



# Comparing efficacy and safety of mirabegron, tamsulosin, and solifenacin in ureteral stent-related symptoms: outcomes from a network meta-analysis

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**Background:** Although ureteral stents are a well-established and commonly used method for renal drainage, the ureteral stent-related symptoms (SRSs) they cause in patients cannot be ignored. It is currently unclear whether mirabegron has a place in the treatment of SRSs. Our study aims to systematically evaluate the efficacy and safety of mirabegron in treating SRSs in adult patients.

**Methods:** Through a systematic search of multiple scientific databases before August 2023, we performed a systematic review and meta-analysis of the primary outcomes of interest according to the PRISMA. Analysis was performed under multivariate random-effects network models and effects of drugs was ranked with surface under the cumulative ranking curves (SUCRA) probabilities.

**Results:** Sixteen studies involving 2,002 patients were included. All regimens (including mirabegron, solifenacin, and tamsulosin) were significantly better than placebo in urinary symptoms. Solifenacin was associated with more adverse drug events than mirabegron and tamsulosin. The SUCRA values showed that mirabegron was the best in the outcomes of body pain (71.5%), sexual matters (76.4%), and adverse events (70.5%). Solifenacin was the best in the outcomes of urinary symptoms (73.1%), general health (81.0%), and work performance (85.1%). Tamsulosin had the lowest rate of all outcomes.

**Conclusions:** Compared with traditional drugs for relieving SRSs, mirabegron performs best in terms of alleviating body pain, sexual matters, and adverse events, with little difference in urinary symptoms and general health. Further high-quality prospective double-blinded randomized controlled trials (RCTs) are required to provide sufficient evidence supporting our observations.

**Keywords:** Mirabegron; ureteral stent-related symptoms (ureteral SRSs); network meta-analysis; urolithiasis; drug therapies

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## Introduction

Since its first application in 1967, ureteral stents have gradually become an indispensable tool in urology (1). However, the use of this tool causes great majority of

patients to suffer from stent-related symptoms (SRSs) and reduces their quality of life (2). Studies have shown that more than 80% of patients experience stent-related pain, 58% have reduced work capacity, and 32% have sexual

dysfunction (2,3).

It is reported that the most commonly used medications for treating SRSs are alpha-blockers and anticholinergic agents (4). Nevertheless, it has been found that they might result in some adverse effects in clinical practice, such as headache, constipation, and orthostatic hypotension (5). These adverse effects bring about poor treatment compliance in patients (6).

Pathogenesis of ureteral SRSs are close to the storage subset of lower urinary tract symptoms caused by overactive bladder syndrome. Treatment options for overactive bladder syndrome might also be effective for SRSs (7). Mirabegron, as an effective treatment for overactive bladder syndrome, has been evaluated by some studies for its efficacy and safety for SRSs (8-10). Although its evaluation results are encouraging, the research limitations caused by sample size and quality of currently available data still raise concerns about the reliability of the conclusion.

In addition, there has been no high-quality evidence of the superiority of mirabegron versus alpha-blockers and anticholinergic agents in SRSs. To provide more sufficient evidence for clinical practice, we performed this network meta-analysis to assess the efficacy and safety among mirabegron, tamsulosin, and solifenacin. We present this article in accordance with the PRISMA-NMA reporting checklist (available at <https://tau.amegroups.com/article/view/10.21037/tau-23-642/rc>) (11).

### Highlight box

#### Key findings

- Mirabegron is an effective and safe treatment method for alleviating stent-related symptoms, with a low incidence of adverse events.

#### What is known and what is new?

- Mirabegron is a selective agonist for beta-3 adrenergic receptors, and its efficacy in the treatment of ureteral stent-related symptoms is still controversial.
- Compared with traditional drugs for relieving stent-related symptoms, mirabegron performs best in terms of alleviating body pain, sexual matters, and adverse events, with little difference in urinary symptoms and general health.

#### What is the implication, and what should change now?

- Mirabegron may be more effective and safer for patients with ureteral stent-related symptoms.

## Methods

### Literature search and eligibility criteria

A systematic search was performed to identify studies in PubMed, Embase, Web of Science, and Cochrane Library before August 2023. Search terms included: “stent-related symptoms”, “stent-related discomfort”, “ureteral”, “stent”, “mirabegron”, “beta-3 receptor agonist”, “beta-3 agonist”, “alpha blocker”, “tamsulosin”, “antimuscarinic”, “solifenacin”, “RCT”, and “randomized controlled trial”. The above search fields with logical operators were combined to get as many search results as possible and language of publication was not limited.

Randomized controlled trials (RCTs) that met all of the following criteria were included: (I) drug treatments for ureteral SRSs should contain mirabegron, tamsulosin, and solifenacin. (II) Patients underwent ureteral stent placement after extracorporeal shock wave lithotripsy, ureteroscopic lithotripsy, or percutaneous nephrolithotomy. (III) Ureteral stent symptom questionnaire (USSQ) was used to evaluate all outcomes before removal of stents. (IV) Crossover trials, dose titration studies, daily dosing studies, and studies for which full text was not available were excluded.

### Quality assessment

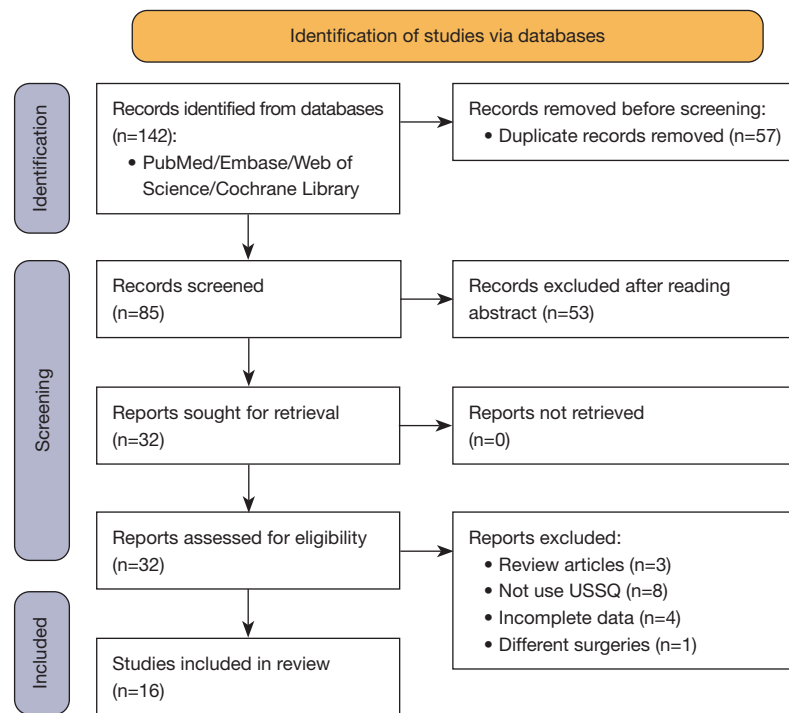
Two independent reviewers assessed each study by using the Cochrane risk-of-bias 2 tool for randomized trials (ROB2) (12), and their differences were resolved through discussion. ROB2 covered the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result.

### Data extraction

The following information will be recorded on a pre-designed standardized form: first author's name, publication year, region, sample size, intervention, follow-up time, USSQ score, and adverse events. The primary outcomes were the USSQ urinary symptom and body pain scores related to SRSs treated with mirabegron, as well as adverse events.

### Statistical analysis

Data analysis was performed by using Stata 17 (StataCorp,



**Figure 1** Flow diagram of the studies selection process. USSQ, ureteral stent symptom questionnaire.

College Station, Texas, USA), and the standard multivariate random effects network model was used to assess outcomes (13). Using surface under the cumulative ranking curves (SUCRA) probabilities and relative ranking probability to assess the efficacy of different drugs (14). Furthermore, inconsistency was tested by Higgins and Dias model, and small-study effects and publication bias were evaluated by a comparison-adjusted funnel plot.

### Registration

This study registered on PROSPERO and registration number was CRD42023473188.

## Results

### Characteristics of the individual studies

The whole process of literature retrieval and screening for network meta-analysis is shown in *Figure 1*. One hundred and forty-two studies were screened from the database, and ultimately 16 studies with 2,002 patients were enrolled in our analysis (5,8,9,15-27). All trials involved urinary symptoms efficacy assessment, but only 14 trials involved

general health and sexual performance (5,8,9,15,17-20,22-27), 13 trials involved pain-relief efficacy and work performance (5,8,9,15,18-20,22-27), 5 trials involved adverse effects (9,16,21,23,27). The detailed information of included studies is presented in [Table S1](#).

Quality assessment of each trial is shown in [Figure S1](#). SUCRA and mean rank are described in detail in [Table 1](#).

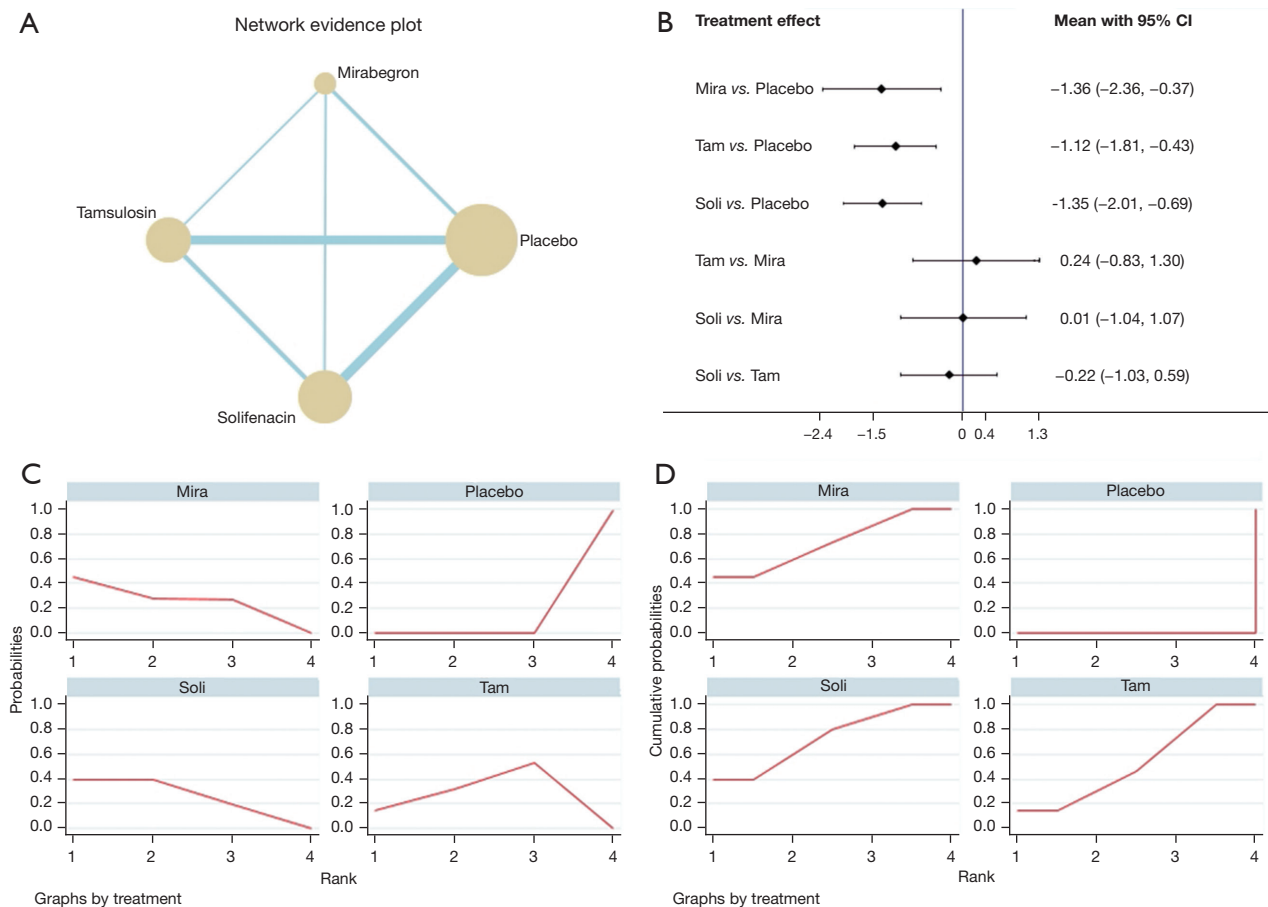
### Network meta-analysis of urinary symptoms

The results of urinary symptoms are shown in *Figure 2*. Network graph is shown in *Figure 2A*. When placebo was used as the comparative reference, three treatments, mirabegron [mean difference (MD), -1.36; 95% confidence interval (CI): -2.36, -0.37], tamsulosin (MD, -1.12; 95% CI: -1.81, -0.43) and solifenacin (MD, -1.35; 95% CI: -2.01, -0.69) were associated with a statistically significant improvement. Furthermore, no significant differences were observed among these three regimens (*Figure 2B*). The analysis results based on SUCRA advocated that solifenacin had the highest probability of being the best intervention for urinary symptom relief (SUCRA 73.1%, mean rank 1.8). Ranking of mirabegron was in the middle (SUCRA 72.9%, mean rank 1.8), and tamsulosin (SUCRA 53.9%, mean

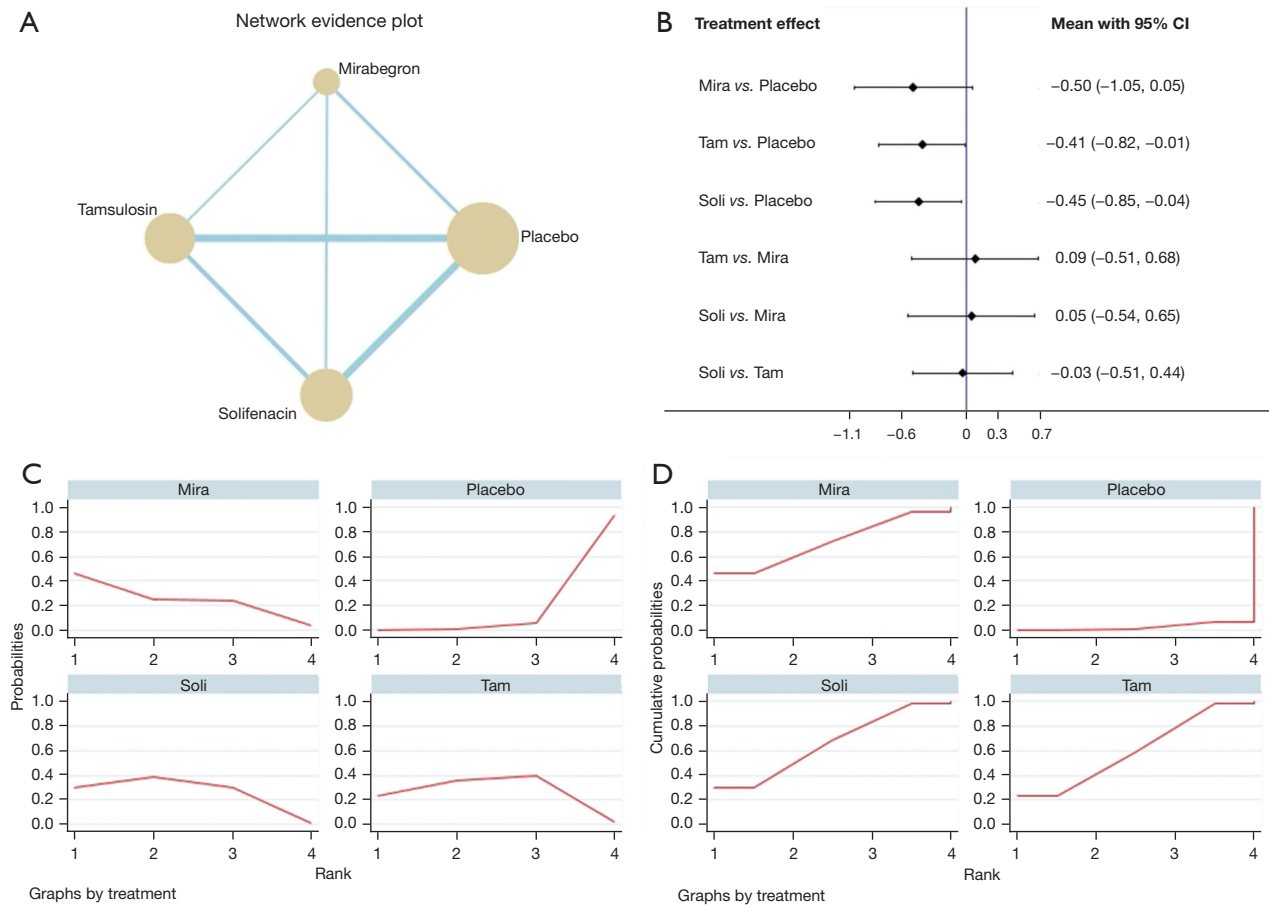
**Table 1** The summary of SUCRA and mean rank

Outcomes	SUCRA (%)				Mean rank			
	Mirabegron	Solifenacin	Tamsulosin	Placebo	Mirabegron	Solifenacin	Tamsulosin	Placebo
Urinary symptoms	72.9	73.1	53.9	0.1	1.8	1.8	2.4	4.0
Body pain	71.5	66.1	59.8	2.6	1.9	2.0	2.2	3.9
General health	80.9	81.0	31.6	6.6	1.6	1.6	3.1	3.8
Work performance	56.5	85.1	12.8	45.5	2.3	1.4	3.6	2.6
Sexual matters	76.4	63.7	31.3	28.5	1.7	2.1	3.1	3.1
Adverse events	70.5	4.6	53.6	71.2	1.9	3.9	2.4	1.9

SUCRA, surface under the cumulative ranking curves.



**Figure 2** Network analysis of urinary symptom relieve efficacy. (A) Network plots of the comparisons between different interventions. (B) Forest plot of network meta-analysis. (C) Ranking probability plot. (D) Cumulative probability ranking plot. CI, confidence interval; Mira, mirabegron; Tam, tamsulosin; Soli, solifenacin.



**Figure 3** Network analysis of body pain relieve efficacy. (A) Network plots of the comparisons between different interventions. (B) Forest plot of network meta-analysis. (C) Ranking probability plot. (D) Cumulative probability ranking plot. CI, confidence interval; Mira, mirabegron; Tam, tamsulosin; Soli, solifenacin.

rank 2.4) was the worst one among the three interventions (Figure 2C,2D).

**Network meta-analysis of body pain**

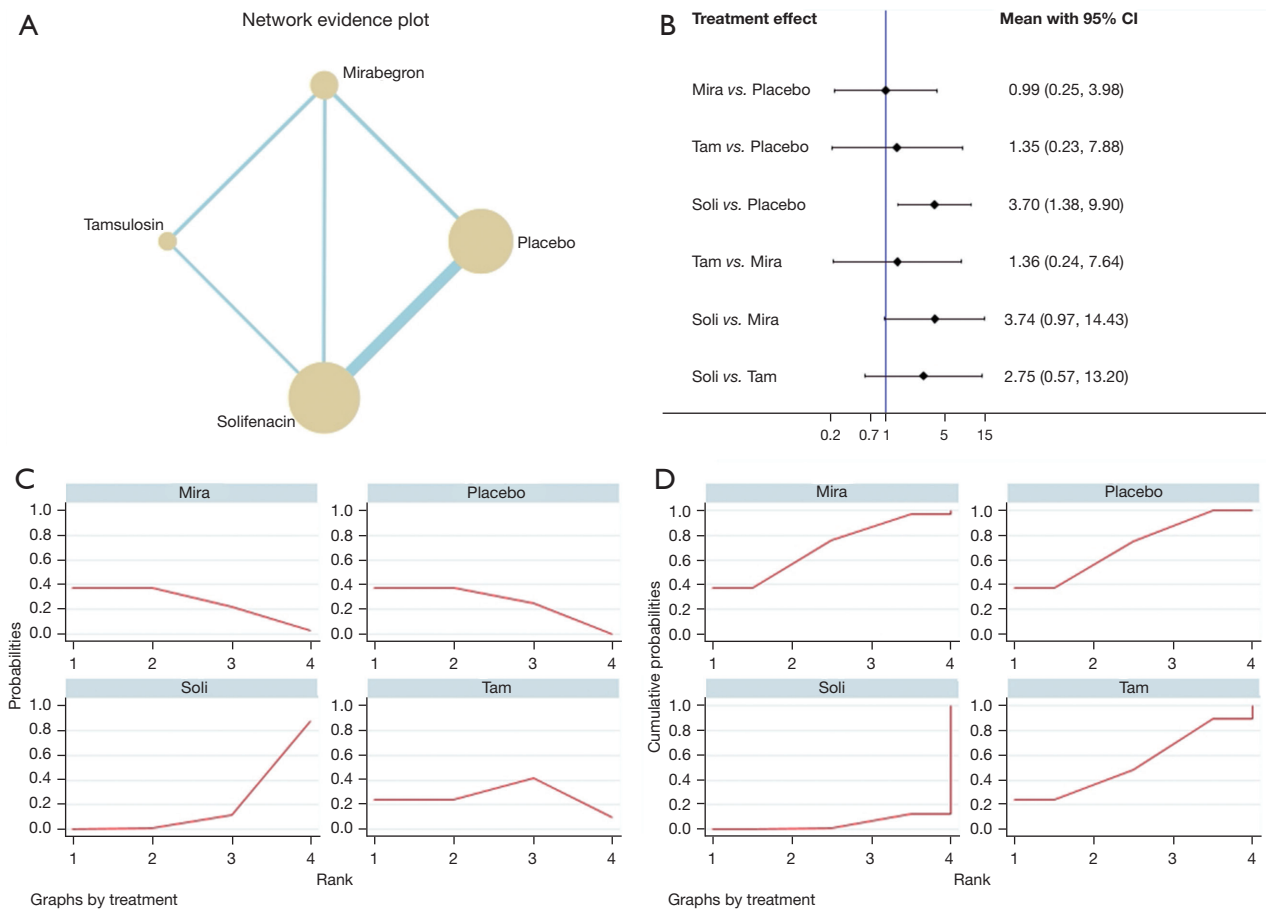
The results of body pain are shown in Figure 3. Network graph is shown in Figure 3A. When placebo was used as the comparative reference, tamsulosin (MD, -0.41; 95% CI: -0.82, -0.01) and solifenacin (MD, -0.45; 95% CI: -0.85, -0.04) had shown remarkable efficacy in relieving body pain. In addition, no significant differences were observed among these three regimens in relieving body pain (Figure 3B). Mirabegron had the highest probability of being the best intervention for urinary symptom relief (SUCRA 71.5%, mean rank 1.9). Solifenacin (SUCRA 66.1%, mean rank 2.0) came off second best, and tamsulosin (SUCRA 59.8%,

mean rank 2.2) was the worst one (Figure 3C,3D).

**Network meta-analysis of general health, working performance and sexual matters**

Compared to the placebo, mirabegron (MD, -0.50; 95% CI: -0.95, -0.04) and solifenacin (MD, -0.48; 95% CI: -0.82, -0.15) showed a significant advantage in terms of general health. In addition, solifenacin was likely to be the first choice (SUCRA 81.0%, mean rank 1.6) in this domain of general health. Mirabegron (SUCRA 80.9%, mean rank 1.6) came off second best, and tamsulosin ranked third (SUCRA 31.6%, mean rank 3.1) (Figure S2).

There were no significant differences in working performance scale. SUCRA values provided potential efficacy for these three active treatment regimens at 85.1%



**Figure 4** Network analysis of adverse events. (A) Network plots of the comparisons between different interventions. (B) Forest plot of network meta-analysis. (C) Ranking probability plot. (D) Cumulative probability ranking plot. CI, confidence interval; Mira, mirabegron; Tam, tamsulosin; Soli, solifenacin.

for solifenacin, 56.5% for mirabegron, and 12.8% for tamsulosin (Figure S3).

Similar to the previous result, no significant differences were observed in terms of sexual matters. The analysis results based on SUCRA suggested that mirabegron might be the best intervention to improve sexual function for patients with SRSs (SUCRA 76.4%, mean rank 1.7). Solifenacin (SUCRA 63.7%, mean rank 2.1) came off second best, and tamsulosin might be the worst one (SUCRA 31.3%, mean rank 3.1) (Figure S4).

#### Network meta-analysis of adverse events

The results of adverse events are shown in Figure 4. Network graph is shown in Figure 4A. When placebo was used as the comparative reference, the difference in

adverse events of solifenacin was statistically significant [risk ratio (RR), 3.70; 95% CI: 1.38, 9.90] (Figure 4B). Based on the outcome of SUCRA, mirabegron might be the best one (SUCRA 70.5%, mean rank 1.9). Tamsulosin came off second best (SUCRA 53.6%, mean rank 2.4), and solifenacin was worst among the three interventions (SUCRA 4.6%, mean rank 3.9) (Figure 4C,4D).

#### Risk of bias

Comparing the differences between direct and indirect evidence to evaluate inconsistency, all P value was more than 0.05. No evidence showed inconsistency existing in the network model. Besides, publication bias was analyzed by the comparison-adjusted funnel plot, and no obvious publication bias was detected in most outcomes (Figure S5).

## Discussion

Ureteral stents, as an adjunctive treatment to alleviate or prevent obstruction in the upper urinary tract, have taken an important role in urologic surgery for nearly five decades (9). Moreover, they are also used extensively in endoscopic ureteral stone surgery (5). Though ureteral stents are routinely used, significant discomfort has been reported in up to 80% of patients (4). To alleviate the discomfort, researchers have developed several personalized types of stents by altering stent size, design, composition, and the use of drug coating. However, up to the present time, there is no ideal stent that could avoid SRSs (1). Medical management of SRSs has gradually become a research priority.

In our research, 16 studies recruiting 2,002 patients were included and analyzed. According to the network meta-analysis results, we found that all treatments (including mirabegron, solifenacin, and tamsulosin) were significantly better than placebo in urinary symptoms, and solifenacin was associated with more adverse events than the other two. The SUCRA values indicate that mirabegron is the best in terms of body pain, sexual matters, and adverse events, with little difference from the optimal option in urinary symptoms and general health. Solifenacin performs best in terms of work performance, with little difference from mirabegron in urinary symptoms and general health. Tamsulosin had the lowest ranking of all outcomes.

Previous studies had demonstrated that compared with a placebo, mirabegron significantly improved urinary symptom, which was consistent with our study (25). Several trials have shown that mirabegron was comparable to solifenacin or tamsulosin in improving urinary symptoms (8,9). Interestingly, another study indicated that tamsulosin was better than mirabegron (24). Mirabegron has no known effect on voiding symptoms, whereas tamsulosin affects voiding and storage symptoms, which might explain why mirabegron did not perform as well as tamsulosin on the USSQ urinary symptom score (10).

In terms of relieving body pain, a meta-analysis, including 546 patients, demonstrated that mirabegron was the same as placebo (4). The dosage of analgesics was lower, suggesting that mirabegron might be beneficial in reducing pain (4). Our study further revealed that there was no significant difference in the three treatment regimens, but mirabegron might be the best drug for alleviating body pain. Beta-adrenoceptor agonists could dilate the ureter by targeting  $\beta$ -adrenergic receptors in the mucosa and muscular layers of the ureter, thereby relieving body pain (28). When the

patient took mirabegron before ureteroscopy, it was observed that the success rate of ureteroscopy has been improved due to ureteral dilatation (29). In addition, inhibiting involuntary bladder contractions caused by mechanical stimulation of ureteral stents might be another potential mechanism for pain relief (25). However, the choice of different analgesic drugs, and patients' tolerance of pain, may lead to potential risks of bias.

Regarding safety, compared with the blank control group, patients in the solifenacin group had a higher risk of adverse events. In the comparison of these three drugs, although there was no significant difference, the effect size was comparatively in favor of mirabegron. Constipation and dry mouth are the primary adverse events of mirabegron, which usually are mild and rare (4). Among patients with SRSs treated with 50 mg mirabegron per day during 2 weeks, 4.2% reported constipation and 2.1% reported dry mouth (25). In addition, there were almost no reports of relatively serious adverse events (8,25). The incidence of adverse events in patients with overactive bladder syndrome was roughly consistent (less than 2% for constipation and 0.5% for dry mouth) (30). The above evidence implies that it is safe to treat SRSs with mirabegron.

To our knowledge, our study was the first network meta-analysis that focused on the efficacy and safety of mirabegron treatment for SRSs based on all RCTs using USSQ which might provide a new choice for ureteral stenting patients. Nevertheless, some limitations should be acknowledged. First, only two included studies had a double-blind design, which may cause subjective bias. Second, different stent sizes and lengths, different outcome assessment times, and different use of analgesics may lead to potential biases. Nevertheless, this heterogeneity could better represent the real scenario in every day clinical practice. Third, only two representative drugs, tamsulosin and solifenacin, were included, and some other common drugs such as terazosin, doxazosin, and tolterodine were not included in the analysis. Fourth, although all the included studies used USSQ, the sample size of per arm in some studies were not enough (at least 64 patients) to detect the differences in the mean index scores for each domain of the USSQ with 80% power, which may lead to potential bias. We strongly encourage further high-quality RCTs to improve the quality of meta-analysis on the treatment of SRSs.

## Conclusions

In conclusion, our network meta-analysis reveals that

compared with traditional drugs for relieving SRSs, mirabegron performs best in terms of alleviating body pain, sexual matters, and adverse events, with little difference in urinary symptoms and general health. Further high-quality prospective double-blinded RCTs are required to provide sufficient evidence supporting our observations.

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## Footnote

*Reporting Checklist:* The authors have completed the PRISMA-NMA reporting checklist. Available at <https://tau.amegroups.com/article/view/10.21037/tau-23-642/rc>

*Peer Review File:* Available at <https://tau.amegroups.com/article/view/10.21037/tau-23-642/prf>

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <https://tau.amegroups.com/article/view/10.21037/tau-23-642/coif>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are 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.

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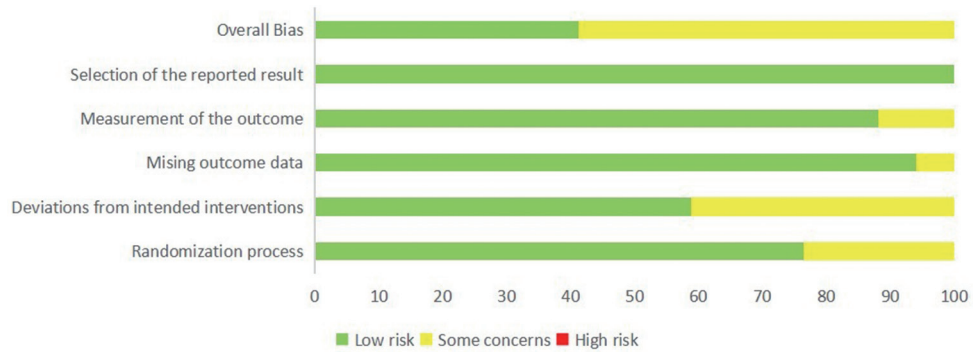


Figure S1 Summary of quality assessment included in the study.

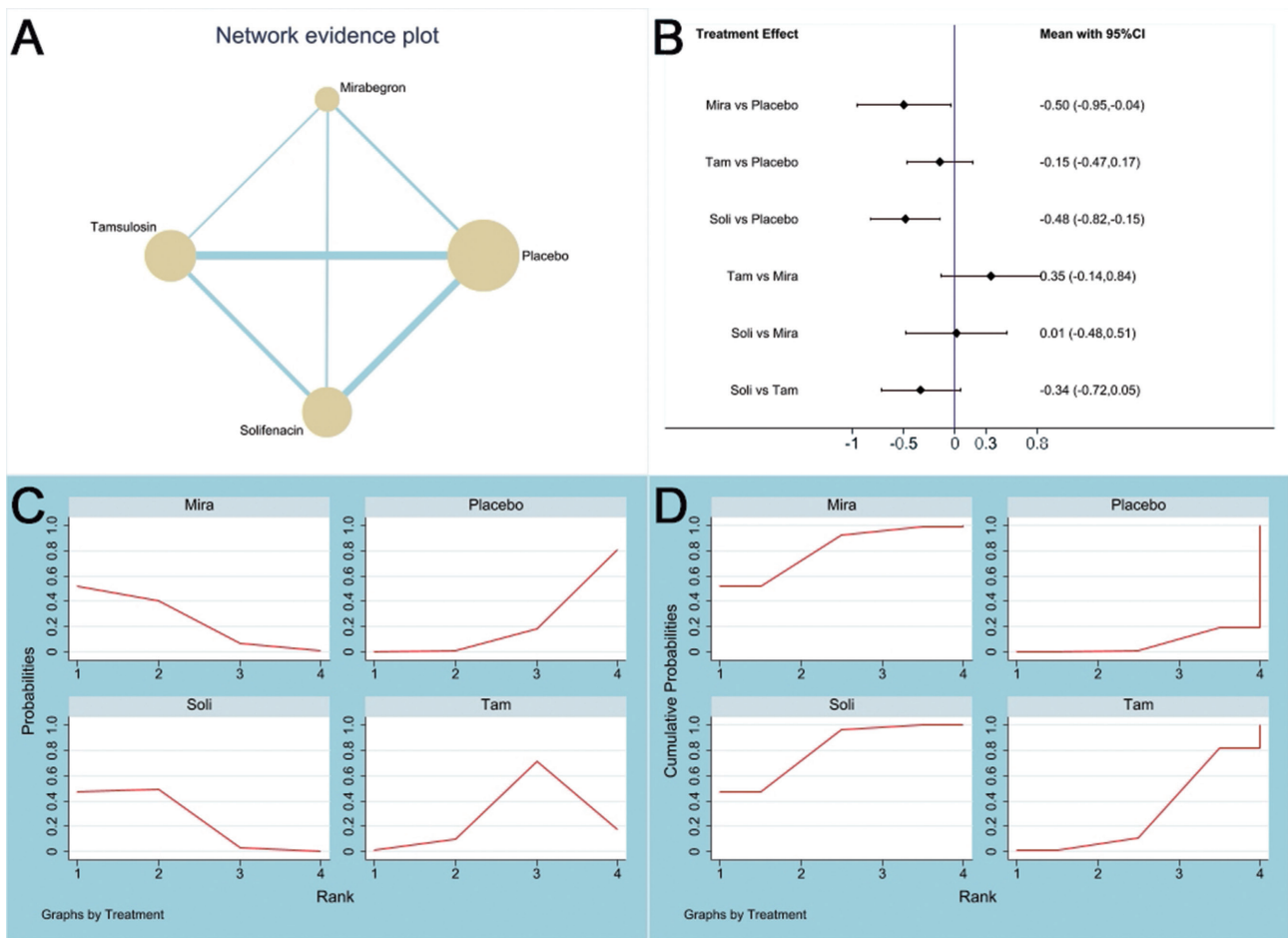
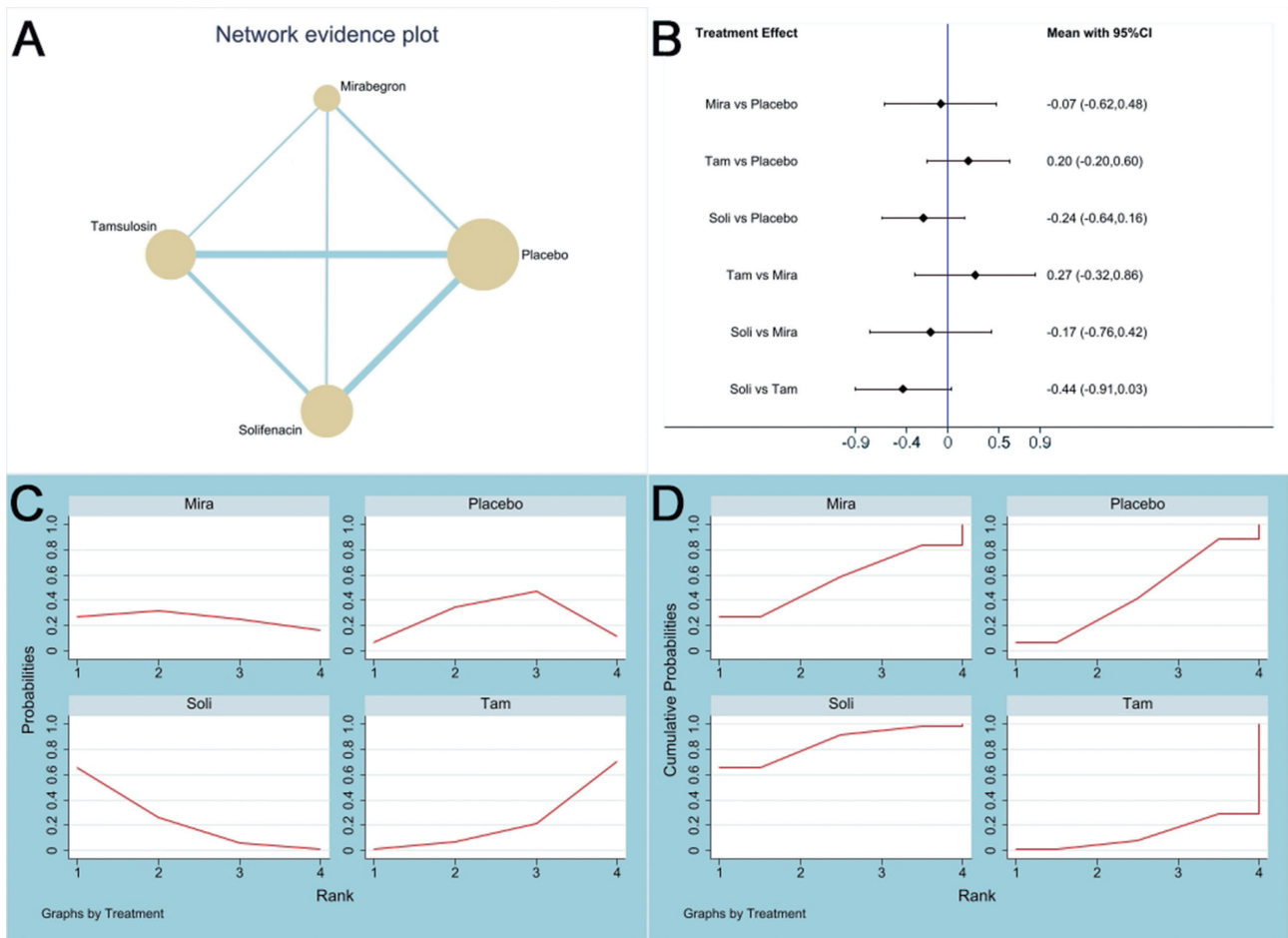
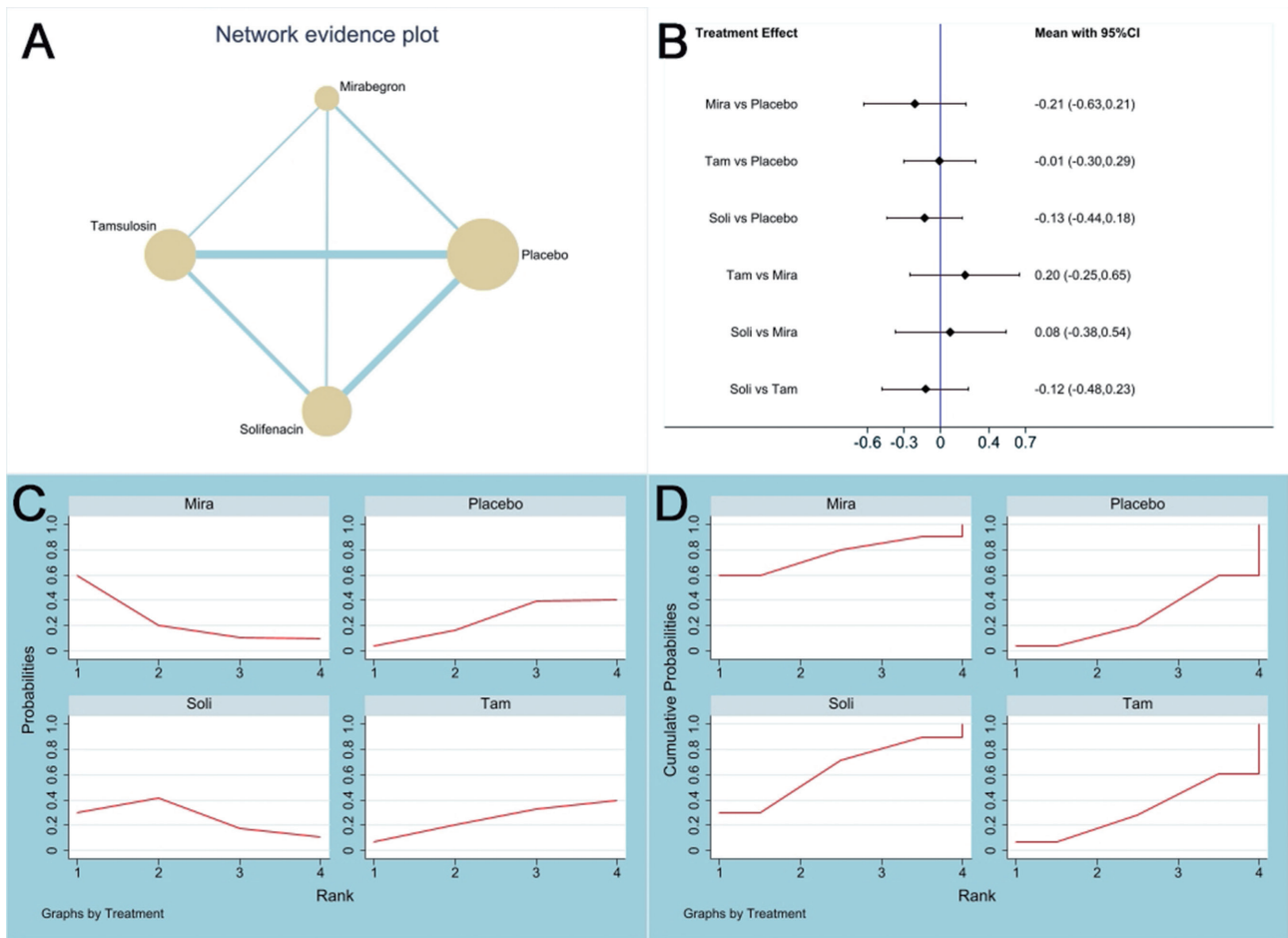


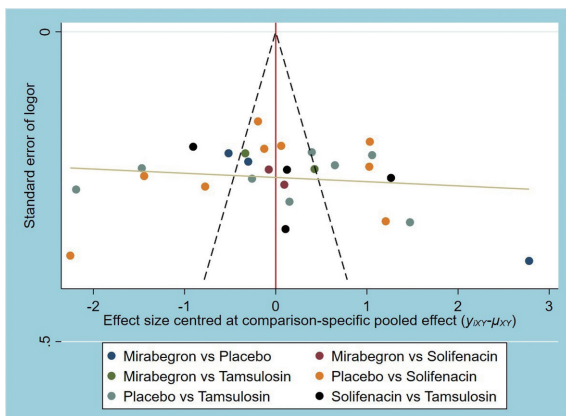
Figure S2 Network analysis of general health. (A) Network plots of the comparisons between different interventions. (B) Forest plot of network meta-analysis. (C) Ranking probability plot. (D) Cumulative probability ranking plot.



**Figure S3** Network analysis of working performance. (A) Network plots of the comparisons between different interventions. (B) Forest plot of network meta-analysis. (C) Ranking probability plot. (D) Cumulative probability ranking plot.



**Figure S4** Network analysis of sexual matters. (A) Network plots of the comparisons between different interventions. (B) Forest plot of network meta-analysis. (C) Ranking probability plot. (D) Cumulative probability ranking plot.



**Figure S5** Comparison-adjusted funnel plot of the studies included in this meta-analysis.

**Table S1** The characteristics of included studies

Authors	Year	Region	Number of patients	Therapy (daily dosage, sample size)	Start of therapy	Follow-up time (week)
Wang	2009	China	154	Tamsulosin (0.4 mg, n=79), control (n=75)	POD1	1
Lee	2013	China	140	Solifenacin (10 mg, n=70), control (n=70)	POD1	2
Dellis	2014	Greece, United Kingdom	100	Tamsulosin (0.4 mg, n=50), control (n=50)	POD1	4
Singh	2014	India	60	Tamsulosin (0.4 mg, n=30), control (n=30)	POD3	4
Aggarwal	2015	India	101	Tamsulosin (0.4 mg, n=51), control (n=50)	POD7	3
Park	2015	Korea	63	Tamsulosin (0.2 mg, n=20), solifenacin (5 mg, n=20), control (n=23)	POD1	2
El-Nahas	2016	Egypt	131	Tamsulosin (0.4 mg, n=44), solifenacin (5 mg, n=43), control (n=44)	POD1	1 to 2
Abdelhamid	2017	Egypt	140	Solifenacin (10 mg, n=70), control (n=70)	POD1	2
Dellis	2017	Greece	180	Tamsulosin (0.4 mg, n=60), solifenacin (5 mg, n=60), control (n=60)	POD1	4
Ragab	2017	Egypt	243	Solifenacin (5 mg, n=121), control (n=122)	POD1	15 days
Bhattar	2018	India	85	Solifenacin (10 mg, n=43), control (n=42)	POD7	3
Tae	2018	Korea	96	Mirabegron (50 mg, n=48), control (n=48)	POD1	2
Yavuz	2021	Turkey	161	Tamsulosin (0.4 mg, n=55), mirabegron (50 mg, n=50), control (n=56)	POD1	4
Falahatkar	2021	Iran	128	Solifenacin (5 mg, n=64), control (n=64)	POD1	2
Abdelaziz	2022	Saudi Arabia	97	Mirabegron (50 mg, n=34), solifenacin (5 mg, n=32), control (n=31)	POD4	2
Chandna	2022	India	123	Mirabegron (50 mg, n=41), solifenacin (5 mg, n=40), tamsulosin (0.4 mg, n=42)	POD1	4

POD, postoperative day.