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ORIGINAL ARTICLE

Male Health

Efficacy and safety of solifenacin plus tamsulosin oral controlled absorption system in men with lower urinary tract symptoms: a meta-analysis

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We performed a meta-analysis to compare treatment with a combination of solifenacin plus tamsulosin oral controlled absorption system (TOCAS) with placebo or TOCAS monotherapy. The aim of the meta-analysis was to clarify the efficacy and safety of the combination treatments method for lower urinary tract symptoms (LUTS). We searched for trials of men with LUTS that were randomized to combination treatment compared with TOCAS monotherapy or placebo. We pooled data from three placebo-controlled trials meeting inclusion criteria. Primary outcomes of interest included changes in International Prostate Symptom Score (IPSS) and urinary frequency. We also assessed postvoid residual, maximum urinary flow rate, incidence of urinary retention (UR), adverse events. Data were pooled using random or fixed effect models for continuous outcomes and the Mantel–Haenszel method to generate risk ratio. Reductions in IPSS storage subscore and total urgency and frequency score (TUFS) were observed with solifenacin 6 mg plus TOCAS compared with placebo ($P < 0.0001$ and $P < 0.0001$, respectively). Reductions in IPSS storage subscore and TUFS were observed with solifenacin 9 mg plus TOCAS compared with placebo ($P = 0.003$ and $P = 0.0006$, respectively). Reductions in TUFS was observed with solifenacin 6 mg plus TOCAS compared with TOCAS ($P = 0.01$). Both combination treatments were well tolerated, with low incidence of UR. Solifenacin 6 mg plus TOCAS significantly improved total IPSS, storage and voiding symptoms compared with placebo. Solifenacin 6 mg plus TOCAS also improved storage symptoms compared with TOCAS alone. There was no additional benefit of solifenacin 9 mg compared with 6 mg when used in combination with TOCAS.

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Keywords: combination therapy; lower urinary tract symptoms; solifenacin; tamsulosin oral controlled absorption system

INTRODUCTION

Lower urinary tract symptoms (LUTS) are very common in men aged >45 years old,[1] which have a significant effect on health-related quality of life,[2,3] including voiding, storage, and post micturition symptoms.[4] More than 40% of men have a significant storage component to their symptoms and 16% exhibit symptoms of an overactive bladder (OAB).[5] Antimuscarinics are first-line therapy for OAB; while there are concerns about antimuscarinics increasing the risk of retention in men with possible bladder outlet obstruction, these remain unsubstantiated.[6] Recent randomized controlled trials (RCTs) have demonstrated the safe and effective use of antimuscarinics plus α-blockers for male LUTS.[5]

Recent RCTs have demonstrated the efficacy and safety of combination therapy of a once-daily fixed-dose combination (FDC) tablet containing solifenacin and tamsulosin oral controlled absorption system (TOCAS).[7–9]

To better make certain the efficacy and safety of this treatment method, we performed a meta-analysis of randomized clinical trials to define the effects of combination therapy solifenacin and TOCAS compared with placebo or TOCAS monotherapy.

MATERIALS AND METHODS

Eligibility criteria

This systematic review was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement criteria.[10] We planned to include only placebo-controlled, RCTs of men with LUTS that compared combination of solifenacin and TOCAS compared with TOCAS monotherapy or placebo.

Search strategy

We searched PubMed, Web of Science and EMBASE for trials of interest. We considered all publications in any language published before January 14, 2014. Our search strategy combined and exploded terms for "LUTS" "solifenacin," "oral controlled absorption system" and "tamsulosin."

Inclusion criterion

The study inclusion criterion was an RCT design of patients with LUTS. All RCT articles had a placebo group as a control group and described at least one outcome of urinary symptoms. Any disagreement on trial eligibility was resolved by consensus.

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Methodological quality

The methodological quality of eligible articles was critically appraised independently by two of us using The Cochrane Collaboration quality assessment tool, including a judgment on randomization sequences, blinding method, allocation concealment and evaluation of other possible biases. Any discrepancy was resolved by discussion with a third author.

Outcome measures and data extraction

The primary outcome measures were changes in the total International Prostate Symptom Score (IPSS), IPSS voiding, IPSS storage, total urgency and frequency score (TUFS), micturitions per 24 h, volume voided per micturition, urgency episodes per 24 h, incontinence episodes per 24 h, urgency incontinence episodes per 24 h. Secondary outcomes of interest included postvoid residual volume (PVR), maximal urinary flow rate (Q_{max}), incidence of acute urinary retention (AUR) and common adverse events (AEs) and drug-related AEs.

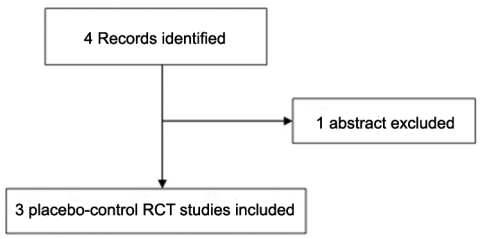

Figure 1: Study selection process for trials included in meta-analysis.

Statistical analysis

All meta-analyses were performed using RevMan 5.2 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2012, Copenhagen, Denmark). Continuous outcomes were presented as standard mean difference, and discontinuous data were presented as risk ratio, both with 95% confidence interval. Statistical heterogeneity was assessed with the I^2 statistic, When $I^2 > 50\%$, we considered it to be high heterogeneity. When heterogeneity was present, data were analyzed using a random effect model. Otherwise, a fixed effect was used. Differences were considered as statistically significant at $P < 0.05$.

RESULTS

A total of four references were identified in the initial database search (**Figure 1**). We excluded all references related to conference abstract, other topics, nonhuman studies, editorials and duplicate studies.

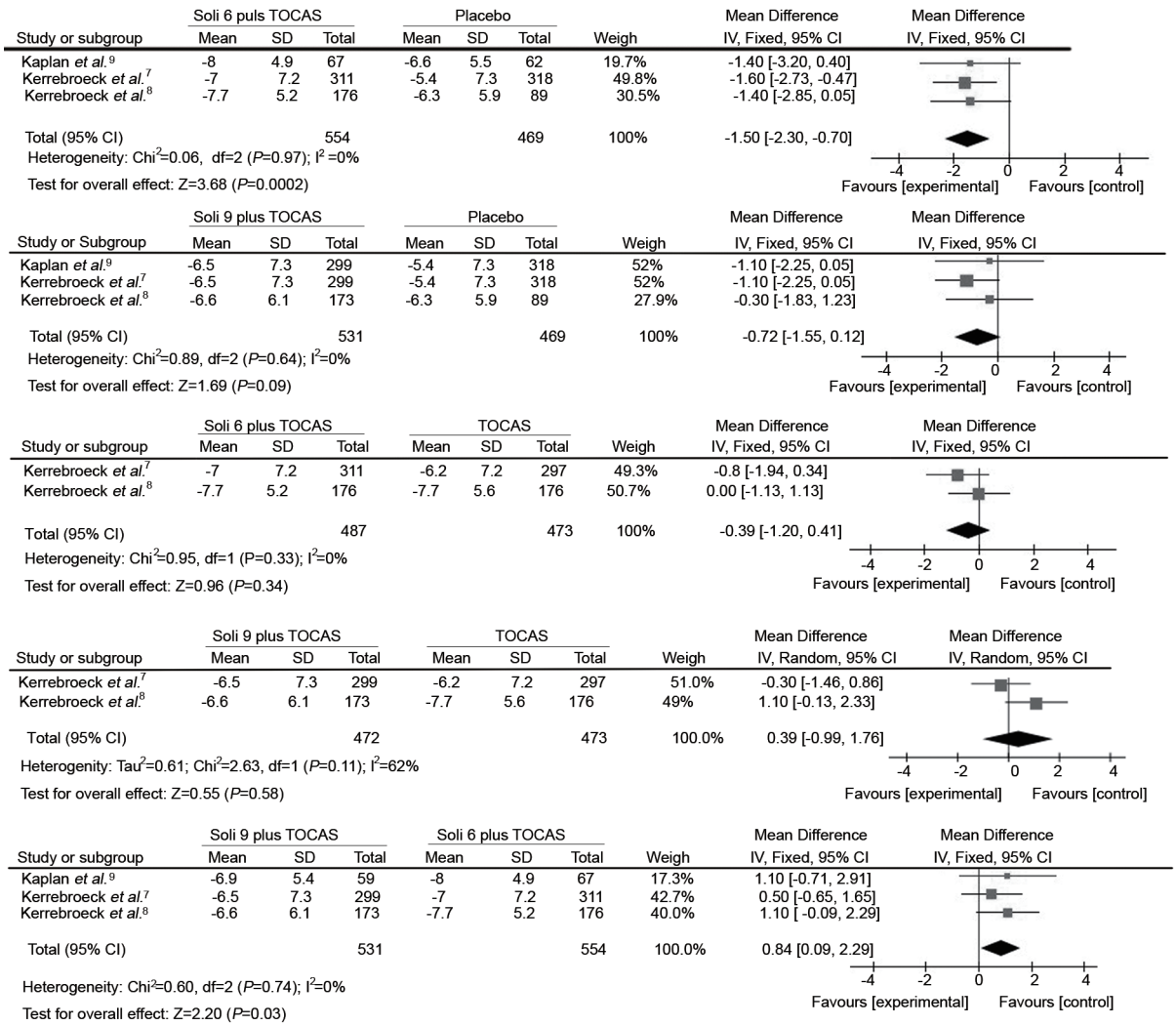

Figure 2: Pooled data analysis of total International Prostate Symptom Score.

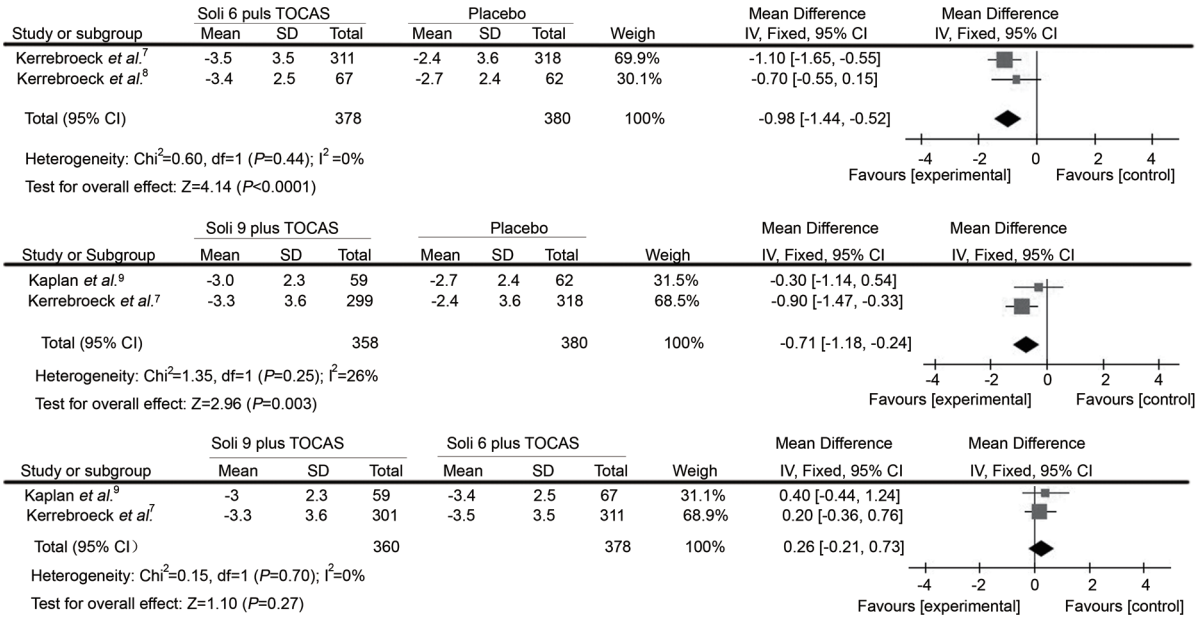

Figure 3: Pooled data analysis of International Prostate Symptom Score storage subscore.

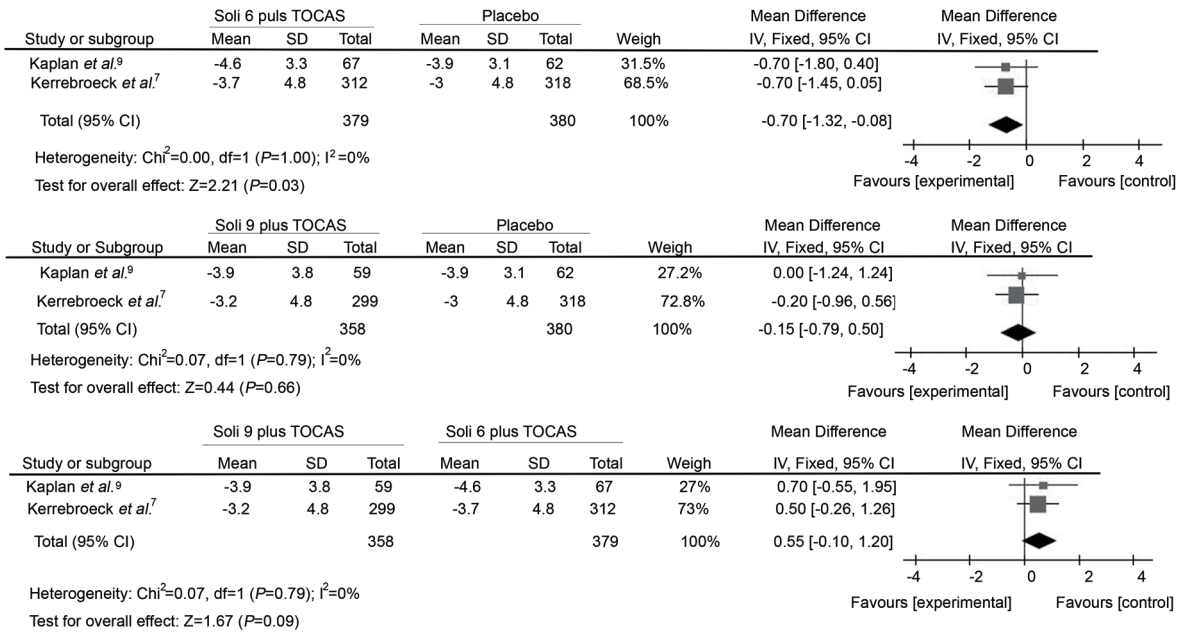

Figure 4: Pooled data analysis of International Prostate Symptom Score voiding subscore.

1 conference abstract article was then excluded resulting in a total of three RCTs which met study criteria. 3 studies included 2036 patients receiving either solifenacin 6 mg plus TOCAS, solifenacin 9 mg plus TOCAS, TOCAS or placebo (**Table 1**).

Total international prostate symptom score

International Prostate Symptom Score storage subscore was investigated in all trials.[7–9] For total IPSS, significant improvement from baseline to end of treatment compared with placebo was achieved with solifenacin 6 mg plus TOCAS (−1.50 [−2.30, −0.70], P = 0.0002, **Figure 2**). There was no significant improvement from baseline to end of treatment compared with placebo was achieved with solifenacin 9 mg plus TOCAS (−0.72 [−1.55, 0.12], P = 0.09). There was no significant improvement from baseline to end of treatment compared with TOCAS was achieved with solifenacin 6 mg plus TOCAS (−0.39 [−1.20, 0.41], P = 0.34) and solifenacin 9 mg plus TOCAS (0.39 [−0.99, 1.76], P = 0.58). Solifenacin 6 mg plus TOCAS significant improved total IPSS when compared with solifenacin 9 mg plus TOCAS (−0.84 [−1.60, −0.09], P = 0.03, **Figure 2**).

International prostate symptom score storage subscore

International Prostate Symptom Score storage subscore was investigated in 2 trials.[7,9] For IPSS storage subscore, significant improvements from baseline to end of treatment compared with placebo were achieved with solifenacin

Table 1: Characteristics of included randomized clinical trials

References	*Dura (week)*	*Rand*	*Blind*	*Placebo*	*Soli 9*	*Soli 6*	*TOCAS (0.4 mg)*	*Placebo*	*Total*	*Inclusion criteria*	*Exclusion criteria (ml)*	*Dis AE)*
van Kerrebroeck, 2013[7]	12	Yes	Yes	Yes	302	314	299	319	1234	IPSS≥13 Q_{max}: 4.0–12.0 ml s^{-1} Urgency episodes: Grade 3 or 4 Voided volume>120 ml	PVR>150	37
van Kerrebroeck, 2013[8]	12	Yes	Yes	Yes	173	176	176	89	614	IPSS≥13 Q_{max}: 4.0–15.0 ml s^{-1} Voided volume>120 ml	PVR>200	18
Kaplan, 2013[9]	12	Yes	Yes	Yes	59	67	0	62	188	IPSS≥13 Q_{max}: ≤12 ml s^{-1} Voided volume>120 ml		12

Blind: double-blinded; Dis (AE): discontinued for AE; Rand: randomized; Dura: treatment duration; TOCAS: tamsulosin oral controlled absorption system; Soli 6: solifenacin 6 mg plus TOCAS; Soli 9: solifenacin 9 mg plus TOCAS; PVR: postvoid residual volume; IPSS: International Prostate Symptom Score; Q_{max}: maximal urinary flow rate; AE: adverse events

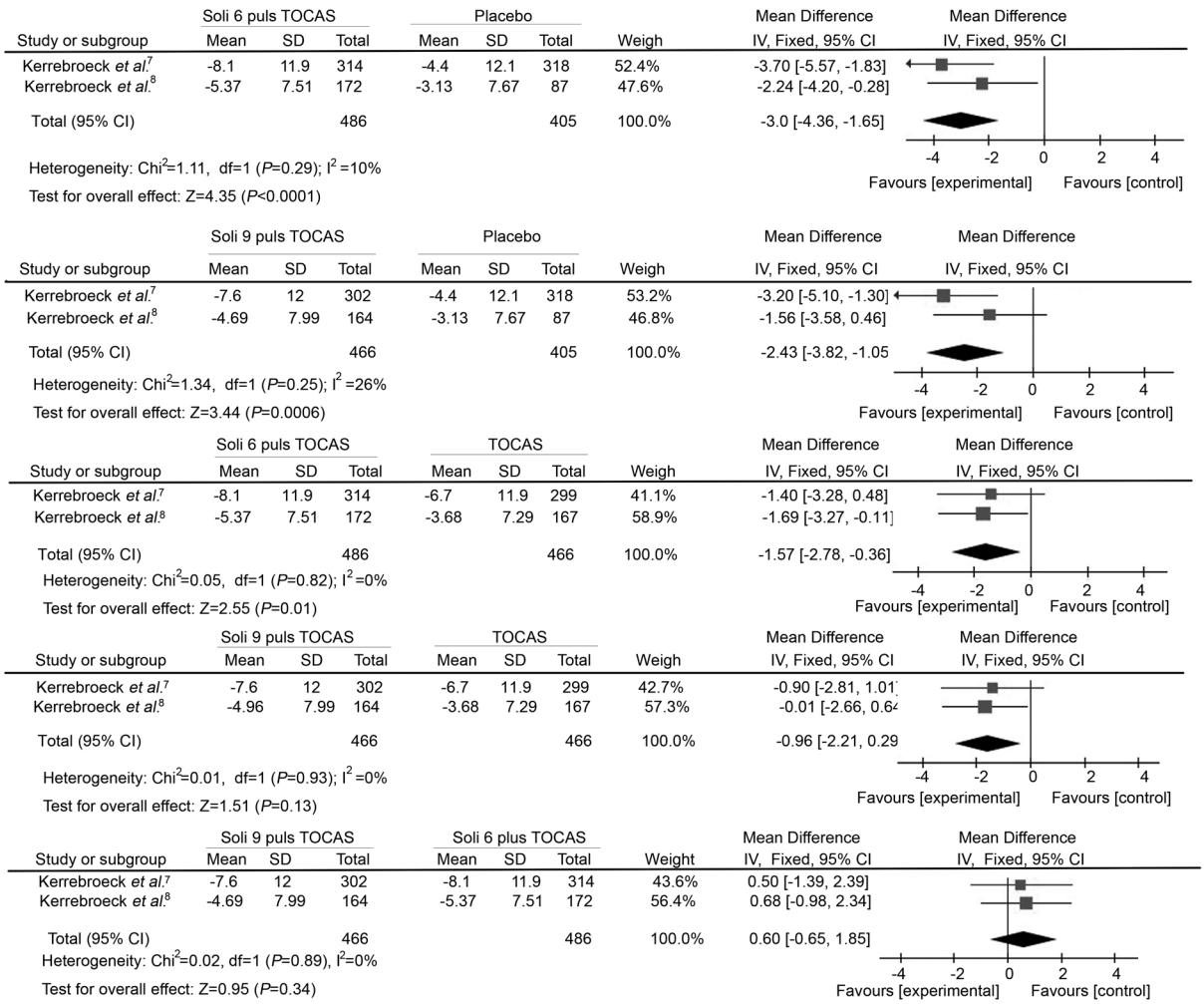

Figure 5: Pooled data analysis of total urgency and frequency score.

6 mg plus TOCAS (−0.98 [−1.44, −0.52], $P < 0.0001$, **Figure 3**) and solifenacin 9 mg plus TOCAS (−0.71 [−1.18, −0.24], $P = 0.003$, **Figure 3**). There was no significant difference in IPSS storage subscore improvement between solifenacin 6 mg plus TOCAS and solifenacin 9 mg plus TOCAS.

International prostate symptom score voiding subscore

International Prostate Symptom Score voiding subscore was investigated in two trials.[7,9] For IPSS voiding subscore, significant improvement from baseline to end of treatment compared with placebo was achieved with solifenacin 6 mg plus TOCAS (−0.70 [−1.32, −0.08], $P = 0.03$, **Figure 4**). There was no significant improvement from baseline to end of treatment compared with placebo was achieved with solifenacin 9 mg plus TOCAS (−0.15 [−0.79, 0.50], $P = 0.66$, **Figure 4**). There was no significant difference in IPSS voiding subscore improvement between solifenacin 6 mg plus TOCAS and solifenacin 9 mg plus TOCAS.

Total urgency and frequency score

Total urgency and frequency score was investigated in 2 trials.[7,8] For TUFS, significant improvements from baseline to end of treatment compared with placebo were achieved with solifenacin 6 mg plus TOCAS (−3.01 [−4.36, −1.65], $P < 0.0001$, **Figure 5**) and solifenacin 9 mg plus TOCAS (−2.43 [−3.82, −1.05], $P = 0.0006$, **Figure 5**). Significant improvement in TUFS from baseline to end of treatment compared with TOCAS was achieved with solifenacin 6 mg plus TOCAS (−1.57 [−2.78, −0.36], $P = 0.01$, **Figure 5**). There was no significant difference in TUFS improvement between solifenacin 9 mg plus TOCAS and TOCAS. There was no significant difference in TUFS improvement between solifenacin 6 mg plus TOCAS and solifenacin 9 mg plus TOCAS.

Micturitions per 24 h

Micturitions per 24 h was investigated in 3 trials.[7–9] Decreases from baseline to end of treatment in micturitions per 24 h were significantly greater with solifenacin 6 mg plus TOCAS (−1.03 [−1.36, −0.71], $P < 0.00001$, **Figure 6**) and solifenacin 9 mg plus TOCAS (−0.81 [−1.13, −0.48], $P < 0.00001$, **Figure 6**) versus placebo. Decreases from baseline to end of treatment in micturition per 24 h were significantly greater with solifenacin 6 mg plus TOCAS (−0.65 [−0.96, −0.35], $P < 0.0001$, **Figure 6**) versus TOCAS monotherapy. There was no significant difference in micturitions per 24 h improvements between solifenacin 6 mg plus TOCAS and solifenacin 9 mg plus TOCAS.

Volume voided per micturition

Volume voided per micturition was investigated in three trials.[7–9] Increases from baseline to end of treatment in volume voided per micturition were significantly greater with solifenacin 6 mg plus TOCAS (27.23 [21.25, 33.20], $P < 0.00001$, **Figure 7**) and solifenacin 9 mg plus TOCAS (28.13 [21.97, 34.30], $P < 0.00001$, **Figure 7**) versus placebo. Increases from baseline to end of treatment in volume voided per micturition were significantly greater with solifenacin 6 mg plus TOCAS (21.11 [15.05, 27.18], $P < 0.00001$, **Figure 7**) and solifenacin 9 mg plus TOCAS (23.88 [17.53, 30.22], $P < 0.00001$, **Figure 7**) versus TOCAS monotherapy. There was no significant difference in volume voided per micturition improvement between solifenacin 6 mg plus TOCAS and solifenacin 9 mg plus TOCAS.

Urgency episodes per 24 h

Urgency episodes per 24 h was investigated in three trials.[7–9] Decreases from baseline to end of treatment in urgency episodes per 24 h were

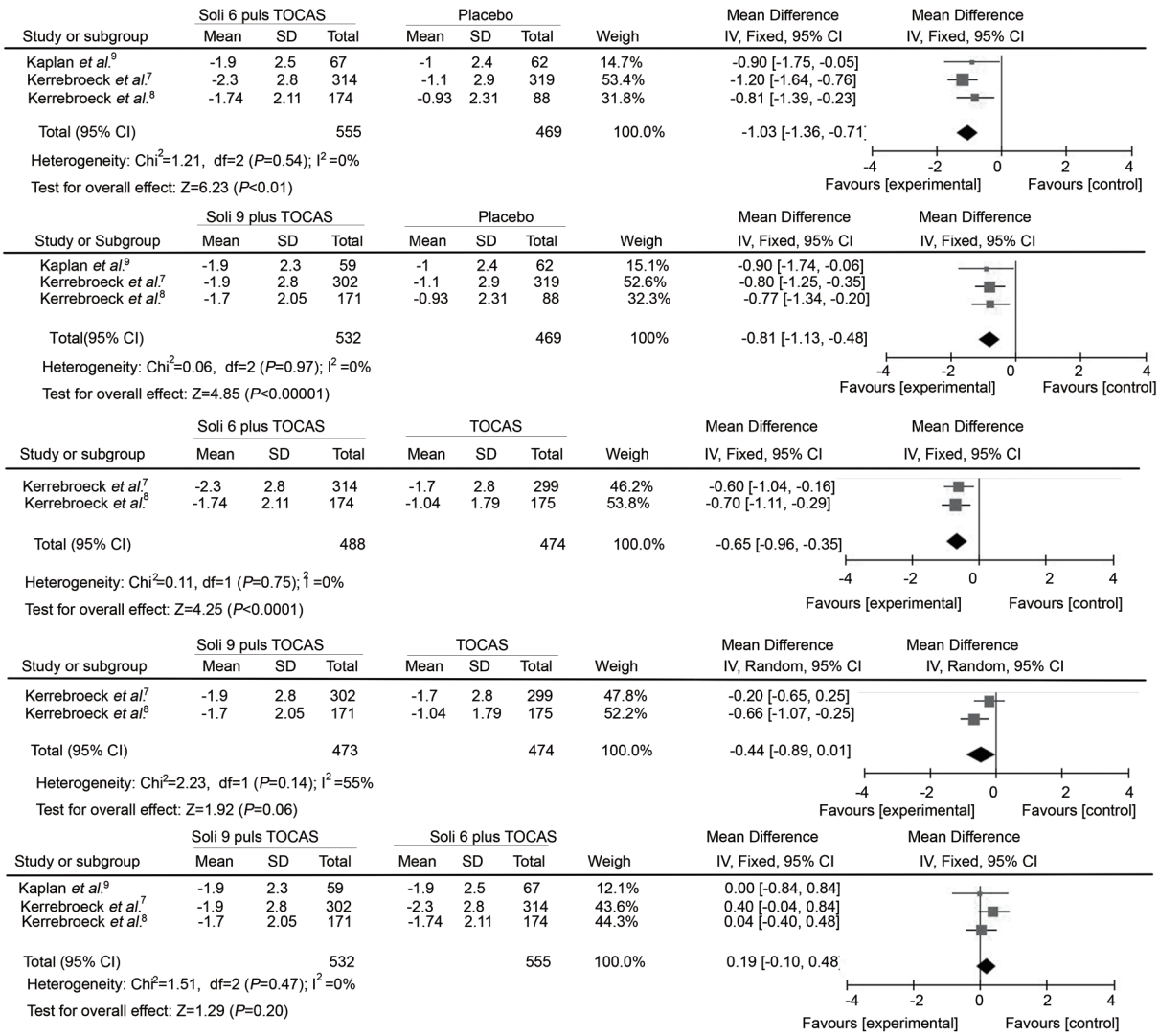

Figure 6: Pooled data analysis of micturitions per 24 h.

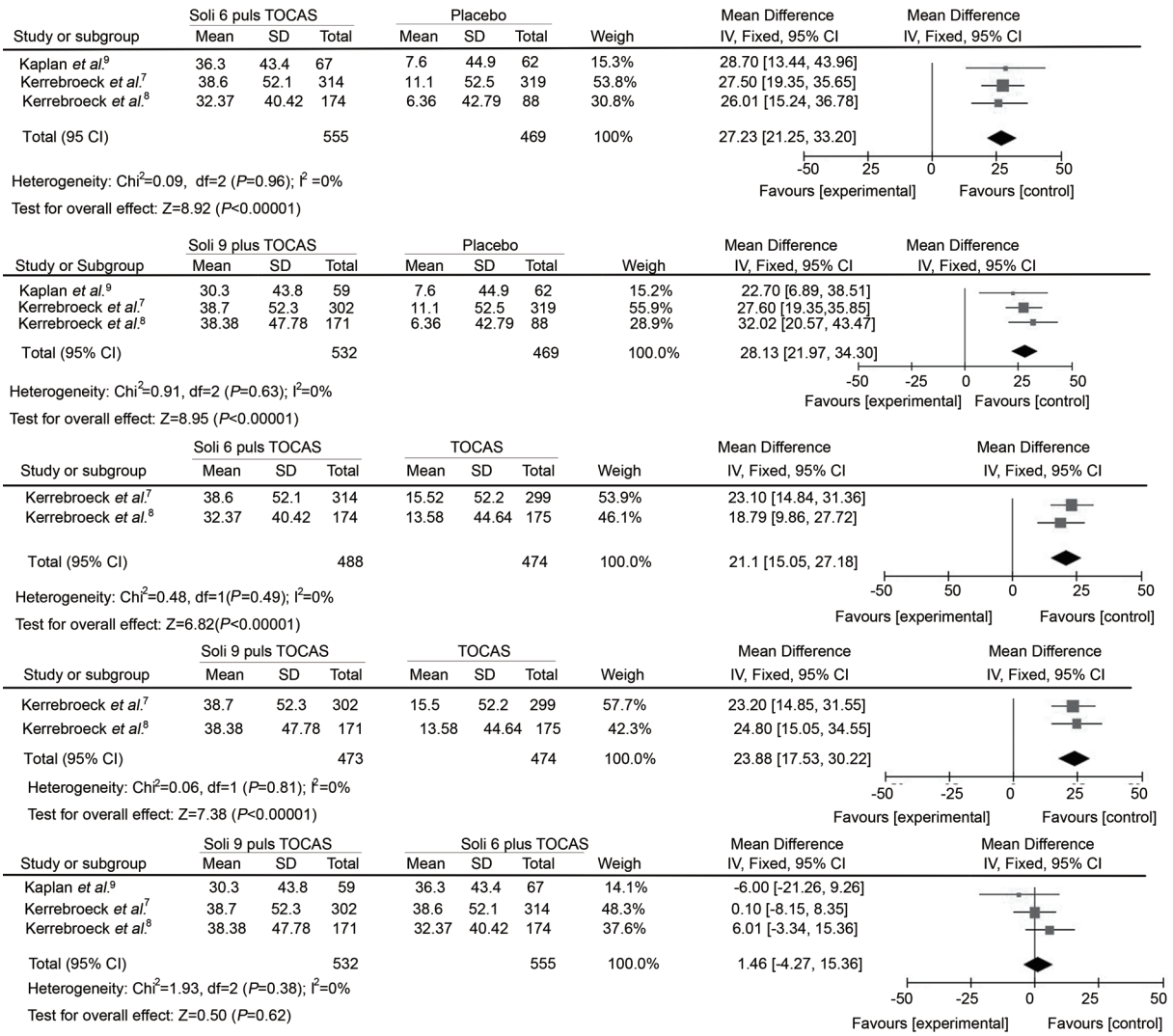

Figure 7: Pooled data analysis of volume voided per micturition.

significantly greater with solifenacin 6 mg plus TOCAS (−0.64 [−1.05, −0.22], P = 0.003, **Figure 8**) versus placebo Solifenacin 9 mg plus TOCAS did not significantly improve urgency episodes per 24 h compare placebo. Solifenacin 6 mg plus TOCAS and solifenacin 9 mg plus TOCAS did not significantly improve urgency episodes per 24 h compared with TOCAS monotherapy. There was no significant difference in urgency episodes per 24 h improvement between solifenacin 6 mg plus TOCAS and solifenacin 9 mg plus TOCAS.

Incontinence episodes per 24 h

Incontinence episodes per 24 h were investigated in two trials.[7,9] Solifenacin 6 mg plus TOCAS and solifenacin 9 mg plus TOCAS did not significantly improve incontinence episodes per 24 h compared with placebo. There was no significant difference in incontinence episodes per 24 h improvement between solifenacin 6 mg plus TOCAS and solifenacin 9 mg plus TOCAS.

Urgency incontinence episodes per 24 h

Urgency incontinence episodes per 24 h was investigated in two trials.[7,8] Solifenacin 6 mg plus TOCAS and solifenacin 9 mg plus TOCAS did not significantly improve urgency incontinence episodes per 24 h compared with TOCAS monotherapy or placebo. There was no significant difference in urgency incontinence episodes per 24 h improvement between solifenacin 6 mg plus TOCAS and solifenacin 9 mg plus TOCAS.

Safety

Postvoid residual volume

Postvoid residual was investigated in two trials.[8,9] Increases from baseline to end of treatment in PVR were significantly greater with solifenacin 6 mg plus TOCAS (16.23 [6.31, 26.15], P = 0.001, **Figure 9**) and solifenacin 9 mg plus TOCAS (14.81 [4.80, 24.82], P = 0.004, **Figure 9**) versus placebo. There was no significant difference in PVR change between solifenacin 6 mg plus TOCAS and solifenacin 9 mg plus TOCAS.

Maximum urinary flow rate

Maximal urinary flow rate was investigated in two trials.[7,9] Solifenacin 6 mg plus TOCAS and solifenacin 9 mg plus TOCAS did not significantly improve Q_{max} compared with placebo. There was no significant difference in Q_{max} improvement between solifenacin 6 mg plus TOCAS and solifenacin 9 mg plus TOCAS.

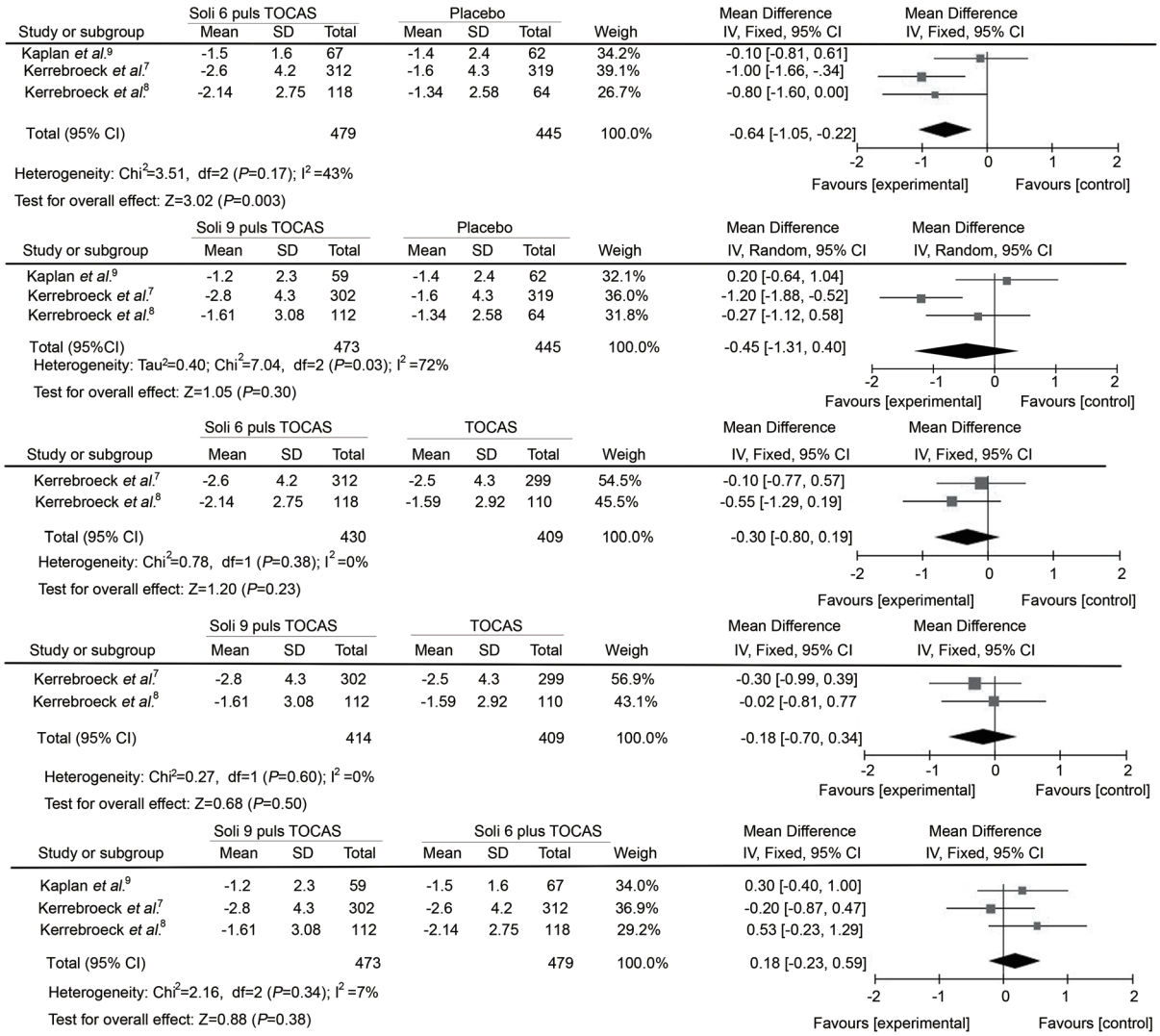

Figure 8: Pooled data analysis of urgency episodes per 24 h.

Urinary retention

Urinary retention was investigated in two trials.[7,8] Solifenacin 6 mg plus TOCAS and solifenacin 9 mg plus TOCAS do not significantly increase UR risk compared with TOCAS monotherapy or placebo. There was no significant difference in UR risk improvement between solifenacin 6 mg plus TOCAS and solifenacin 9 mg plus TOCAS (**Figure 10**).

Acute urinary retention (requiring catheterization)

Acute urinary retention was investigated in two trials.[7,8] Solifenacin 6 mg plus TOCAS and solifenacin 9 mg plus TOCAS did not significantly increase AUR risk compared with TOCAS monotherapy or placebo. There was no significant difference in AUR risk improvement between solifenacin 6 mg plus TOCAS and solifenacin 9 mg plus TOCAS.

Adverse events

Adverse events were reported in all the studies.[7–9] Combination therapy was well tolerated, and most AEs were of mild or moderate intensity. The types of AEs were in line with the known safety profiles of each individual drug. The most common AEs in all treatment groups were dry mouth and constipation. Dry mouth was significantly higher in the solifenacin 6 mg plus TOCAS (6.39 [2.94, 13.91], $P < 0.00001$, **Figure 11**) and solifenacin 9 mg plus TOCAS (8.62 [4.02, 18.50], $P < 0.00001$, **Figure 11**) than placebo. Dry mouth was significantly higher in the solifenacin 6 mg plus TOCAS (9.03 [1.46, 55.71], $P = 0.02$, **Figure 11**) and solifenacin 9 mg plus TOCAS (11.79 [1.88, 74.14], $P = 0.009$, **Figure 11**) than TOCAS monotherapy. Constipation was significantly higher in the solifenacin 6 mg plus TOCAS (4.97 [1.51, 11.36], $P = 0.008$, **Figure 12**) and solifenacin 9 mg plus TOCAS (7.87 [2.5, 24.77], $P < 0.0004$, **Figure 12**) than placebo. Constipation was significantly higher in the solifenacin 6 mg plus TOCAS (4.58 [1.32, 15.87], $P = 0.02$, **Figure 12**) than TOCAS monotherapy. All other reported AEs, including dyspepsia, nausea, headache, fatigue, retrograde ejaculation and erectile dysfunction did not differ significantly between solifenacin 6 mg plus TOCAS or solifenacin 9 mg plus TOCAS and placebo or TOCAS monotherapy.

DISSCUSION

To our knowledge this was the first meta-analysis of the role of combination of solifenacin plus TOCAS to improve LUTS.

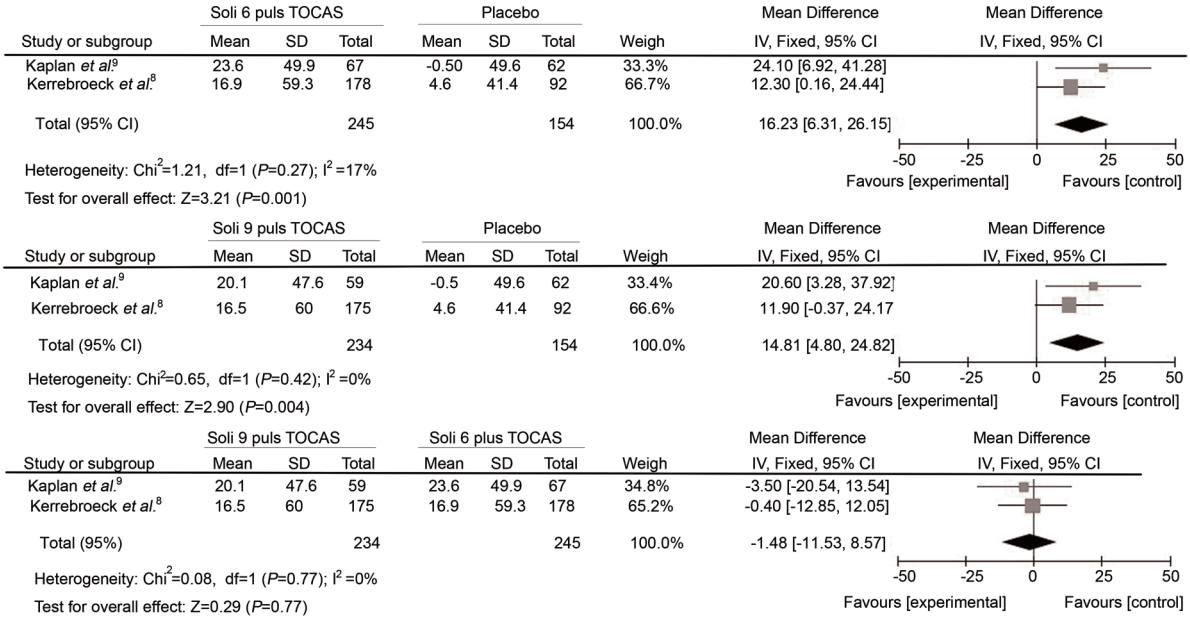

Figure 9: Pooled data analysis of postvoid residual volume.

Male LUTS can be classified into three categories, including voiding (hesitancy, slow stream, intermittency, incomplete emptying), storage (frequency, urgency, nocturia, urgency urinary incontinence) and postmicturition (postvoid dribbling).[11] The number of pharmacologic options were available for the treatment of LUTS. Antimuscarinics were first-line therapy for OAB symptoms but were used less often in men owing to a perceived association with UR. α-blockers were used primarily for the treatment of symptoms relating to voiding symptoms.[4,12–14] A recent meta-analysis showed that combination treatment with α-blockers and anticholinergics significantly improved storage voiding parameters compared to men treated with α-blocker therapy alone.[15] Current European Association of Urology treatment guidelines suggest that antimuscarinics (e.g. solifenacin) can be added to α-blockers to manage storage symptoms that persist after α-blocker monotherapy.[7] A once-daily FDC tablet containing solifenacin and TOCAS has been developed to address both storage and voiding symptoms in men with LUTS.[7]

Solifenacin 6 mg plus TOCAS was superior to placebo and noninferior to TOCAS in reducing the total IPSS as well as superior to TOCAS and placebo in reducing TUFS; solifenacin 6 mg plus TOCAS was superior to placebo in reducing storage and voiding symptoms. Because of solifenacin's effect, the benefit of adding that drug was expected to be further improvement of storage symptoms. Indeed, combination therapy resulted in significant improvements in the IPSS storage subscore compared with placebo. Solifenacin 6 mg plus TOCAS was significant superior to placebo and TOCAS monotherapy in reducing micturition per 24 h, in increasing in mean volume voided per micturition. Solifenacin 6 mg plus TOCAS was superior to placebo and noninferior to TOCAS in reducing urgency episodes per 24 h. There was no significant difference in LUTS improvement between solifenacin 3 mg plus TOCAS and TOCAS alone.

Solifenacin 9 mg plus TOCAS was noninferior to placebo and TOCAS in reducing the total IPSS, was superior to placebo and noninferior TOCAS in reducing TUFS. Solifenacin 9 mg plus TOCAS was superior to placebo in reducing the IPSS storage symptoms and noninferior to placebo in reducing the IPSS voiding symptoms. Solifenacin 9 mg plus TOCAS was significant superior to placebo and TOCAS monotherapy in reducing micturition per 24 h, in increasing in mean volume voided per micturition. Solifenacin 9 mg plus TOCAS was superior to placebo and noninferior to TOCAS in reducing urgency episodes per 24 h. However, solifenacin 9 mg plus TOCAS no additional benefits above those seen with solifenacin 6 mg plus TOCAS were observed, which may be explained by a possible plateau of effect with the 6 mg combination.

The finding of our meta-analysis was that the use of combination therapy among men with LUTS did not have a clinically significant impact on important safety parameters (i.e. PVR and Q_{max}).

Although combination therapy enhanced PVR compare with placebo, there was no statistical evidence of an increased risk of UR. The incidence of UR is exceedingly rare with combination therapy, UR was reported by 2 of 515 (0.39%) patients on solifenacin 6 mg plus TOCAS, of whom no one required catheterization, compared with two patients with TOCAS alone. UR was reported by 6 of 499 (1.2%) patients on solifenacin 9 mg plus TOCAS of whom 4 required catheterization requiring treatment, compared with two patients with TOCAS alone. The incidence of UR was lower than that of a meta-analysis in which combination of solifenacin and tamsulosin to treat LUTS.[15] Combination therapy did not enhance Q_{max} compared with placebo.

Erectile dysfunction was evaluated as AE in one RCT article.[8] The incidence of Erectile dysfunction was very low. There was no significant difference in the incidence of erectile dysfunction between solifenacin 6 mg plus TOCAS or solifenacin 9 mg plus TOCAS and placebo or TOCAS monotherapy. A study showed that α-blocker can slightly improve erectile function in LUTS patients with ED for inhibition of the α1- and α1D-adrenoceptor subtypes predominating in cavernosal smooth muscle.[13] There was no evaluation in improvement of erectile function in the 3 RCT articles. We thought that a once-daily FDC tablet containing solifenacin and TOCAS might improve erectile function, which need further study.

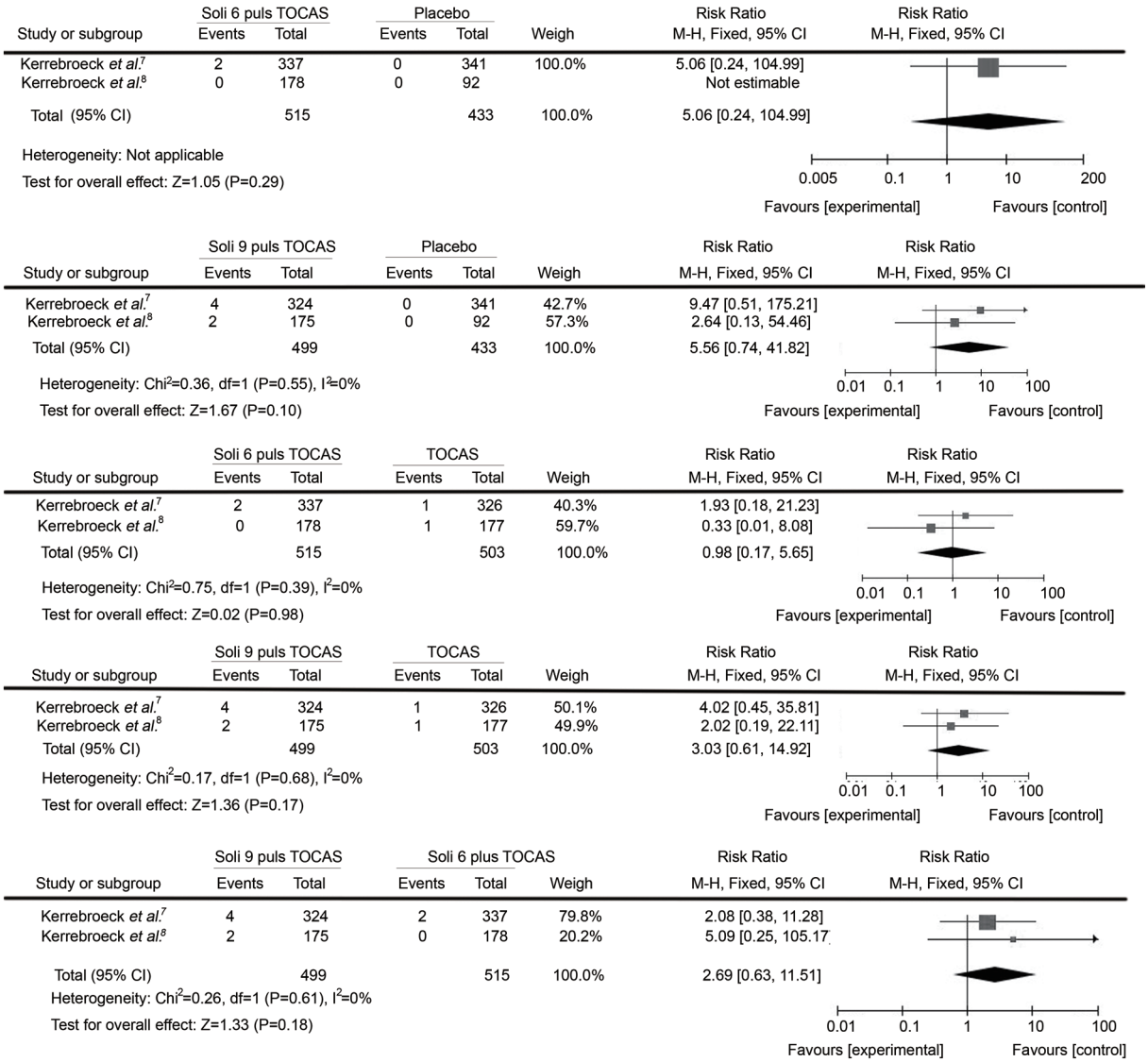

Figure 10: Pooled data analysis of urinary retention.

Several limitations of our analysis should be considered. Our meta-analysis only included three RCT articles. Size populations were not large, duration was short (12 weeks) although NEPTUNE two report will give 1 year data.[7] Some efficacy and safety data were in one article but not in another. The number of groups in every RCT article was not the same. We included trials with differences in clinical characteristics. Some analyses depended on imputed or extrapolated data using validated statistical techniques.

Although above limitations, our analysis quality was high, and the results were reliable. There was no significant statistical heterogeneity among the RCT articles. This was addressed with sensitivity analyses that changed the correlation coefficient, which did not result in any significant variation in our overall results.

CONCLUSIONS

Solifenacin 6 mg plus TOCAS FDC and solifenacin 9 mg plus TOCAS FDC were well tolerated, the risk of UR associated with combination therapy was minimal. There appears to be no additional benefit of the higher dose of solifenacin (9 mg) compared to the lower dose (6 mg) when used in combination with TOCAS. Solifenacin 6 mg plus TOCAS FDC significantly improved storage and voiding symptoms compared with placebo, as well as storage symptoms compared with TOCAS, in men with storage and voiding LUTS. These data provided evidence of patient benefits offered by an FDC of solifenacin 6 mg plus TOCAS in men with storage symptoms and voiding symptoms.

AUTHOR CONTRIBUTIONS

XLG and JY extracted and analyzed the data. TW and JHL conceived and designed the study. SGW and ZQY participated in the critical revision of the manuscript. MCL and ZYW drafted the paper.

COMPETING INTERESTS

The authors declare no competing interests.

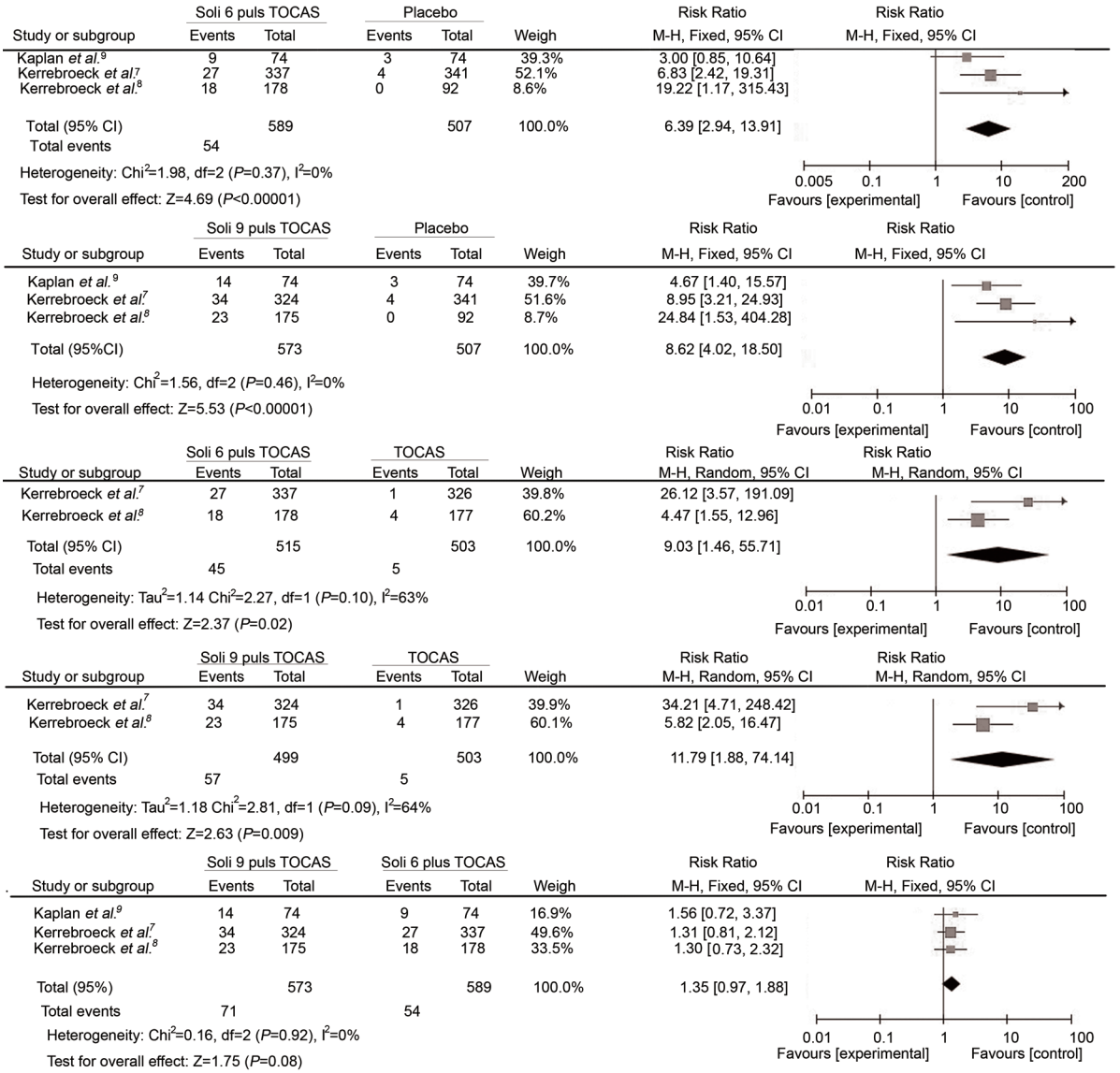

Figure 11: Pooled data analysis of dry mouth.

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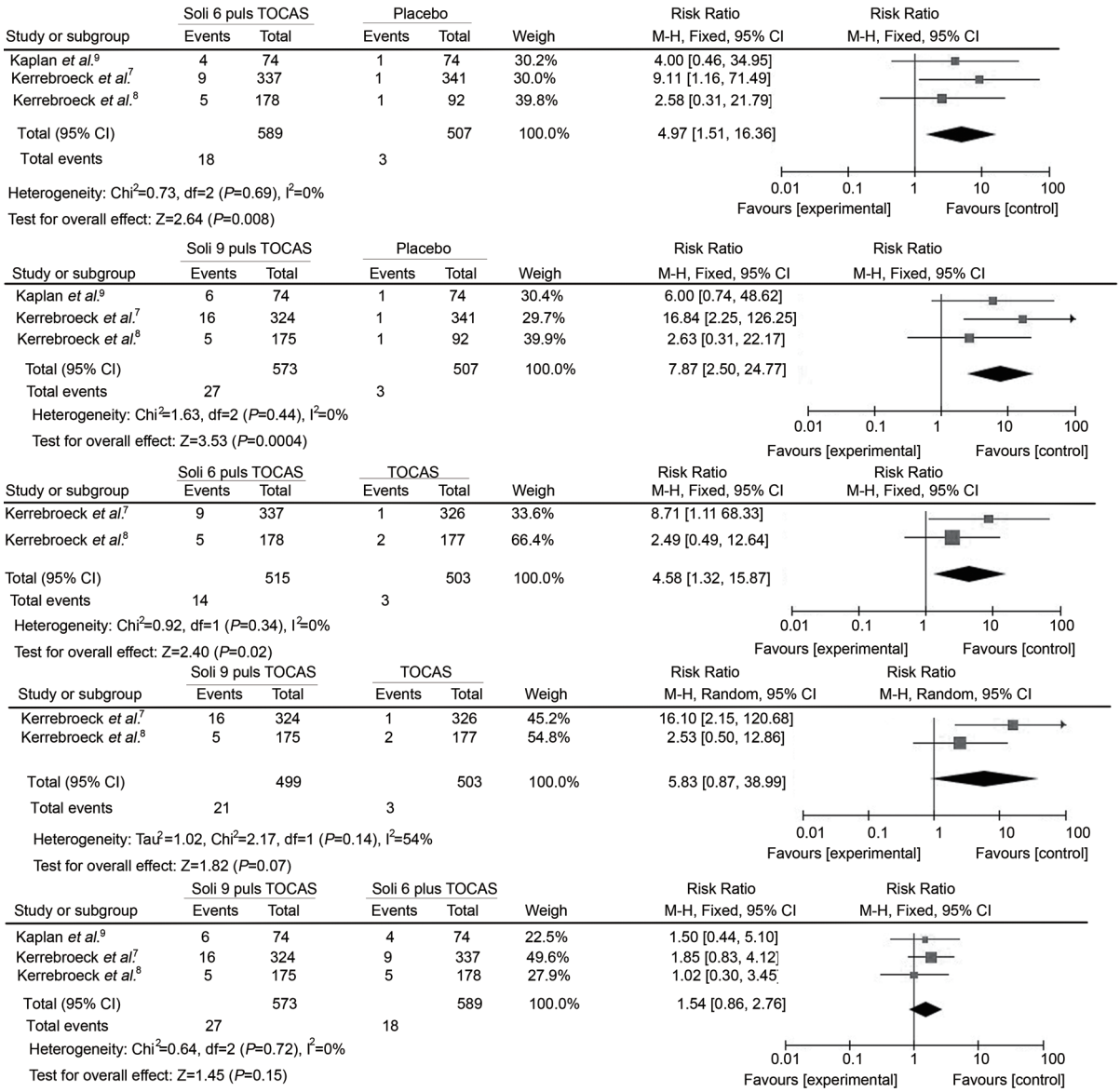

Figure 12: Pooled data analysis of constipation.

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