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The effects of statins on benign prostatic hyperplasia and the lower urinary tract symptoms

A Meta-analysis

Xuesong Yang, MD, Qiang Zhang, MD, Guo Jiang, MD, Junbo Liu, MD, Chaofan Xie, MD, Shu Cui, MD, Tao Wu, MD, PhD*

Abstract

Background: The aim of this meta-analysis was to understand the relationship between statin with benign prostatic hyperplasia (BPH) and lower urinary tract symptoms (LUTS).

Methods: A systematic literature search was conducted using PubMed, Embase, Cochrane Library, Chinese Medical and Biological Literature Database, China HowNet, Vip, and Wanfang. We calculated pooled odds ratios (OR) and 95% CI and standardized mean difference (SMD). Using Stata 12.0 and Review 5.3 for meta-analysis.

Results: This meta-analysis included 11 articles and 49,128 participants. Results show statins could not reduce the incidence of BPH [OR = 0.77 (0.57, 1.03, $P = .08$]. For patients over 60 years old, statins could reduce the incidence of BPH [OR = 0.35 (0.22, 0.55), $P < .0001$]. Statins can slow down the progression of LUTS in BPH [SMD = −0.32 (−0.54, −0.10), $P = .004$], but there is no significant correlation between them in patients taking drugs for less than 1 year.

Conclusion: Statins have no significant effect on the incidence of BPH, but statins can reduce the risk of BPH for patients over 60 years old. For patients with hyperlipidemia, the duration of medication is more than 1 year, which can slow down the progression of LUTS. However, more high-quality and large sample size studies are needed to further improve and verify.

Abbreviations: BOO = bladder outlet obstruction, BPH = benign prostatic hyperplasia, IPSS = international prostate symptom score, LUTS = the lower urinary tract symptoms, MD = mean difference, NOS = Newcastle-Ottawa Scale, OR = Odds ratio, SMD = standardized mean difference.

Keywords: benign prostatic hyperplasia, HMG-CoA, lower urinary tract symptoms, meta-analysis

1. Introduction

Macroscopic BPH represents the enlargement of the prostate arising from the stromal and epithelial proliferation; the main symptoms were LUTS; urodynamic manifestations were bladder outlet obstruction (BOO).[1] If the international prostate symptom score (IPSS) was ≥8, peak flow rate was <15 mL/s, and prostate volume was >20 cm^3, it can diagnose clinical BPH.[2] LUTS refers to various abnormal manifestations in the urination cycle caused by changes in the structure and function of the lower urinary tract including storage symptoms, voiding symptoms, post micturition symptom.[3] IPSS score has been proposed as a guide for initial treatment of men with mixed voiding and storage symptoms.[4] LUTS is most generally correlated with an increasing incidence of BOO. Many studies have shown that lower urinary tract symptoms (LUTS) are also associated with prostate cancer and bladder cancer.[5] Relevant epidemiological data show that BPH may be closely related to metabolic disorders and cardiovascular and cerebrovascular diseases.[6] Conventional drug treatment regimens for BPH patients are mainly alpha-receptor blockers and 5alpha-reductase inhibitors. M-receptor blockers can improve bladder storage symptoms. However, there are still many patients who need surgical treatment. It is particularly important to explore the preventive measures of BPH.

Statin is a hydroxymethylglutaryl coenzyme A reductase inhibitor, which can significantly improve blood lipid levels and reduce cholesterol, triglyceride and low-density lipoprotein. At the same time, with the deepening of research, statins can also regulate apoptosis and antioxidant effect.[7] It can also reduce the fibrosis of prostate and bladder,[8] and regulate the expression of growth factor in connective tissue.[9] On the other hand, the role of statin in reducing inflammation has been paid more and more

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Department of Urology, Affiliated Hospital of North Sichuan Medical College, Nanchong, Sichuan, P. R. China.

* Correspondence: Tao Wu, Department of Urology, Affiliated Hospital of North Sichuan Medical College, Wenhua Road 57, Shunqing District, Nanchong, 637000, Sichuan, P. R. China (e-mail: alhawking@163.com).

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attention. The role of statins in the development of benign prostatic hyperplasia (BPH) is controversial. All randomized controlled trials and cohort trials of statins and BPH in the database were summarized. To provide reference for clinical medication and reducing the Medical and Economic Burden of Patients.

2. Methods

2.1. Literature search and study selection

This meta-analysis database mainly consists of PubMed, Embase, and Cochrane Library in English, and includes Chinese literature databases such as Chinese Medical Biology Literature Database, Chinese HowNet, Vip, and Wanfang Data. Search the database until November 01, 2018. The retrieval strategy is free word and subject word method. Detailed Retrieval Strategy in the Supplementary material 1, http://links.lww.com/MD/C952 (Search strategy). Additional sources of literature mainly come from subject-related reference lists. The original text cannot be retrieved from the database. Contact the author by e-mail to obtain the data. The identification and selection of the studies were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) criteria and the Population, Intervention, Comparator, Outcomes (PICO) methodology. PICO was defined as follows: population consisted of prostate hyperplasia patients or hyperlipidemia patients (P) Take statins (I). Placebo (C). Differences in incidence of BPH or progression of lower urinary tract syndrome (O).[10,11]

The meta-analysis is based on the analysis and evaluation of previous published articles, so it does not involve medical ethics.

2.2. Data extraction and study quality

This Meta-analysis has the following criteria:

1. The risk point estimate was reported as an OR with the 95% CI, or the data were presented such that an OR and 95% CI could be calculated; LUTS score before and after medication was reported in detail.
2. Types of study: randomized controlled trials, cohort studies, case-control studies;
3. the study evaluated statins with LUTS or BPH; and
4. the study language was published in English or Chinese.

For each selected study, the following items were recorded in an Excel: first author's name, the year of publication, Source, country, study design, number of cases and controls, average age, statin group, and LUTS stage, follow-up time, medication time. The cohort study used Newcastle-Ottawa Scale (NOS) scoring criteria. The NOS scale consisted of 3 parts: selection, comparability, exposure or outcome evaluation. Randomized controlled study mainly used Cochrane Collaborative Network bias risk assessment criteria.

2.3. Statistical analysis

The meta-analysis method mainly relies on Stata 12.0 and Review 5.3 software systems. mean difference (MD) is selected as the effect statistic and SMD is selected if the unit is different or the difference between the experimental group and the control group was large for continuous variables. Statistical Effect Selection OR for Bicategorical Variables. Heterogeneity was assessed using Cochran Q statistic and quantified using the I2 statistic, If the study group had no statistical heterogeneity, using fixed effect model, if there is statistical heterogeneity between the study group, using random effects model for Meta. If high heterogeneity ($I^2 > 50$) was still found, subgroup analysis or influence analysis (sensitivity analysis) would be performed. In this Meta-analysis, the test level was set at alpha = 0.05. Sensitivity analysis was used to determine the stability, and Eggre test was used to analyze the bias factors.

3. Results

3.1. Characteristics of studies

Through preliminary search, 490 documents were obtained. After gradual screening, 11[12–22] documents were finally included in this meta-analysis. The process of literature search and screening are detailed in Figure 1, and the basic characteristics of each meta-analysis document are detailed in Table 1. The risk of bias is detailed in Supplementary Figure 1, http://links.lww.com/MD/C952.

3.2. Association between statins and BPH

The effects of statins on the risk of BPH were included in 5 articles.[12–16] Meta-analysis of random effect model showed that statins could not reduce the incidence of BPH in patients with hyperlipidemia [OR = 0.77 (0.57, 1.03, $P = .08$] (Fig. 2A). however, it also introduced significant heterogeneity into the analysis ($I^2 = 95$). Sensitivity analysis and subgroup analysis were carried out to find heterogeneous factors. Sensitivity analysis of outcome indicators showed that the results were basically consistent (Supplementary Fig. 2, http://links.lww.com/MD/C952). According to age subgroup analysis, statins can reduce the incidence of BPH [OR = 0.35 (0.22, 0.55), $P < .0001$] for groups older than 60 years, but there is no significant difference between statins and BPH [OR = 0.78 (0.54, 1.11), $P = .17$]for groups less than 60 years. There was no significant difference between statins and BPH [OR = 0.65 (0.38, 1.13), $P = .13$] in the group taking more than one year, and there was no significant difference between statins and BPH [OR = 0.76 (0.42, 1.38), $P = .37$] in a group with longer medication time less than 1 year (Fig. 2B).

3.3. Association between statins and LUTS

Meta-analysis of the progress of LUTS by statins was included in 6 articles,[17–22] including 5 randomized controlled trials and 1 cohort analysis. Meta-analysis of the random effect model showed that statins could slow down the progress of LUTS in patients with hyperlipidemia [SMD = −0.32 (−0.54, −0.10) $P = .02$] (Fig. 3A). it also introduced significant heterogeneity into the analysis ($I^2 = 61$). Sensitivity analysis and subgroup analysis were carried out to find heterogeneous factors. Sensitivity analysis of outcome indicators showed that the results were basically consistent (Supplementary Fig. 3, http://links.lww.com/MD/C952). Subgroup analysis was performed according to the time and type of medication. Three articles were included in a group with longer medication time than 1 year. Meta-analysis showed that the progression of LUTS could be delayed [SMD = −0.40 (−0.66, −0.13), $P = .02$]. Three articles were included in a group with longer medication time less than 1 year, Meta-analysis showed that the progression of LUTS could not be delayed [SMD = −0.15 (−0.35, 0.04), $P = .54$]. Atorvastatin group was included in 2 articles. Meta-analysis showed that it

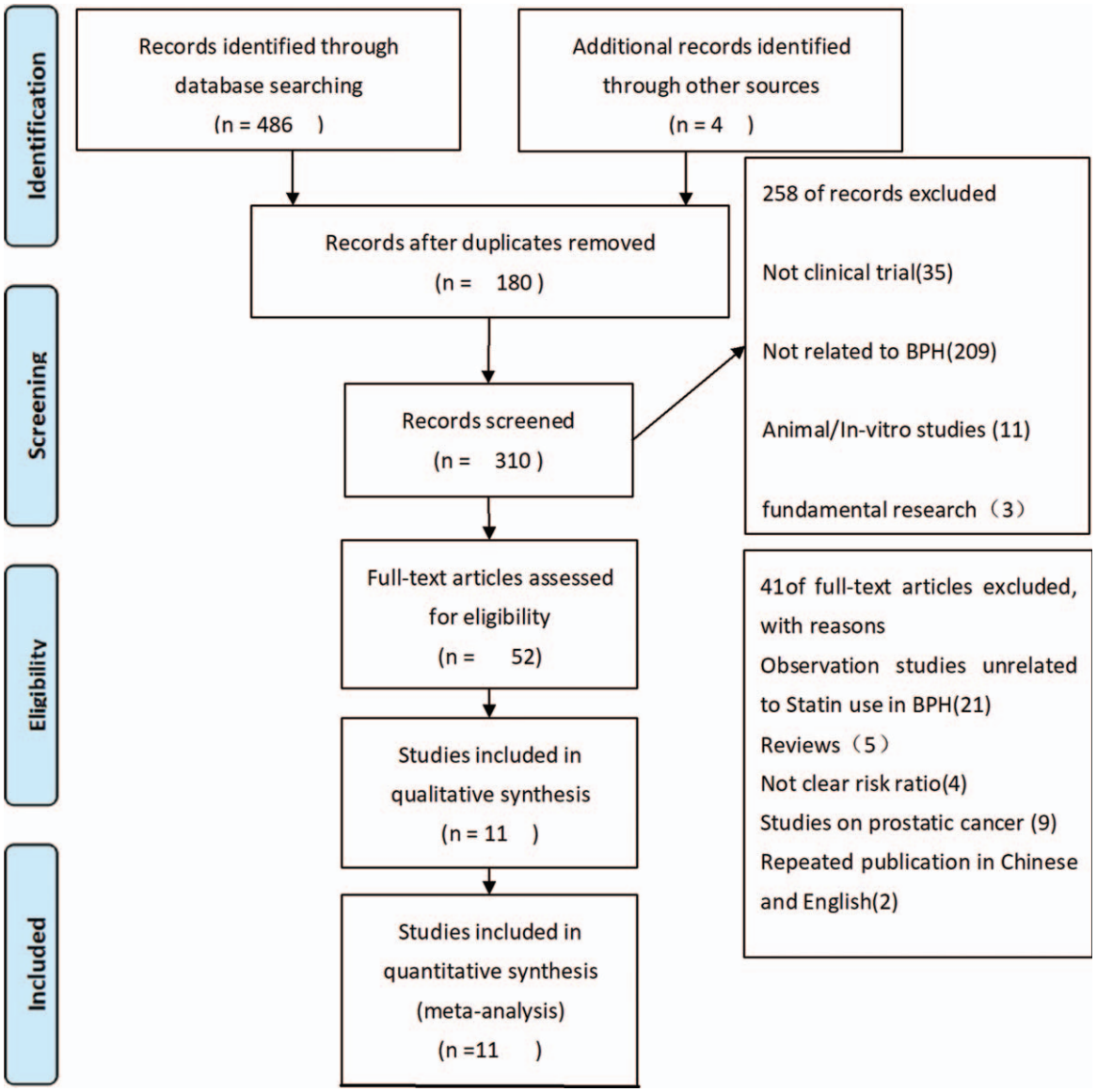

Figure 1. Preferred reporting items for systematic reviews and meta-analyses flow chart for study selection. RCT, cohort study. RCT = randomized controlled trial.

Table 1

Study methodology and characteristics among the included studies.

Author et al.	Country	Study type	Source	Publishing time	Statin group (n)	Control group (n)	Medication time (month)	Average age (year)	Follow-up time (year)	Statin type	Quality score
Ian W. Mills et al[12]	UK	RCT	European Urology	2007	176	174	6.5	65.4	2013–2014	a	–
Konstantinos et al[13]	Greece	RCT	Clinical Urology	2008	18	15	4	>50	2006–2007	c	–
Xiangyu et al[14]	China	RCT	World J Urol	2015	83	41	12	a:74.88 b:75.19	2007–2008	a+b	–
MingGen et al[15]	China	RCT	Chinese Journal of Andrology	2014	259	335	60	61.4	2003–2008	d	–
XiuFang et al[16]	China	RCT	Chinese Journal of Geriatrics	2011	15	15	2	72.7	2011–2011	b	–
Alison et al[17]	USA	cohort study	American Journal of Epidemiology	2013	4557	4008	2-192	63.7	1992–2008	N/A	7
Hung et al[18]	Taiwan,China	cohort study	The Aging Male	2018	7961	4092	3-12 (n=6357) >12 (n=1604)	53.4	2000–2012	N/A	7
Jennifer et al[19]	USA	cohort study	BJU international	2010	2447	11388	≤12 (2115) >12 (1296)	NR	1990–2006	N/A	8
Richard et al[20]	USA	cohort study	The journal of sexual medicine	2015	7961	4092	24	53.6	2005–2012	N/A	6
Susana et al[21]	USA	cohort study	Annals of epidemiology	2011	231	319	22	52.3	2003–2005	N/A	6
Han et al[22]	South Korea	cohort study	European Urology Supplements	2016	119	45	36	NR	2012–2015	N/A	6

*N/A: not applicable. a: Atorvastatin; b: Simvastatin; c: lovastatin; d: not reported.

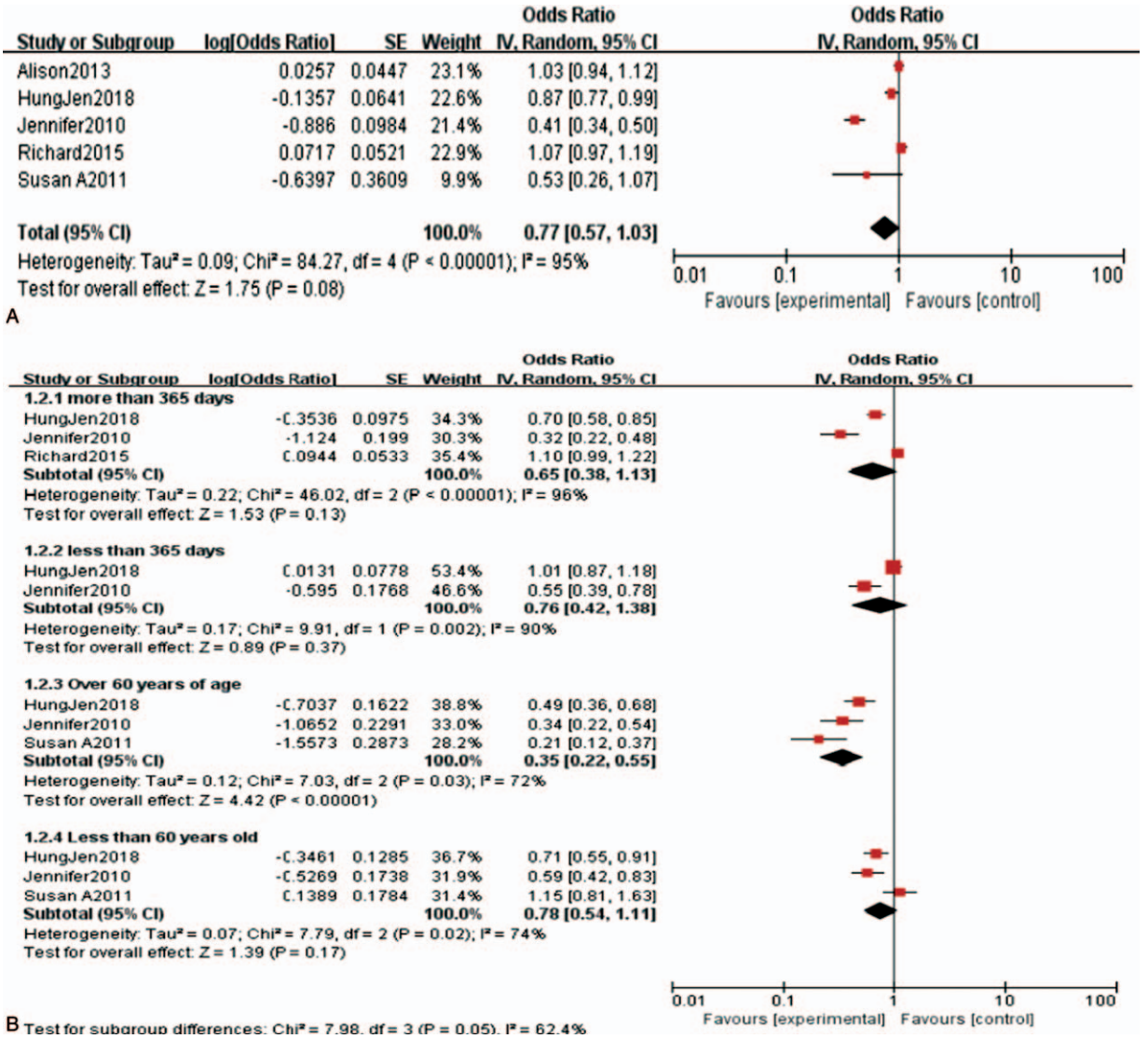

Figure 2. (A) Forest plots on the association of statins with Risk of benign prostatic hyperplasia. (B) Forest plots on the association of statins with Risk of benign prostatic hyperplasia, Subgroup analysis:(1.2.1) more than 365 days;(1.2.2) less than 365 days; (1.2.3) over 60 years; (1.2.4) less than 60 years.

could not delay the progress of LUTS [SMD = −0.16 (−0.35, 0.03), $P = .34$]. Simvastatin group was included in 2 articles. Meta-analysis showed that it could delay the progress of LUTS [SMD = −0.50 (−0.88, −0.13), $P = .89$] (Fig. 3B).

3.4. Publication bias

We did not find evidence of publication bias. LUTS disease progression, Egger test results showed that $t = 0.46$, $P = .673$ (Supplementary Fig. 4, http://links.lww.com/MD/C952), indicating that the possibility of publication bias is low. BPH incidence, Egger's test results showed that $t = 0.46$, $P = .673$ (Supplementary Fig. 5, http://links.lww.com/MD/C952), indicating that the possibility of publication bias is low.

4. Discussion

This meta-analysis is the first systematic report on the relationship between statin and BPH and lower urinary tract syndrome. It is also the most detailed meta-analysis with 49,128 participants; The results of meta-analysis suggest that statins can reduce the risk of BPH for patients over 60 years old. For patients with hyperlipidemia, the duration of medication is more than 1 year, which can slow down the progression of LUTS. Eleven articles were included, of which 6 cohort studies had NOS scores above 6, of which 5 RCT had a low risk of bias according to Cochrane Collaborative Network bias risk assessment criteria.

The pathological mechanisms underlying the relationship between statins with BPH and LUTS have yet to be clearly established. Statins can significantly reduce blood lipid levels, cholesterol, triglycerides, and low-density lipoprotein. While statins are studying their hypolipidemic effects, their research on adjuvant therapy for other diseases is also deepening. Several studies have revealed the role of statins in anti-inflammation of rheumatoid arthritis,[23] sepsis,[24] and multiple sclerosis.[25] In animal experiments, high cholesterol diet can change the histomorphology of rat prostate.[26] In addition, epidemiology shows that dyslipidemia has a statistical correlation with obesity

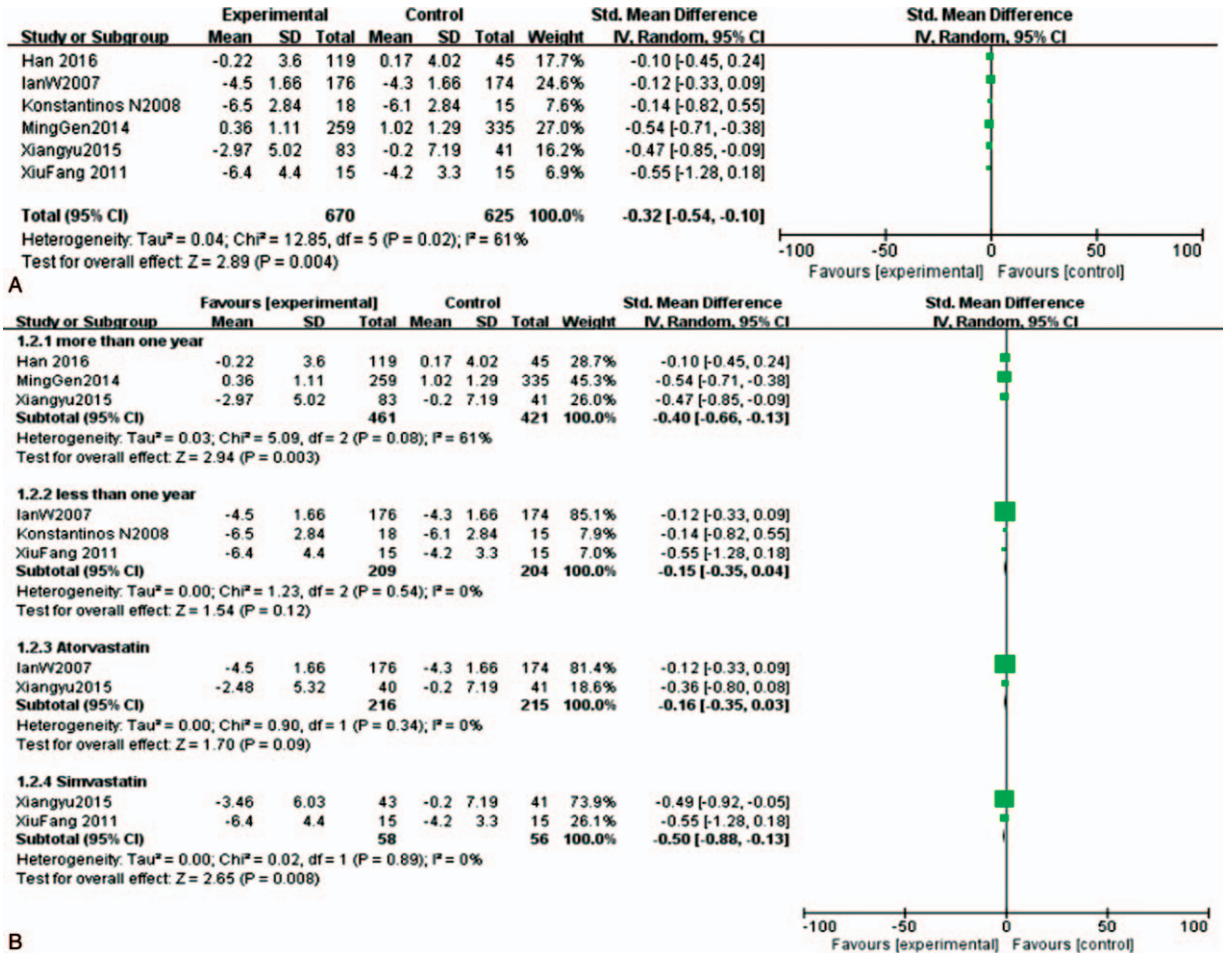

Figure 3. (A) Forest plots on the association of statins with LUTS progression. (B) Forest plots on the association of statins with LUTS progression. Subgroup analysis:(1.2.1) more than 1 year;(1.2.2) less than 1 year; (1.2.3) Atorvastatin; (1.2.4) Simvastatin. LUTS = the lower urinary tract symptoms.

and the incidence of prostatic hyperplasia.[27] Banez et al[28] report that statins can reduce the risk of inflammatory infiltration in Prostate neoplasms, it also affects the development and prognosis of prostate cancer. Sun et al[29] reported that cholesterol can enhance the activity of TRPM7 calcium channel, which can induce the activation of AKT and promote the proliferation of prostate cells. Hindler[30] summary finding that statins have advantages and disadvantages in angiogenesis. High-dose statins have anti-angiogenesis effects and inhibit capillary formation and reduce the release of vascular endothelial growth factor. However, low-dose statins have angiogenesis stimulation. These findings may partly explain the meta-analysis results. Further research is needed to better understand the potential links between statins with BPH and LUTS.

Recent cohort studies have shown that statin cannot reduce the incidence of BPH.[17,20,21] Alison reported a cohort study, total of 8565 participants were followed up for more than 15 years. This study[17] had found no association between statins and Incidence of BPH (OR = 1.03, 95% CI: 0.94–1.12). At the same time, another cohort study showed the same conclusion. Susana[16] found that the incidence of BPH is unrelated to statin use in people younger than 60 years of age (OR = 1.15, 95% CI: 0.81–1.63), but statin can reduce the risk of prostate hyperplasia by about 85% for people older than 60 (OR = 0.21, 95% CI: 0.12–0.37). However several other cohort studies[18,19] show opposite results. A large sample cohort study showed that statin could reduce the incidence of BPH in people over 60 (OR = 0.34, 95% CI: 0.22–0.54)and under 60 years of age (OR = 0.59, 95% CI: 0.42–0.83).[18] After fully considering factors such as age and medication time, our meta-analysis only found a significant association between statin and the incidence of BPH for people older than 60. Why such a conclusion appears in the older may become the point of penetration of pathophysiology research in this field.

The symptoms of lower urinary tract caused by BPH seriously affect the quality of life of patients. The role of statins in LUTS progression is controversial. Including 2 randomized controlled trials indicated that statin could delay progress of LUTS.[15,16] A large-scale RCT published in an authoritative magazine in China,[10] Statistical results show that statin can significantly slow down LUTS progress[SMD = −0.54 (−0.71, −0.38)], but the types of statins were not described in detail. But a high-quality RCT from Europe presents different conclusions[12] that there was no significant relationship between statin and LUTS progression[SMD = −0.12 (−0.33, 0.09)]. However, the authors only followed up for 6.5 months. Whether long-term statin use can affect LUTS progression needs further study. In addition, a retrospective cohort study showed the same conclusion [SMD

= −0.10 (−0.45, 0.24)].[21] Atorvastatin group included 2 articles.[12,14] The results showed that there was no correlation between Atorvastatin and the progression of LUTS [SMD = −0.16 (−0.35, 0.03), $P = .34$]. However, the other 2 randomized controlled trials for simvastatin showed opposite results,[14,16] and simvastatin could slow down the progress of LUTS [SMD = −0.50 (−0.88, −0.13), $P = .89$]. However, only 2 papers were included in the 2 groups, and the differences between different statins need to be verified by large sample data. Although we found that statin slowed LUTS progression in patients over 60 years of age and in patients taking Simvastatin, further researches are necessary to better understand the potential association between statins and LUTS.

There are still many limitations in this meta-analysis. First, this data review is limited to Chinese and English literature, so there is a possibility of publication bias. Second, the sample size of randomized controlled trials included in this meta is small, which may affect the generalization of the results. Third, LUTS progress evaluation only refers to IPSS score, but other quantitative indicators are not included because of the limitation of original literature data. Fourth, in an attempt to reduce or explain the high heterogeneity of the results, sensitivity analysis, and subgroup analysis were carried out. Despite subgroup analysis of age and duration of medication, heterogeneity remained high.

5. Conclusion

Statins have no significant effect on the incidence of BPH in patients with hyperlipidemia, but for patients over 60 years of age, statins can reduce the risk of BPH. For patients with BPH, the duration of medication is more than 1 year, which can slow down the progression of LUTS. Due to the lack of relevant research, the number and sample size of this meta-analysis are limited. More high-quality and large sample size studies are needed to further improve and verify the above results.

Author contributions

Conceptualization: Xuesong Yang, Qiang Zhang.
Data curation: Xuesong Yang, Qiang Zhang, Chaofan Xie, Shu Cui.
Formal analysis: Xuesong Yang, Junbo Liu, Chaofan Xie, Tao Wu.
Funding acquisition: Xuesong Yang, Qiang Zhang.
Methodology: Xuesong Yang, Qiang Zhang, Tao Wu.
Investigation: Qiang Zhang.
Resources: Guo Jiang.
Writing – original draft: Tao Wu.
Writing – review & editing: Tao Wu.

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