Author’s response to reviews

Title: Meta-Analysis of the Efficacy and Safety of Combination of Tamsulosin plus Dutasteride compared with Tamsulosin Monotherapy in treating Benign Prostatic Hyperplasia

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Author’s response to reviews:

Jan 14, 2019

Editor-in-Chief BMC Urology

Dear editor:

Thank you and all the reviewers for the comments with the original manuscript, and we are now submitting the revised version titled “Meta-Analysis of the Efficacy and Safety of Combination of Tamsulosin plus Dutasteride compared with Tamsulosin Monotherapy in treating Benign Prostatic Hyperplasia(BURO-D-18-00414)” in response to all comments for your consideration for publication in BMC Urology. We appreciate the reviewer’s suggestions and have revised the manuscript extensively and believe that it is now substantially improved in many important areas. On the following pages we also include responses to the reviewer’s suggestions.

All authors disclosed no direct or indirect commercial financial incentive associated with this article. This paper has not been published elsewhere in whole or in part. All authors contributed significantly to this work and have approved the final version of the manuscript. This study received ethical committee, and our hospital institutional animal care and use committee
approval. There is no ethical/legal conflicts involved in the article. All authors agree to transfer all copyright ownership to BMC Urology, in the event that such work is published.

We thank you in advance for your consideration of this manuscript.

Yours Sincerely,

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Please note:
The comments from reviewers and the editor are marked in bold below.
Our responses are in normal font.
Quoted sentences from the manuscript are in bold font.
Modifications to the original manuscript are in a red font in response to the reviewers’ comments.
Editor Comments:

Reviewer #1:

The Authors conducted a meta-analysis to confirm the efficacy and safety of the combination of tamsulosin plus dutasteride compared with tamsulosin monotherapy in treating benign prostatic hyperplasia (BPH) during a treatment period of at least 1 year.

We appreciate the reviewer’s positive comments.

This meta-analysis involved five RCTs and the quality of each RCT was high. The Authors found that the combination of tamsulosin plus dutasteride provides a preferable therapeutic effect for BPH with a higher incidence of sexual side effects, but the combination therapy can markedly reduce risk of BPH-related symptom progression and 2 acute urinary retention relative to tamsulosin.

We appreciate the reviewer’s positive comments.

This conclusion is already present in several urological guidelines for the management of male LUTS. However this meta-analysis corroborates data already present in the urological literature.

We appreciate the reviewer’s positive comments. This meta-analysis enriches information of urological literature with respect to the individual trials and previous reviews on the same topic.

Actually it is well known that several studies have investigated the efficacy of combination therapy against an $\alpha_1$-blocker, 5-ARI or placebo alone. Long-term data (four years) from Combination of Avodart and Tamsulosin (CombAT) study showed that combination treatment is superior to monotherapy for symptoms and Qmax, and superior to $\alpha$-blocker alone in reducing the risk of AUR or need for surgery. The CombAT study demonstrated that combination treatment is superior to either monotherapy regarding symptoms and flow rate starting from
month nine, and superior to α1-blocker for AUR and the need for surgery after eight months. Combination therapy was superior to monotherapy in preventing clinical progression as defined by an IPSS increase of at least four points, AUR, UTI, incontinence, or an increase in creatinine > 50%.

We thank the reviewer for this suggestion and detailed analysis. We made some adjustments for the description in the discussion section: Besides, in the CombAT study, the combination treatment is superior to either monotherapy regarding symptoms and flow rate starting from month nine, and superior to α1-blocker for acute urinary retention and the need for surgery after eight months. Combination therapy was superior to monotherapy in preventing clinical progression as defined by an IPSS increase of at least four points, acute urinary retention, urinary tract infection, incontinence, or an increase in creatinine > 50%. (line 11-16, page 15)

In the CombAT study, combination therapy reduced the relative risks of AUR by 68%, BPH-related surgery by 71%, and symptom deterioration by 41% compared with tamsulosin, after four years. To prevent one case of urinary retention and/or surgical treatment thirteen patients need to be treated for four years with dutasteride and tamsulosin combination therapy compared to tamsulosin monotherapy while the absolute risk reduction (risk difference) was 7.7%.

We thank the reviewer for this suggestion about CombAT study. We made some additions for the description in the discussion section: Combination therapy reduced the relative risks of acute urinary retention by 68%, BPH-related surgery by 71%, and symptom deterioration by 41% compared with tamsulosin after four years. To prevent one case of urinary retention and/or surgical treatment thirteen patients need to be treated for four years with dutasteride and tamsulosin combination therapy compared to tamsulosin monotherapy while the absolute risk reduction was 7.7%. (line 16-21, page 15)

The adverse events observed during combination treatment were typical of α1-blockers and 5-ARIs. The frequency of adverse events was significantly higher for combination therapy.

We appreciate the reviewer’s positive comments.
EAU guidelines recommend to offer combination treatment with an α1-blocker and a 5α-reductase inhibitor to men with moderate-to-severe LUTS and an increased risk of disease progression (e.g. prostate volume > 40 mL).

We thank the reviewer for this suggestion. We made some additions for the description in the discussion section: Currently, EAU guidelines recommend to offer combination treatment with an α1-blocker and a 5ARI to men with moderate-to-severe LUTS and an increased risk of disease progression (e.g. prostate volume > 40mL) [28].


Carrying out the meta-analysis, the Authors could not infer the long-term efficacy and tolerance of combination therapy, and selection bias, subjective factors and publication bias may also affect the final results of their study. Thus they stated that it still needs a lot of RCTs including sufficient sample size and statistics to confirm our findings. More high-quality RCTs with suitable study cohorts are needed to ascertain the efficacy and tolerance of combination of tamsulosin plus dutasteride and tamsulosin monotherapy in treating BPH.

We thank the reviewer for this suggestion. We made some descriptions in the discussion section about limitations of our study and methods for improvement.

Reviewer #2:

Zhou et al. conducted a meta-analysis to evaluate the efficacy and safety of the combination of tamsulosin plus dutasteride compared with tamsulosin monotherapy in treating benign prostatic hyperplasia (BPH) during a treatment period of at least 1 year. The meta-analysis is conducted in a methodologically accurate manner. The methods are well described. Figures and tables show the findings of the research in detail.

We appreciate the reviewer’s positive comments.
Among the adverse events, the authors may even include cases of prostate cancer in the enrolled population of the trials included in the review.

We appreciate the reviewer’s positive comments.

Discussion section is a bit wordy and should be shortened to increase the readability of the manuscript.

We thank the reviewer for this suggestion. We made some cuts and modifications in the discussion section to increase the readability of the manuscript (line 12-20, page 12).

The deleted portions are as follows:

BPH is the most widespread benign disease of men over the age of 50 and its occurrence rate increases with the growth of age, which is manifested as the symptoms of lower urinary tracts (LUTS), increase of total PV, decrease of peak urinary flow, and improvement of IPSS. Of all the pathogenesis we have known formerly, androgenic disorder are the vital factors for the progress of BPH, resulting in prostate gland enlarging irregularly, compressing the prostatic part of the urethra, changing the trait of urinary. If no any treatment, the quality of life and sexual function of the patient will be severely declined.

For the regimen of treatment, pharmacological treatments are generally reserved for patients with moderate-severe BPH, as it helps to alleviate symptoms of bladder outlet obstruction and preoperative to postoperative risk of the acute urinary retention. Currently the differences between the combination of tamsulosin plus dutasteride and tamsulosin monotherapy are still debatable, and there is a lack of systematic analysis to demonstrate the feasibility of this combination regimens.

Finally, the authors should better clarify in the discussion the elements of novelties brought about by this meta-analysis and in what enriches information with respect to the individual trials and previous reviews on the same topic.

We thank the reviewer for this suggestion. We made some descriptions for the elements of novelties brought about by this meta-analysis in the discussion section as follows: For safety, including AEs, erectile dysfunction, ejaculation disorder, retrograde ejaculation, decreased
libido, loss of libido, the combination group had a higher incidence than the tamsulosin group with the exception of dizziness. (line 20-21-1 page 13-14) Two RCTs containing data on PSA demonstrated the combination group was obviously superior to the tamsulosin group in reducing serum PSA level. (line 10-11 page 14) Our analysis found that the combination group may be noteworthy in reducing diagnostic ratio of prostate cancer. If PSA has a significant change during the treatment of combination for patients suffering from BPH, we need to think about more possibilities. (line 17-20 page 14) About clinical progression after drug administration, the combination therapy can markedly lower risk of BPH-related symptom progression and acute urinary retention than tamsulosin monotherapy. In other BPH-related clinical progression, involving urinary incontinence, urinary tract infection and renal insufficiency, no significant differences were found among two treatment groups. (line 21-1-4 page 14-15)

There are some typing mistakes (e.g. "methodds" on the title of the material and methods section).

We agree with the reviewer and thank the reviewer for this suggestion. These are now corrected throughout the article about typing mistakes.