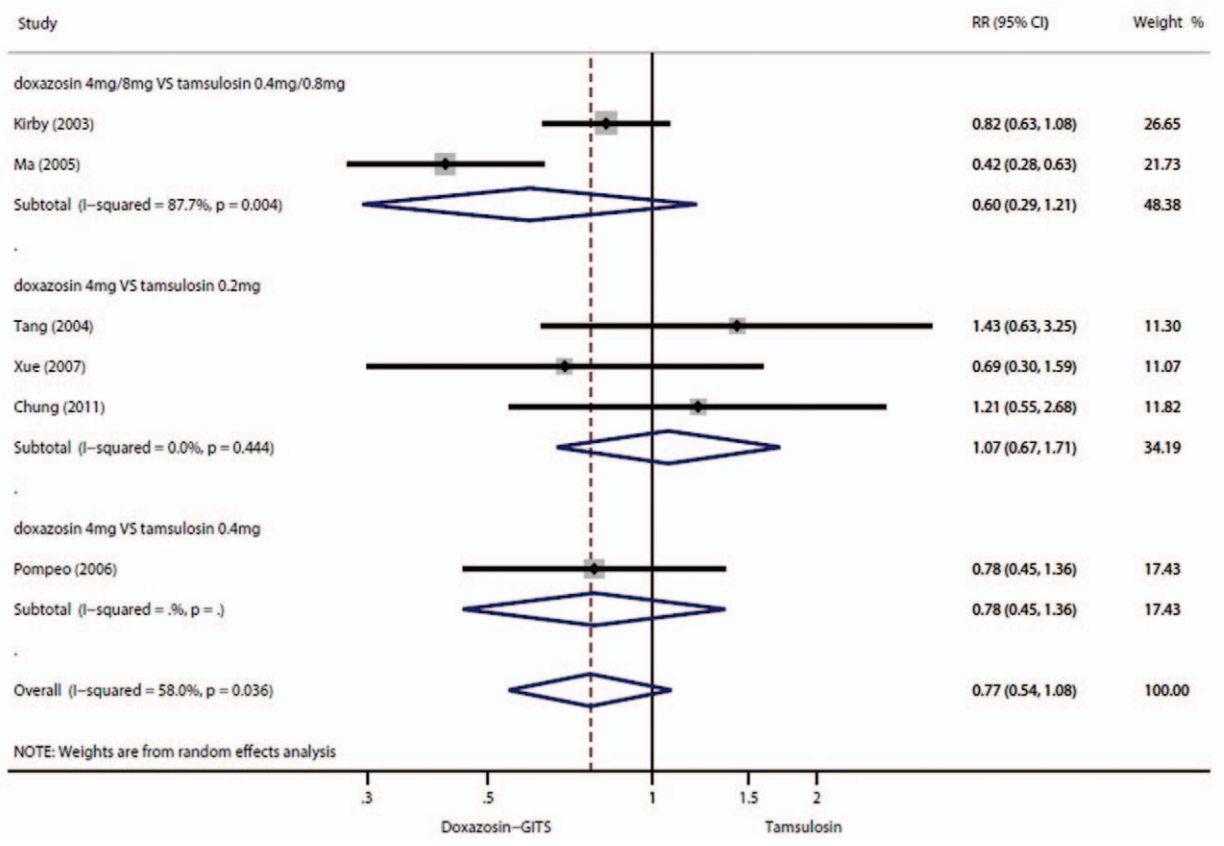

Figure 13. Forest plot and sub-meta-analysis of overall incidence of AEs based on different dosages.

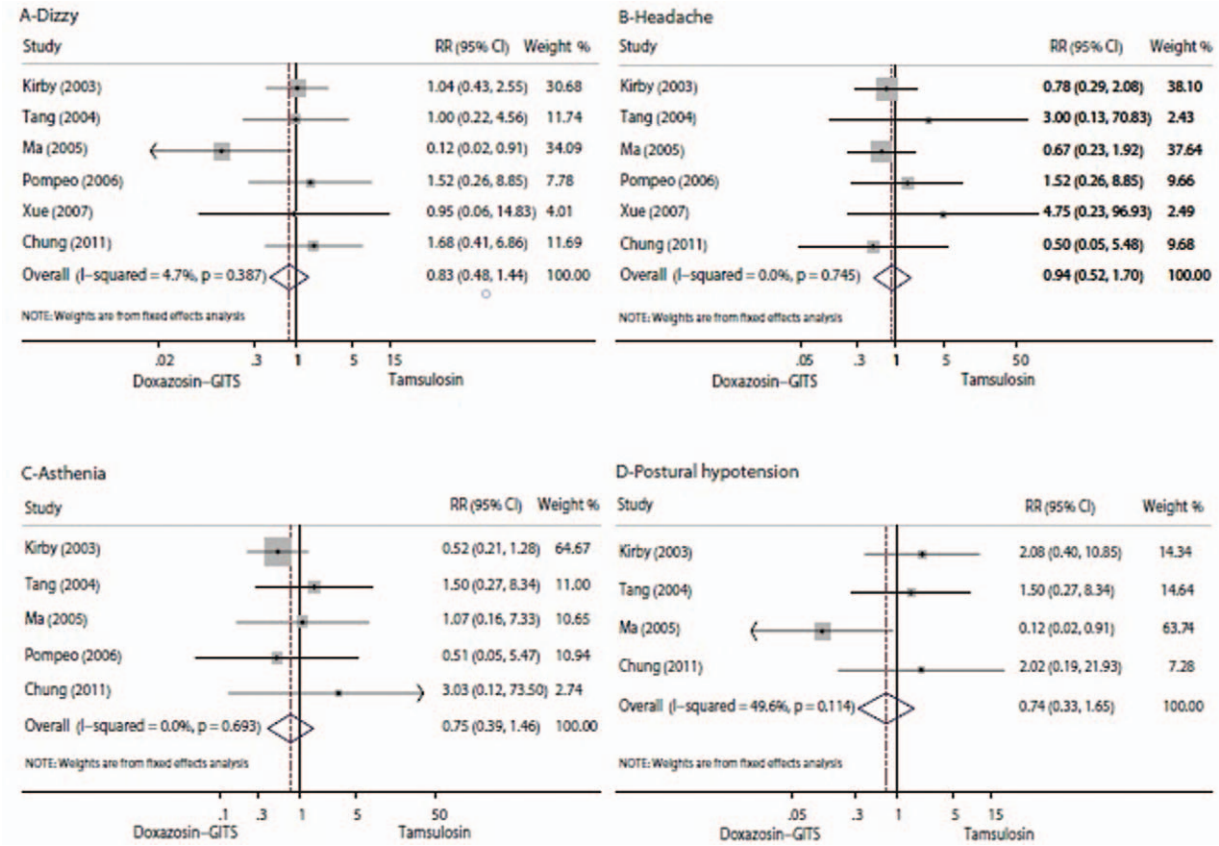

Figure 14. Forest plot and meta-analysis of AEs.

either alone or in combination. Despite the diversity of different drug classes and formulations, α_1-blockers are still first-line drugs to treat LUTS/BPH, and doxazosin and tamsulosin are the most popular ones worldwide. α_1-blockers are available in various forms and formulations, with similar clinical impact but not with the same efficacy and tolerability.[12,34] A study by Rahardjo et al[35] found that tamsulosin had superior efficacy compared to the standard doxazosin formulation. Standard doxazosin formulation more adversely affects the blood pressure and cause dizziness and hypotension. Doxazosin GITS has better pharmacokinetic profile and drug delivery rate compared to the standard doxazosin formulation.[36] A standard treatment option for individual patients is still lacking,[37] and, therefore, a systematic comparison of widely used formulations of α_1-blockers is necessary. Our present meta-analysis closed this information gap and revealed that doxazosin-GITS had advantages in terms of total IPSS-T, IPSS-S, IPSS-V, and total AEs over tamsulosin.

Table 2

Detailed JADAD scores of the selected RCTs.

	Random sequence generation			Randomized concealment			Blind method			Withdrawal		
Study	Appropriate (2)	Unclear (1)	Not appropriate (0)	Appropriate (2)	Unclear (1)	Not appropriate (0)	Appropriate (2)	Unclear (1)	Not appropriate (0)	Described (1)	Not described (0)	Total
Kirby (2003)		√				√		√		√		3
Tang (2004)	√					√			√	√		3
Zhifang (2005)		√				√	√			√		4
Pompeo (2006)		√			√			√		√		4
Xue (2007)		√				√			√	√		3
Hong (2009)		√				√			√		√	1
Chung (2011)	√				√			√		√		5
Zhang (2011)		√				√			√	√		2

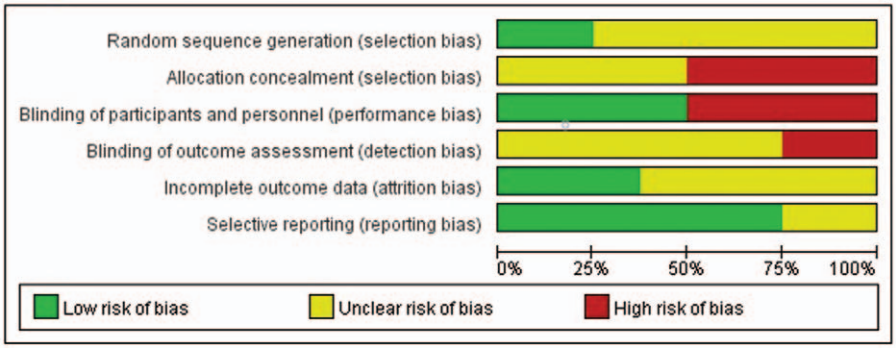

Figure 15. Graph of risk of bias for each selected trial.

Our meta-analysis results show superior efficacy of doxazosin-GITS over tamsulosin in terms of IPSS-T, IPSS-S, and IPSS-V. Our findings are in line with a previously published network meta-analysis, where doxazosin also demonstrated a superior improvement in IPSS and Q_{max} in comparison to other α_1-blockers and 5α-reductase inhibitors as mono-drug therapy.[38]

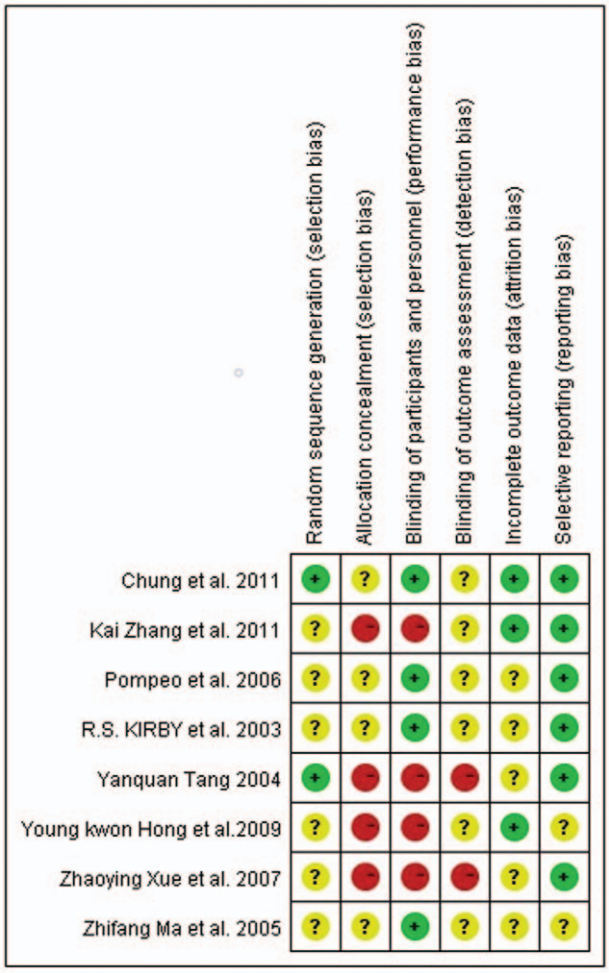

Figure 16. Summary of the risk of bias assessment for each selected trial.

It was mentioned in the latest European Association of Urology (EAU) Guideline on Male LUTS that α_1-receptors not only located within the prostate but also in the bladder, spinal cord, and other places could also be related to LUTS.[32] The more robust efficacy of doxazosin could be explained by it being a relatively nonspecific α_1-blocker, while tamsulosin is a relatively specific α_{1A}-blocker.[37–41] Therefore, doxazosin can block more α_1-and receptors located in the prostate, bladder, and spinal cord. Nasu et al[42] found that α_{1A}-adrenoceptor was the most abundant receptor in the human prostate. Kojima et al[43] demonstrated that the percentages of α_{1A}, α_{1B}, and α_{1D} were 41.2%, 9.8%, and 49.1%, respectively. Hence, doxazosin-GITS may have a better efficacy by blocking more α_1-adrenoceptors in the prostate. Second, LUTS/BPH is caused not only by bladder outlet obstruction but also by detrusor overactivity. And in the human detrusor, the expression level of α_{1A}-adrenoceptor is much less than α_{1D}-adrenoceptor.[44,45] Since tamsulosin primarily blocks α_{1A}-adrenoceptor, its relieving effects of LUTS/BPH are much more limited than doxazosin. Third, Smith et al[46] found that α_{1D}-adrenoceptor predominates in the human spinal cord. Ishizuka et al[47] further demonstrated that doxazosin, when administered intrathecally, decreased micturition pressure in both normal rats and rats with postobstruction bladder hypertrophy. Hence, doxazosin may better relieve LUTS/BPH symptoms by blocking α_{1D}- adrenoceptor in the spinal cord. Fourth, the serum half-life of doxazosin (immediate release and GITS) is approximately 20 hours, whereas tamsulosin is only 10 to 13 hours (modified release) or 14 to 15 hours (OCAS formulation).[48] Therefore, doxazosin is more effective in relieving nocturia due to more stable drug concentrations during the night than tamsulosin.[28,49]

The previous study demonstrated that tamsulosin has fewer cardiovascular side effects,[46] which may be due to its high α_{1A}- and α_{1D}-adrenoceptor selectivity. However, FAERS Database showed that doxazosin-GITS was lower in the rank-order of signal scores compared to alfuzosin, tamsulosin, and terazosin.[50] The present study demonstrated no statistically significant differences in AEs incidences between those 2 drugs, both of which were well tolerated by patients.

The general dose of tamsulosin varies from 0.2 mg, 0.4 mg, and 0.8 mg per day, and for doxazosin-GITS, it varies between 4 mg and 8 mg per day. In the 8 included trials, the dosage was adjusted in only 2 trials. That meant both of these 2 α_1-blockers could achieve effective response quickly and decrease the risk of the first-dose effect. Based on our experience, the most common dose

Table 3

Overall analysis of a_1-blockers induced AEs.

	Doxazosin GITS AE (N)	Tamsulosin AE (N)	RR	95% CI	*P* value
Dizziness	21	26	0.830	(0.478,1.442)	.509
Headache	18	20	0.936	(0.516,1.696)	.826
Asthenia	13	18	0.754	(0.389,1.462)	.403
Postural hypotension	10	14	0.741	(0.334,1.646)	.461
Dizziness/headache/asthenia/postural Hypotension	62	78	0.918	(0.554,1.521)	.739
Retrograde ejaculation/	0	3	0.257	(0.029,2.270)	.221
abnormal ejaculation	3	5	0.616	(0.151,2.518)	.500
Retrograde ejaculation/ abnormal ejaculation	3	8	0.457	(0.143,1.461)	.187
Flu-like syndrome	2	3	0.722	(0.144,3.627)	.692

CI = confidence Interval, GITS = gastro-intestinal therapeutic system, RR = relative risk.

in China for doxazosin-GITS and tamsulosin for BPH is 4 mg/d and 0.2 mg/d, respectively. Based on the subgroup analyses (doxazosin-GITS 4 mg/d vs tamsulosin 0.2 mg/d), doxazosin-GITS was associated with better IPSS, IPSS-V, and IPSS-S improvement.

Our present meta-analysis demonstrated that doxazosin-GITS had better efficiency and less overall AEs compared to tamsulosin. To our knowledge, this is the first meta-analysis comparing doxazosin-GITS with tamsulosin, providing sound evidence for the treatment of BPH-related LUTS. However, our meta-analysis does have some limitations. First, the number of high-quality RCTs was limited, with some trials having low quality. Second, the analyses revealed heterogeneities, which may have affected the whole analyses' stability, but were difficult to evaluate. For example, one single trial[21] had a major influence on the result of Q_{max} based on the sensitivity analyses. Small-study effects also might be a problem in our meta-analysis, which in turn might lead to exaggerated summary estimates. However, the use of subgroup analysis and sensitivity analyses allowed us to explore the potential causes for the observed heterogeneity. Third, we only searched for original trials published in English and Chinese, and publication bias was inevitable. Fourth, stratified analyses focused on the dose of intervention and control and whether the effectiveness between groups is differing based on ethnics and the duration of follow-up were not calculated due to a smaller number of included studies. Fifth, various evaluation parameters for treatment efficacy, including IPSS, storage IPSS, voiding IPSS, Qmax, and PVR, were used among studies in our meta-analysis, resulting in the impossibility of pooling all the data collected. Therefore, they might be another source of heterogeneity. Subgroup analysis and sensitivity analysis were performed to assess the risks of pooled results. We did not find any significant publication bias in our meta-analysis.

In summary, we performed an up-to-date meta-analysis based on 8 RCTs comparing the efficacy and tolerability of doxazosin-GITS versus tamsulosin. Our meta-analysis demonstrated that doxazosin-GITS was superior with higher efficiency in improving the IPSS (total IPSS, IPSS-S, IPSS-V) with lower total adverse events. More multicenter randomized control studies with larger sample sizes with high quality are required to support our conclusions based on our meta-analysis.

Author contributions

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Investigation: Jianming Guo.
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Writing – original draft: Jianming Guo.
Writing – review & editing: Rong Tang.

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