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FUNCTIONAL UROLOGY

The effect of pharmacotherapy on prostate volume, prostate perfusion and prostate-specific antigen (prostate morphometric parameters) in patients with lower urinary tract symptoms and benign prostatic obstruction. A systematic review and meta-analysis

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Introduction The clinical effect of pharmacotherapy on prostate morphometric parameters is largely unknown. The sole exception is 5α-reductase inhibitors (5-ARI) that reduce prostate volume and prostate-specific antigen (PSA). This review assesses the effect of pharmacotherapy on prostate parameters effect on prostate parameters, namely total prostate volume (TPV), transitional zone volume (TZV), PSA and prostate perfusion.

Material and methods We conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) reporting on morphometric parameters' changes after pharmacotherapy, as primary or secondary outcomes. The study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. RCTs' quality was assessed by the Cochrane tool and the criteria of the Agency for Healthcare Research and Quality. The effect magnitude was expressed as standard mean difference (SMD). The study protocol was published on PROSPERO (CRD42020170172).

Results Sixty-seven RCTs were included in the review and 18 in the meta-analysis. The changes after alpha-blockers are comparable to placebo. Long-term studies reporting significant changes from baseline, result from physiologic growth. Finasteride and dutasteride demonstrated large effect sizes in TPV reduction ([SMD]:-1.15 (95% CI:-1.26 to-1.04, p <0.001, and [SMD]:-0.66 (95% CI:-0.83 to-0.49, p <0.001, respectively), and similar PSA reductions. Dutasteride's effect appears earlier (1st vs 3rd month), the changes reach a maximum at month 12 and are sustained thereafter. Phosphodiesterase-5 (PDE-5) inhibitors have no effect on morphometric parameters. Phytotherapy's effect on TPV is non-significant [SMD]: 0.12 (95% CI:-0.03 to 0.27, p = 0.13). Atorvastatin reduces TPV as compared to placebo (-11.7% vs +2.5%, p <0.01). Co-administration of testosterone with dutasteride spares the prostate from the androgenic stimulation as both TPV and PSA are reduced significantly.

Conclusions The 5-ARIs show large effect size in reducing TPV and PSA. Tamsulosin improves perfusion but no other effect is evident. PDE-5 inhibitors and phytotherapy do not affect morphometric parameters. Atorvastatin reduces TPV and PSA as opposed to testosterone supplementation.

Key Words: prostate volume changes ‹› prostate perfusion ‹› lower urinary tract pharmacotherapy ‹› morphometric parameters

INTRODUCTION

Benign prostatic obstruction (BPO) is a common cause of lower urinary tract symptoms (LUTS) in men older than 50 years [1]. Benign prostatic enlargement (BPE) is defined as prostatic enlargement due to histologic benign prostatic hyperplasia [2]. BPO involves the static component or the physical mass of the prostate and the dynamic component or smooth muscle tone of the prostate stroma and the bladder neck [1, 2]. It is reasonable to assume a potential relation between prostate size, degree of obstruction and LUTS severity, but population-based studies failed to demonstrate a direct link [3].
Prostate morphometric parameters are prognostic indicators of BPE progression. Data analysis from the placebo arm of Medical Therapy of Prostatic Symptoms (MTOPS) trial showed that men with baseline total prostate volume (TPV) 31 ml and prostate-specific antigen (PSA) of 1.6 ng/dl or greater are at significantly higher risk of BPE progression, defined as a 4-point or more increase in AUA-SS, acute urinary retention, urinary incontinence, renal insufficiency or recurrent urinary tract infections [4]. Baseline flow rate, post-void residual and age were the additional predictors. TPV and PSA are among the baseline factors which could predict conservative treatment failure and/or the need for combination therapy [5]. Baseline PSA is higher in men with larger prostates and is associated with higher annual volume increase (2.2%) compared to smaller prostates (1.7%) [6]. However, a multivariate analysis of the Baltimore Longitudinal Study of Aging in 242 men without prostate cancer, reported no correlation between PSA or PSA changes and annual prostate growth rate during 4.2 years of follow-up [6]. The median rate of TPV and PSA change per year was 0.6 ml and 0.03 ng/ml respectively.
Existing data supports the hypothesis that ischemia of the lower urinary tract may cause BPE and LUTS. Azadzoi et al. were first to document bladder dysfunction and increased prostate contractility in an animal model of pelvic atherosclerosis [7]. The underlying mechanism of ischemic injury involves oxidative stress, free radical injury to smooth muscle cells, epithelium, mitochondria, endoplasmic reticulum and nerve fibers, impairment of the nitric oxide (NO/cGMP) pathway, activation of degenerative processes and deposition of collagen [7]. Chronic ischemia induces prostate stromal fibrosis, decreases cGMP and increases prostate tissue sensitivity to contractile stimuli [7].
The clinical effect of pharmacotherapy on prostate morphometric parameters is largely unknown. The sole exception is 5α-reductase inhibitors (5-ARI) which reduce TPV, transitional zone volume (TZV) and PSA. There is preclinical evidence that all medications influence prostate volume or perfusion. Experiments have shown the anti-apoptotic effect of sympathomimetics, and the potent apoptotic effect on human prostate cancer cell cultures of quinazoline-based α-blockers [8].
Phosphodiesterase-5 (PDE-5) inhibitors influence prostate cell proliferation via upregulation of NO/cGMP and Rho-kinase activity [9, 10]. Evidence supports that finasteride reduces prostate blood flow via downregulation of vascular endothelial growth factor (VEGF) [11]. Tamsulosin antagonizes vesical arteries adrenoceptors, thus improving LUT perfusion [12]. PDE5 inhibitors improve perfusion via the reduction of endothelin-1 levels and regulation of vascular smooth muscle cells proliferation [10].
This review aims to investigate the effect of both urological and non-urological medication on prostate morphometric parameters, namely TPV, TZV, PSA and prostate perfusion.

MATERIAL AND METHODS

Literature search

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement [13]. The Embase, MEDLINE, Cochrane Database of Systematic Reviews, Cochrane Central (Cochrane Health Technology Assessment, Database of Abstracts of Reviews of Effects, Health Economics Evaluations Database) and Google Scholar were searched with no restriction on publication date. Additional sources for articles were the reference lists of included studies and relevant review articles.

Study selection

We included randomized-controlled trials (RCTs) of adult men with LUTS due to BPE, who received pharmacotherapy, and reported post-intervention changes of prostate parameters as primary or secondary outcome. The included studies had 10 participants minimum, were written in English language and used ultrasound or MRI to assess morphometric parameters. There was no restriction in study duration. In the event of open extension of double-blind studies, only data from the double-blind period were included. If data were not reported separately, studies were excluded.
Two reviewers (AG and DC) screened the titles and abstracts of identified records, and the full text of potentially eligible records was evaluated using a stan-

dardized form. Disagreement was resolved by discussion. If there was no agreement, a third independent party acted as an arbitrator (VS).

Data extraction

Data from eligible studies were extracted in duplicate. Discrepancies were resolved by a third reviewer. The variables assessed included the year of publication, number of randomized subjects, number of subjects who completed the follow up, baseline values and post treatment changes in morphometric parameters presented as mean (±standard deviation) and percentage changes from baseline.

Risk of bias and study quality assessment

Risk of bias (RoB) was assessed using the revised version of Cochrane Collaboration's RoB Assessment tool [14]. Two reviewers (AG and DC) independently assessed RoB in each study, while a third reviewer (VS) acted as an arbitrator. The RoB was considered high if the confounder had not been considered by the individual study. The RoB tables were developed in Review Manager 5.3 (RevMan-Informatics and Knowledge Management Department, Cochrane, London, UK).

To ensure reliability and validity of measures and reported measurements, each included RCT had an overall rating based on the criteria developed by Agency for Healthcare Research and Quality (AHRQ). The ratings were 'Low-risk', 'Moderate-risk' or 'High-risk' [15, 16]. The RCTs should have been characterized as low risk in measurement bias (points 3d & 3e) based on the criteria developed by AHRQ.

Statistical analysis

The primary outcome was the post-intervention changes in TPV. The secondary outcomes were the changes in TZV, PSA and prostate perfusion as defined by the trialist. Owing to the expected heterogeneity, a narrative synthesis of all included studies was planned [17]. Data are presented as post-treatment absolute mean changes (±SD) and percentage changes.

Statistical heterogeneity was tested using chi-square test. A value of $p < 0.10$ or $I2 > 50\%$ was used to define heterogeneity. A list of potential confounders was developed a priori: use of LUTS-related medications, follow-up duration, LUTS not related to BPE, previous catheter use, previous LUT surgery and history of LUT malignancy.

A meta-analysis was considered for each endpoint if two or more RCTs had similar study design, dosing scheme and follow-up duration. Meta-analysis was conducted using RevMan. The effect magnitude was expressed as standard mean difference (SMD) with 95% confidence interval (CI) for continuous outcomes. The treatment effect size was considered small for SMD values of 0–0.2, moderate for SMD range 0.2–0.8 and large if SMD was >0.8.

RESULTS

Evidence acquisition

Study selection

Sixty-seven RCTs were eligible for inclusion (Figure 1). Eighteen were eligible for quantitative synthesis. The search was updated in October 2020.

Study characteristics

We identified 28 placebo-controlled RCTs and 39 non-placebo RCTs. Since the included RCTs had 2 or more study arms, we studied 36 active medications versus placebo comparisons and 48 active medications versus active medication comparisons. Phytotherapy's effect on morphometric parameters was assessed in 18 comparisons, α-blockers' effect in 18 comparisons, 5-ARI's effect in 23 comparisons, PDE5's effect in 6 comparisons, combination treatments

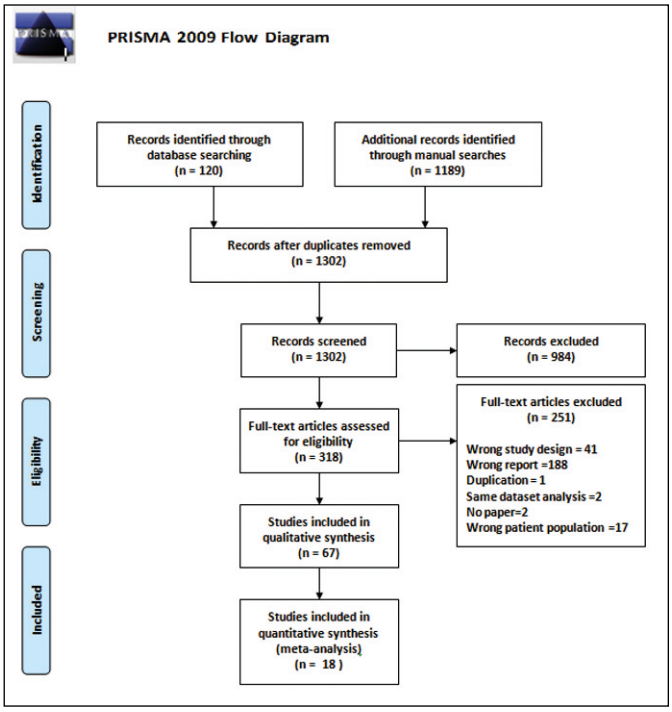

Figure 1. *Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart.*

Table 1. *The characteristics of included trials*

Study, [reference]	Comparator 1, Daily dosage	Comparator 2, Daily dosage	Comparator 3, Daily dosage	Comparator 4, Daily dosage	No. subjects randomized	Duration of Follow up	Reported parameters	Primary or Secondary endpoints	Study rating based on AHRQ criteria
Lepor 1996, [18]	Terazosin, 10 mg OD	Finasteride, 5 mg OD	Terazosin 10 mg OD plus Finasteride, 5 mg OD	Placebo	1230	12 months	TPV, PSA	Secondary	Low Risk
McConnell 2003, [19]	Doxazosin, 4 or 8 mg OD	Finasteride, 5 mg OD	Doxazosin, 4 or 8 mg OD plus Finasteride, 5 mg OD	Placebo	3047	4.5 years	TPV, PSA	Secondary	Low Risk
Yokoyama 2012, [20]	Tadalafil. 2.5 mg OD	Tadalafil 5 mg OD	Tamsulosin, 0.2 mg OD	Placebo	612	3 months	PSA	Secondary	Low Risk
Roehrborn 2006, [21]	Alfuzosin, 10 mg OD	Placebo	n/a	n/a	1522	24 months	PSA	Secondary	Low Risk
Roehrborn 2006, [22]	Alfuzosin, 10 mg OD	Placebo	n/a	n/a	528	3 months	TPV, TZV	Primary	Moderate Risk
Turkeri 2001, [23]	Doxazosin, 4 mg OD	Placebo	n/a	n/a	29	4 weeks	TPV, PSA	Secondary	High Risk
Debruyne 2002, [24]	Tamsulosin, 0.4 mg OD	Serenoa repens, 320 mg OD	n/a	n/a	704	12 months	TPV, PSA	Primary	Low Risk
Sengupta 2011, [25]	Tamsulosin, 0.4 mg OD	Phytotherapy (Non-Sr), OD	n/a	n/a	46	3 months	TPV	Secondary	Moderate Risk
Latil 2015, [26]	Tamsulosin, 0.4 mg OD	Hexanic Extract Serenoa repens, 320 mg OD	n/a	n/a	203	3 months	TPV	Secondary	High Risk
Pande 2014, [27]	Tamsulosin, 0.4 mg OD	Silodosin, 8 mg OD	n/a	n/a	61	3 months	TPV	Secondary	Moderate Risk
Karami 2016, [28]	Tamsulosin, 0.4 mg OD	Tadalafil, 20 mg OD	n/a	n/a	119	3 months	PSA	Primary	High Risk
Griwan 2014, [99]	Tamsulosin, 0.4 mg OD	Naftopidil, 75 mg OD	n/a	n/a	60	3 months	TPV	Secondary	Moderate Risk
Hlzli 2007, [29]	Tamsulosin, 0.4 mg OD	Serenoa repens, 320 mg OD	n/a	n/a	40	6 months	TPV, PSA	Secondary	High Risk
Odysanya 2017, [30]	Tamsulosin, 0.4 mg OD	Finasteride, 5 mg OD	Tamsulosin, 0.4 mg OD plus Finasteride, 5 mg OD	n/a	60	6 months	TPV	Secondary	High Risk
Morgia 2014, [31]	Tamsulosin, 0.4 mg OD	Phytotherapy (Non-Sr)	Tamsulosin, 0.4 mg OD plus Phytotherapy (Non-Sr)	n/a	150	12 months	TPV, PSA	Secondary	Low Risk
Roehrborn 2010, [32]	Tamsulosin, 0.4 mg OD	Dutasteride, 0.5 mg OD	Tamsulosin, 0.4 mg OD plus Dutasteride, 0.5 mg OD	n/a	3221	4 years	TPV, PSA	Secondary	Low Risk
Debruyne 1998, [33]	Alfuzosin SR, OD	Finasteride, 5 mg OD	Alfuzosin SR, OD plus Finasteride, 5 mg OD	n/a	707	6 months	TPV, PSA	Secondary	Low Risk
Sakalis 2018, [34]	Tamsulosin, 0.4 mg OD	Solifenacin, 5 or 10 mg OD	n/a	n/a	69	6 months	TPV, TZV, PSA, Perfusion parameters	Primary	Moderate Risk
Andersen 1995, [35]	Finasteride, 5 mg OD	Placebo	n/a	n/a	707	24 months	TPV, PSA	Secondary	Moderate Risk
Nickel 1996, [36]	Finasteride, 5 mg OD	Placebo	n/a	n/a	613	24 months	TPV, PSA	Primary	Low Risk
McConnell 1998, [37]	Finasteride, 5 mg OD	Placebo	n/a	n/a	312	48 months	TPV	Secondary	Low Risk

Table 1. *Continued*

Study, [reference]	Comparator 1, Daily dosage	Comparator 2, Daily dosage	Comparator 3, Daily dosage	Comparator 4, Daily dosage	No. subjects randomized	Duration of Follow up	Reported parameters	Primary or Secondary endpoints	Study rating based on AHRQ criteria
Marberger 1998, [38]	Finasteride, 5 mg OD	Placebo	n/a	n/a	2902	24 months	TPV	Secondary	Moderate Risk
Kirby 1992, [39]	Finasteride, 5 mg OD	Finasteride, 10 mg OD	Placebo	n/a	66	3 months	TPV, PSA	Secondary	High Risk
Finasteride group 1993, [40]	Finasteride, 1 mg OD	Finasteride, 5 mg OD	Placebo	n/a	750	12 months	TPV, PSA	Secondary	Moderate Risk
Tammela 1995, [41]	Finasteride, 5 mg OD	Placebo	n/a	n/a	36	6 months	TPV	Secondary	High Risk
Pannek 1998, [42]	Finasteride, 5 mg OD	Placebo	n/a	n/a	34	6 months	TPV, PSA	Secondary	High Risk
Marks 1997, [43]	Finasteride, 5 mg OD	Placebo	n/a	n/a	41	6 months	TPV, PSA	Secondary	Moderate Risk
Gormley 1992, [44]	Finasteride, 5 mg OD	Placebo	n/a	n/a	597	12 months	TPV, PSA	Secondary	Moderate Risk
Roehrborn 2002, [45]	Dutasteride, 0.5 mg OD	Placebo	n/a	n/a	4325	24 months	TPV, TZV, PSA	Secondary	Low Risk
Na 2012, [46]	Dutasteride, 0.5 mg OD	Placebo	n/a	n/a	253	6 months	TPV, PSA	Primary	Moderate Risk
Tsukamoto 2009, [47]	Dutasteride, 0.5 mg OD	Placebo	n/a	n/a	378	6 months	TPV, PSA	Secondary	Moderate Risk
Andriole 2010, [48]	Dutasteride, 0.5 mg OD	Placebo	n/a	n/a	8231	48 months	TPV	Secondary	Moderate Risk
Nickel 2011, [49]	Finasteride, 5 mg OD	Dutasteride, 0.5 mg OD	n/a	n/a	1630	12 months	TPV, PSA	Primary	Moderate Risk
Carraro 1996, [50]	Finasteride, 5 mg OD	Serenoa repens, 320 mg OD	n/a	n/a	1098	6 months	TPV, PSA	Secondary	Low Risk
Kuo 1998, [51]	Dibenyline, 10 mg BD	Finasteride, 5 mg OD	n/a	n/a	125	6 months	TPV	Secondary	High Risk
Jeong 2009, [52]	a blocker OD plus Finasteride, 5 mg OD	a blocker OD plus Dutasteride, 0.5 mg OD	n/a	n/a	120	24 months	TPV, PSA	Secondary	Moderate Risk
Pinggera 2014, [53]	Tadalafil, 5 mg OD	Placebo	n/a	n/a	97	8 weeks	Perfusion parameters	Primary	Moderate Risk
Morgia 2018, [54]	Serenoa repens plus Selenium, OD	Tadalafil, 5 mg OD	n/a	n/a	427	6 months	TPV, PSA	Secondary	Moderate Risk
Kosilov 2019, [55]	Tadalafil, 5 mg OD	Tadalafil, 5 mg OD plus Solifenacin, 10 mg OD	n/a	n/a	214	12 months	TPV	Secondary	High Risk
Oztrurk 2011, [56]	Alfuzosin XL OD	Alfuzosin XL OD plus Sildenafil, 50 mg OD	n/a	n/a	100	3 months	TPV, PSA	Secondary	High Risk
Joo 2012, [57]	Tamsulosin, 0.2 mg OD	Tamsulosin, 0.2 mg OD plus Dutasteride, 0.5 mg OD	n/a	n/a	216	12 months	TPV, TZV, PSA	Secondary	High Risk
Choi 2016, [58]	Tamsulosin, 0.2 mg OD	Tamsulosin, 0.2 mg OD plus Dutasteride, 0.5 mg OD	n/a	n/a	118	12 months	TPV, TZV, PSA	Secondary	Low Risk
Mohanty 2006, [59]	Tamsulosin, 0.4 mg OD plus Finasteride, 5 mg OD	Tamsulosin, 0.4 mg OD plus Dutasteride, 0.5 mg OD	n/a	n/a	106	6 months	TPV, PSA	Secondary	High Risk

Table 1. *Continued*

Study, [reference]	Comparator 1, Daily dosage	Comparator 2, Daily dosage	Comparator 3, Daily dosage	Comparator 4, Daily dosage	No. subjects randomized	Duration of Follow up	Reported parameters	Primary or Secondary endpoints	Study rating based on AHRQ criteria
Yamanishi 2017, [60]	Tamsulosin, 0.2 mg OD plus Dutasteride, 0.5 mg OD	Tamsulosin, 0.2 mg OD plus Dutasteride, 0.5 mg OD plus imidafenacin, 0.2 mg OD	n/a	n/a	163	24 weeks	TPV, PSA	Secondary	Moderate Risk
Ryu 2014, [61]	Tamsulosin, 0.2 mg OD	Tamsulosin, 0.2 mg OD plus Serenoa repens, 320 mg OD	n/a	n/a	120	12 months	TPV, PSA	Secondary	Moderate Risk
Argirovic 2013, [62]	Tamsulosin, 0.4 mg OD	Serenoa repens, 320 mg OD	Tamsulosin, 0.4 mg OD plus Serenoa repens, 320 mg OD	n/a	184	6 months	TPV, PSA	Secondary	High Risk
Beiraghdar 2017, [63]	Phytotherapy (Non-Sr)	Placebo	n/a	n/a	86	2 weeks	TPV	Secondary	Moderate Risk
Berges 1995, [64]	Phytotherapy (Non-Sr)	Placebo	n/a	n/a	163	6 months	TPV	Secondary	Moderate Risk
Safarinejad 2005, [65]	Phytotherapy (Non-Sr)	Placebo	n/a	n/a	620	6 months	TPV, PSA	Secondary	High Risk
Bent 2006, [66]	Serenoa repens, 160 mg BD	Placebo	n/a	n/a	225	12 months	TPV, TZV, PSA	Secondary	Low Risk
Marks 2000, [67]	Serenoa repens	Placebo	n/a	n/a	44	24 weeks	TPV, TZV, PSA	Secondary	Moderate Risk
Ye 2019, [68]	Serenoa repens, 320 mg OD	Placebo	n/a	n/a	325	24 weeks	TPV, PSA	Secondary	Low Risk
Zhang 2008, [69]	Phytotherapy (Non-Sr)	Placebo	n/a	n/a	49	4 months	TPV	Secondary	High Risk
Shi 2008, [70]	Serenoa repens	Placebo	n/a	n/a	94	12 weeks	TPV, PSA	Secondary	Moderate Risk
Guzman 2019, [71]	Phytotherapy (Non-Sr), OD	Terazosin, 5 mg OD	n/a	n/a	100	6 months	TPV	Secondary	Moderate Risk
Braeckman 1997, [72]	Serenoa repens, 320 mg OD	Serenoa repens, 160 mg OD	n/a	n/a	84	12 months	TPV	Secondary	High Risk
Allott 2019, [73]	Statin users	Non- Statin users	n/a	n/a	4106	48 months	TPV	Primary	Moderate Risk
Mills 2007, [74]	Atorvastatin, 80 mg OD	Placebo	n/a	n/a	350	26 weeks	TPV, TZV, PSA	Secondary	Low Risk
Zhang 2015, [75]	Atorvastatin, 20 mg OD	Placebo	n/a	n/a	81	12 months	TPV, PSA	Secondary	Moderate Risk
Safwat 2018, [76]	Tamsulosin, 0.4 mg OD	Tamsulosin, 0.4 mg OD plus Cholecalciferol 600IU OD	n/a	n/a	389	24 months	TPV, PSA	Secondary	Moderate Risk
Ghadian 2017, [77]	Ω3 300 mg plus Tamsulosin 0.4 mg plus Finasteride 5 mg	Tamsulosin 0.4 mg plus Finasteride 5 mg	n/a	n/a	100	6 months	TPV	Secondary	High Risk
Di Silverio 2005, [78]	Finasteride, 5 mg OD	Finasteride, 5 mg OD plus Rofecoxib, 25 mg OD	n/a	n/a	46	6 months	TPV, PSA	Secondary	Moderate Risk

Table 1. *Continued*

Study, [reference]	Comparator 1, Daily dosage	Comparator 2, Daily dosage	Comparator 3, Daily dosage	Comparator 4, Daily dosage	No. subjects randomized	Duration of Follow up	Reported parameters	Primary or Secondary endpoints	Study rating based on AHRQ criteria
Goodarzt 2011, [79]	Terazosin, 2 mg OD	Terazosin, 2 mg OD plus Celecoxib, 200 mg OD	n/a	n/a	160	12 weeks	TPV, PSA	Secondary	High Risk
Jhang 2013, [80]	Doxazosin, 4 mg OD	Doxazosin, 4 mg OD plus Celecoxib, 200 mg OD	n/a	n/a	122	3 months	TPV, PSA	Secondary	High Risk
Page 2011, [81]	Testosterone 1% 7.5 mg OD plus placebo	Testosterone 1% 7.5 mg OD plus Dutasteride, 0.5 mg OD	n/a	n/a	53	6 months	TPV, PSA	Secondary	Moderate Risk
Kacker 2014, [82]	Testosterone plus placebo	Testosterone plus Dutasteride, 0.5 mg OD	n/a	n/a	23	12 months	TPV, PSA	Primary	Moderate Risk
Chung 2011, [83]	a blocker OD plus 5ARI	a blocker OD plus 5ARI plus Tolterodine	n/a	n/a	137	12 months	TPV, TZI, PSA	Secondary	Moderate Risk

AHRQ – Agency for Healthcare Research and Quality; BD – Twice Daily; n/a – not applicable; Non-Sr – other than Serenoa repens; OD – once daily; PSA – prostate-specific antigen; Sr – Serenoa repens; TPV – total prostate volume; TZI – transitional zone index; TZV – transitional zone volume

in 10 comparisons, while 9 comparisons assessed the effect of non-urological medications. Among them, only 10 trials were powered to assess changes in morphometric parameters, while 57 reported a morphometric parameter change as secondary outcome. The characteristics of included RCTs are presented in Table 1.

Assessment of study quality

The summary of RoB assessment is presented in Figure 2 and Figure 3. Based on AHRQ criteria, 16 RCTs were graded as low-risk, 31 as moderate-risk and 20 as high-risk (Table 2).

Data Synthesis

α1-blockers

Six trials randomized men (n = 4525) to α-blocker versus placebo (Table 1) [18–23]. The MTOPS randomized men to receive doxazosin, finasteride, combination or placebo and reported +24% (+10.1 ml) change in TPV of patients receiving doxazosin at 4 years, similar to placebo (+24% or +8.8 ml) [19]. The Veteran Affairs Cooperative Study (VA-COOP Study) reported similar changes in terazosin and placebo arms at 12 months (+2.0% or +0.5 ml vs +2.3% or +0.5 ml) [18]. The ALFUS trial reported non-significant changes from baseline at 3 months in men who received alfuzosin or placebo in both TPV (-2% or 0.25 ml vs +3% or +0.46 ml) and TZV (-2% vs -5% or -0.8 ml vs -0.39 ml) [22]. Five RCTs reported on post treatment PSA changes, which were similar to placebo [18–21, 23]. There was no information on prostate perfusion parameters.

Ten RCTs randomized men (n = 5479) to an α-blocker versus an active comparator with a follow-up to 24 weeks [24–33]. All studies reported non-significant TPV changes from baseline (-3.4% to +9.5% or -1.4 ml to +6.32 ml). CombAT randomized men to receive tamsulosin, dutasteride or combination and followed them up for 4.5 years [32]. Men in the tamsulosin arm increased TPV by +4.6% (+2.57 ml) and TZV by +18.2% (+5.5 ml). A single trial compared tamsulosin to silodosin and reported a reduction of TPV after 6 months, which was greater in the silodosin arm (-2.8% vs -8.6% or -1.0 ml vs -3.6 ml, p = 0.594) [27]. TPV changes after 3-months of Naftopidil treatment were negligible and comparable to tamsulosin [99]. A trial with high RoB reported +9.5% (+6.32 ml) increase in TPV after 6 months tamsulosin monotherapy, which was neither significantly different from baseline (p = 0.17) nor from the comparator [30]. The Alfin study reported no significant change in TPV (-1% or -0.2 ml) or PSA value (+3.3% or +0.1 ng/dl) after 6 months of alfuzosin treatment [33]. PSA was reported unchanged in four tamsulosin studies (-5.0% to +7.4%) [24, 28, 29, 31]. Tamsulosin monotherapy enhanced prostate perfusion (+146%) as opposed to

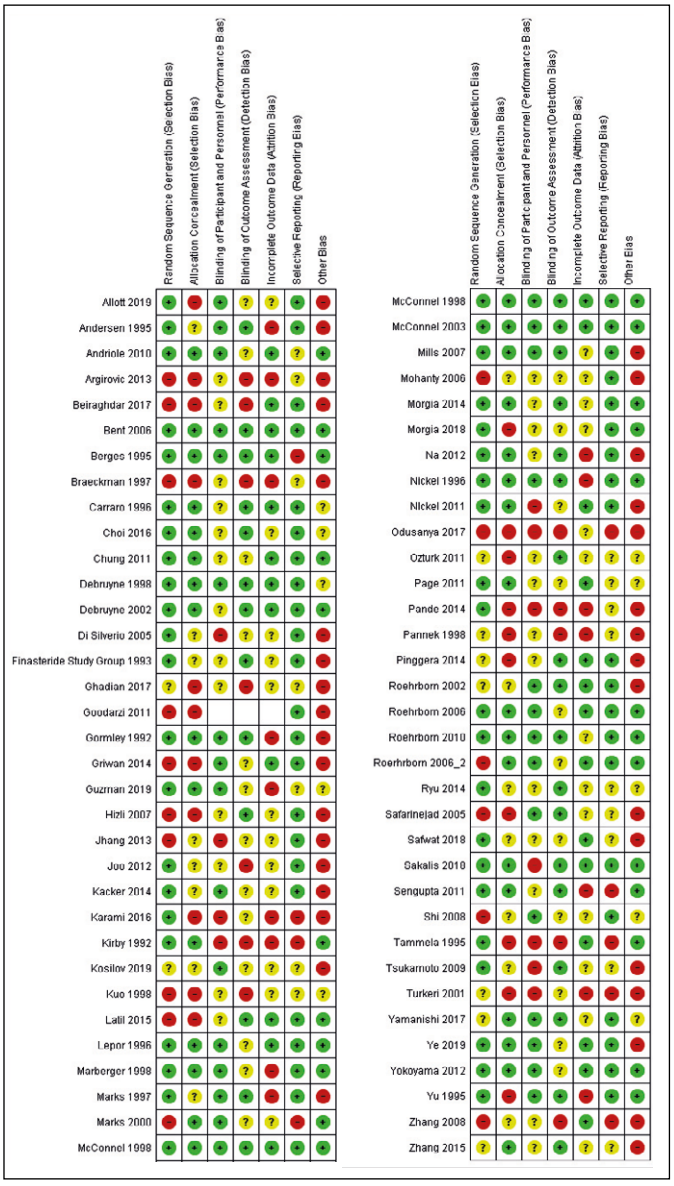

Figure 2. *The risk of bias summary.*

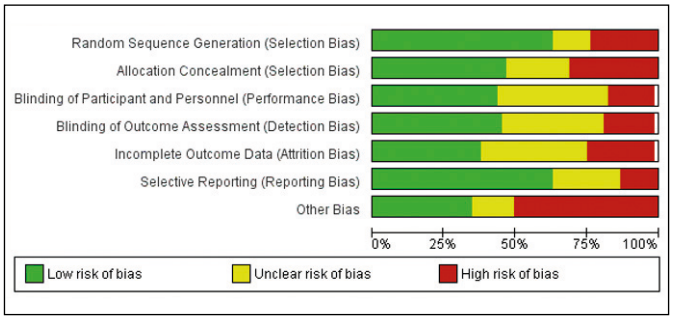

Figure 3. *The risk of bias graph.*

tamsulosin and solifenacin combination treatment (-41%) in a male overactive bladder (OAB) cohort [34].

5-ARIs

Sixteen trials randomized men (n = 21109) to 5-ARI versus placebo (Table 1) [18, 19, 35–48]. Twelve finasteride trials reported significant changes in TPV as compared to baseline and to placebo [18, 19, 35–44]. The quantitative synthesis revealed a large effect size in favor of finasteride [SMD]: -1.15 (95%CI: -1.26 to -1.04, p <0.001) (Figure 2). The effect on TPV varies between studies with different follow-ups. Trials with 3-6 months' follow-up report changes between -4.8% and -26.1%, while trials with follow-up of 12 months or longer report higher TPV changes (-15.3% to -22.4% or -8.1 ml to -10.53 ml). The finasteride study group randomized men to finasteride 1 mg versus finasteride 5 mg versus placebo, and reported similar TPV changes at 12 months (-23.6% vs -22.4% vs -5%), but the later was superior in improvement of clinical parameters such as maximum flow rate and relevant questionnaires scores [40].

Four dutasteride trials reported significant changes in TPV both from baseline or as compared to placebo [45-48]. The quantitative analysis revealed a large size effect [SMD]: -0.66 (95%CI: -0.83 to -0.49, p <0.001) (Figure 4). The effect on TPV appears homogenous among studies with different follow-up and ranges between -17.5% and- 27.0% (-7.2 ml to -13.6 ml). Dutasteride also significantly reduces TZV (-20.1% or -7.1 ml, p <0.001), an effect which is evident from the first month of treatment.

Nine finasteride RCTs report significant changes in PSA as compared to baseline or to placebo [18, 19, 35, 36, 39, 40, 42, 43, 44]. The quantitative analysis revealed a moderate size effect in favor of finasteride ([SMD]:-0.63, 95%CI:-0.76 to 0.51), p <0.001) (Figure 4). Trials with 12 months follow-up or more report a PSA change of -46.0% to -52%. Three dutasteride RCTs, report significant reduction in PSA (-42.2% to -52.4%), compared to both baseline (p <0.05) and placebo (p <0.05) [45, 46, 47].

Five RCTs randomized men (n = 3615) to finasteride versus an active comparator. All studies report significant TPV changes from baseline (-10.5% to -24.3% or -4.3 ml to -7.5 ml) and significant difference from the active comparator [30, 33, 49, 50, 51]. The dutasteride arm of CombAT reported -28.0% (-15.3 ml) and -26.5% (-8.03 ml) reduction of TPV and TZV, respectively [32]. The EPICS study randomized men to finasteride or dutasteride for 12 months and found significant change from baseline in both arms (-26.7% vs -26.3% or -13.99 ml vs -14.2 ml) without intergroup difference (p = 0.65) [49]. Another trial reported similar changes after 12 months' treatment with finasteride or dutas-

Table 2. *Detailed rating for included trials based on criteria developed by the Agency for Healthcare Research and Quality (AHRQ). The ratings were 'Low-risk', 'Moderate-risk' or 'High-risk'*

Study	Individual Quality Assessment Criteria Ratings												Overall Rating	COI Absent?
	1a	1b	1c	2a	2b	3a	3b	3c	3d	3e	4	5		
Lepor 1996, [18]	LR	LR	LR	UR	LR	LR	UR	LR	LR	LR	LR	LR	Low Risk	No
McConnell 2003, [19]	LR	LR	LR	UR	LR	LR	UR	LR	LR	LR	LR	LR	Low Risk	No
Yokoyama 2012, [20]	LR	UR	LR	UR	LR	HR	UR	LR	LR	LR	LR	LR	Low Risk	No
Roerhborn 2006, [21]	LR	UR	LR	LR	LR	UR	UR	LR	LR	LR	LR	LR	Low Risk	No
Roerhborn 2006, [22]	HR	HR	LR	LR	LR	UR	LR	LR	LR	LR	LR	LR	Moderate Risk	No
Turkeri 2001, [23]	UR	UR	HR	HR	LR	UR	UR	UR	LR	LR	HR	HR	High Risk	Unclear
Debruyne 2002, [24]	LR	LR	LR	UR	LR	LR	LR	UR	LR	LR	LR	LR	Low Risk	No
Sengupta 2011, [25]	LR	LR	LR	UR	UR	LR	UR	UR	LR	LR	HR	HR	Moderate Risk	No
Latil 2015, [26]	HR	HR	LR	UR	LR	UR	UR	UR	LR	LR	LR	LR	High Risk	Unclear
Pande 2014, [27]	LR	HR	LR	LR	HR	HR	UR	LR	LR	LR	HR	UR	Moderate Risk	Unclear
Karami 2016, [28]	LR	HR	HR	UR	HR	UR	HR	HR	LR	LR	HR	HR	High Risk	Unclear
Hizli 2007, [29]	HR	HR	HR	UR	LR	HR	HR	UR	LR	LR	UR	LR	High Risk	Unclear
Odusanya 2017, [30]	HR	HR	LR	HR	UR	HR	HR	HR	LR	LR	UR	HR	High Risk	Unclear
Morgia 2014, [31]	LR	LR	LR	UR	LR	LR	UR	LR	LR	LR	UR	LR	Low Risk	Unclear
Roehrborn 2010, [32]	LR	LR	LR	LR	UR	UR	UR	LR	LR	LR	LR	LR	Low Risk	Unclear
Debruyne 1998, [33]	LR	LR	LR	UR	LR	LR	UR	LR	LR	LR	LR	LR	Low Risk	Unclear
Sakalis 2018, [34]	LR	LR	LR	HR	HR	LR	LR	HR	LR	LR	LR	LR	Moderate Risk	Yes
Andersen 1995, [35]	LR	UR	LR	LR	LR	UR	UR	LR	LR	LR	HR	LR	Moderate Risk	No
Nickel 1996, [36]	LR	LR	UR	LR	LR	LR	LR	LR	LR	LR	HR	LR	Low Risk	No
McConnel 1998, [37]	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR	Low Risk	No
Marberger 1998, [38]	LR	UR	LR	UR	LR	LR	LR	LR	LR	LR	HR	LR	Moderate Risk	No
Kirby 1992, [39]	LR	UR	UR	HR	HR	HR	HR	UR	LR	LR	LR	HR	High Risk	Unclear
Finasteride group 1993, [40]	LR	UR	UR	UR	UR	UR	HR	HR	LR	LR	UR	LR	Moderate Risk	No
Tammela 1995, [41]	LR	HR	UR	HR	HR	UR	HR	HR	LR	LR	LR	HR	High Risk	Unclear
Pannek 1998, [42]	UR	HR	HR	UR	UR	UR	UR	UR	LR	LR	HR	UR	High Risk	Unclear
Marks 1997, [43]	LR	UR	UR	LR	UR	UR	UR	UR	LR	LR	HR	LR	Moderate Risk	Unclear
Gormley 1992, [44]	LR	LR	UR	UR	UR	LR	LR	LR	LR	LR	HR	LR	Moderate Risk	Unclear
Roehrborn 2002, [45]	UR	UR	UR	LR	LR	LR	LR	LR	LR	LR	LR	LR	Low Risk	Unclear
Na 2012, [46]	LR	LR	UR	UR	UR	LR	LR	LR	LR	LR	LR	LR	Moderate Risk	Unclear
Tsukamoto 2009, [47]	LR	UR	UR	HR	HR	UR	UR	UR	LR	LR	UR	UR	Moderate Risk	No
Andriole 2010, [48]	LR	LR	UR	UR	UR	UR	LR	UR	LR	LR	LR	UR	Moderate Risk	No
Nickel 2011, [49]	LR	LR	UR	HR	UR	UR	LR	UR	LR	LR	LR	LR	Moderate Risk	No
Carraro 1996, [50]	LR	LR	LR	UR	LR	LR	UR	UR	LR	LR	LR	LR	Low Risk	Unclear
Kuo 1998, [51]	HR	UR	UR	HR	UR	UR	LR	LR	LR	LR	UR	HR	High Risk	Unclear
Jeong 2009, [52]	UR	UR	LR	LR	UR	UR	UR	UR	LR	LR	LR	UR	Moderate risk	Unclear

Table 2. *Continued*

Study	Individual Quality Assessment Criteria Ratings												Overall Rating	COI Absent?
	1a	1b	1c	2a	2b	3a	3b	3c	3d	3e	4	5		
Jeong 2009, [52]	UR	UR	LR	LR	UR	UR	UR	UR	LR	LR	LR	UR	Moderate risk	Unclear
Pinggera 2014, [53]	UR	UR	LR	LR	LR	UR	UR	UR	LR	LR	LR	LR	Moderate Risk	No
Morgia 2018, [54]	LR	HR	LR	UR	LR	UR	UR	UR	LR	LR	UR	LR	Moderate Risk	No
Kosilov 2019, [55]	UR	UR	HR	LR	UR	UR	UR	UR	LR	LR	UR	UR	High Risk	Unclear
Ozturk 2011, [56]	UR	HR	LR	UR	UR	LR	HR	UR	LR	LR	UR	UR	High Risk	Unclear
Joo 2012, [57]	LR	UR	UR	UR	HR	UR	UR	LR	LR	LR	UR	UR	High risk	Unclear
Choi 2016, [58]	LR	LR	UR	LR	UR	UR	UR	LR	LR	LR	LR	UR	Low Risk	Yes
Mohanty 2006, [59]	HR	UR	UR	UR	UR	UR	UR	UR	LR	LR	UR	UR	High Risk	Unclear
Yamanishi 2017, [60]	UR	LR	LR	LR	LR	LR	LR	UR	LR	LR	UR	LR	Moderate Risk	No
Ryu 2014, [61]	LR	UR	UR	UR	UR	UR	UR	UR	LR	LR	UR	UR	Moderate Risk	Unclear
Argirovic 2013, [62]	HG	HG	HR	UR	UR	HR	UR	HR	LR	LR	HR	UR	High Risk	Unclear
Beiraghdar, 2017 [63]	HR	HR	LR	LR	UR	HR	UR	LR	LR	LR	LR	LR	Moderate risk	Yes
Berges, 1995 [64]	LR	LR	LR	LR	LR	UR	UR	LR	LR	LR	UR	LR	Moderate risk	No
Safarinejad, 2005 [65]	HR	HR	LR	UR	LR	LR	LR	UR	LR	LR	UR	UR	High Risk	Yes
Bent, 1995 [66]	LR	LR	LR	LR	UR	LR	UR	LR	LR	LR	LR	UR	Low Risk	Unclear
Marks, 2000 [67]	LR	LR	HR	LR	LR	LR	UR	HR	LR	LR	UR	HR	Moderate risk	Unclear
Ye, 2019 [68]	LR	LR	LR	UR	LR	LR	UR	LR	LR	LR	LR	LR	Low Risk	No
Zhang 2008, [69]	HR	UR	LR	UR	UR	LR	HR	HR	LR	LR	LR	HR	High Risk	Unclear
Shi, 2008, [70]	LR	LR	HR	LR	LR	LR	UR	UR	LR	LR	UR	LR	Moderate risk	Unclear
Guzman 2019, [71]	LR	LR	LR	LR	HR	LR	UR	HR	LR	LR	HR	UR	Moderate Risk	No
Braeckman 1997, [72]	HR	HR	HR	UC	UC	HR	UC	HR	LR	LR	HR	HR	High Risk	Unclear
Allott 2019, [73]	LR	HR	UR	UR	UR	UR	LR	UR	LR	LR	UR	LR	Moderate Risk	Unclear
Mills 2007, [74]	LR	LR	UR	UR	LR	LR	LR	LR	LR	LR	UR	LR	Low Risk	No
Zhang 2015, [75]	UR	LR	UR	LR	UR	UR	UR	LR	LR	LR	UR	LR	Moderate Risk	Yes
Safwat 2018, [76]	LR	UR	UR	LR	LR	UR	UR	HR	LR	LR	UR	UR	Moderate Risk	Yes
Ghadian 2017, [77]	UR	HR	UR	LR	UR	UR	UR	UR	LR	LR	UR	UR	High Risk	Unclear
Di Silverio 2005, [78]	LR	UR	UR	UR	UR	UR	UR	LR	LR	LR	HR	UR	Moderate Risk	Unclear
Goodarzt 2011, [79]	HR	HR	UR	UR	UR	UR	UR	UR	LR	LR	LR	UR	High Risk	Unclear
Jhang 2013, [80]	HR	UR	UR	UR	UR	HR	UR	UR	LR	LR	UR	UR	High Risk	Unclear
Page 2011, [81]	LR	LR	UR	UR	LR	UR	UR	UR	LR	LR	LR	UR	Moderate Risk	Unclear
Kacker 2014, [82]	LR	UR	LR	UR	UR	LR	UR	UR	LR	LR	UR	UR	Moderate Risk	Unclear
Chung 2011, [83]	LR	LR	UR	UR	UR	LR	LR	HR	LR	LR	LR	LR	Moderate Risk	Unclear
Griwan 2014, [99]	LR	HR	UR	LR	UR	UR	UR	LR	UR	UR	LR	LR	Moderate Risk	Unclear

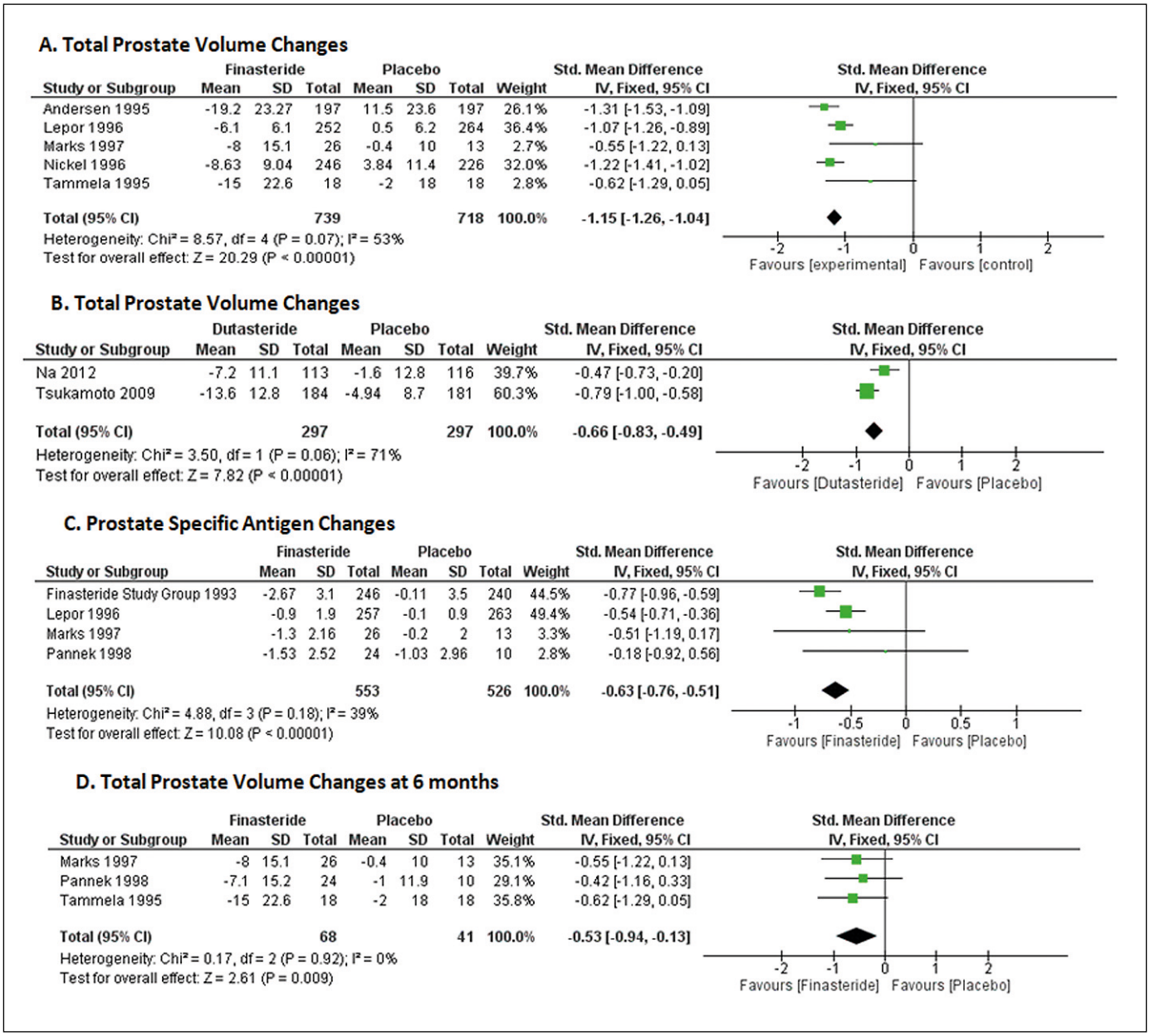

Figure 4. *Meta-analysis of 5-ARI effect on prostate morphometric parameters in placebo-controlled trials.* **A)** *Forrest plot of the effect of finasteride versus placebo on total prostate volume (TPV).* **B)** *Forrest plot of the effect of dutasteride versus placebo on total prostate volume (TPV).* **C)** *Forrest plot of the effect of finasteride versus placebo on prostate-specific antigen (PSA).* **D)** *Forrest plot of the effect of finasteride on total prostate volume in placebo-controlled trials with 6 months follow-up.*

CI – confidence interval; SD – standard deviation

teride (-24.5% vs -26.1% or -9.76 ml vs -10.2 ml) but a significant increase of TPV (+11.2% vs 8.66%) 12 months after discontinuation of 5-ARI therapy [52]. PSA changes were different from baseline (-47.7% vs 49.5%, p <0.01), without difference between groups (p = 0.776). The ALFIN study reported a -50% change (-1.7 ±1.9, p <0.05) in PSA from baseline [33]. There was no information on prostate perfusion parameters.

PDE-5 inhibitors

Yokoyama et al., randomized 612 men to receive tadalafil 2.5 mg, tadalafil 5 mg, tamsulosin 0.2 mg or placebo for 3 months (Table 3) [20]. Authors reported non-significant changes in PSA from baseline in either tadalafil group (-7% vs -2%) that were similar to placebo. Pinggera et al., reported that tadalafil does not affect prostate perfusion as evaluated

Table 3. *Baseline and outcome measures of included studies*

Study Description					Results						Outcome
					Active medication			Placebo			
Author (yr), [ref] (RoB overall rating)	Comparison	Main inclusion criteria	Study duration	Randomized patients (N) in each arm	Baseline mean (mls), ±SD	Total No. of patients (N) Analysed	Mean change from baseline, ±SD) (p value) (% mean change ±SD, p value)	Baseline mean (mls), ±SD	Total No. of patients (N) Analysed	Mean change from baseline, ±SD) (p value) (% mean change ±SD, p value)	
Beiraghdar 2017, [63] Moderate Risk	Viola odorata, Echiumamoneum and Physalis Alkekengi vs Placebo	Men 40–75 yo, with LUTS due to BPH, Prostate volume >30 ml, IPSS ≥13	2 weeks	57 vs 29	TPV: 37.25 ±2.2	57	TPV: not given absolute values (-16.92% ±0.89) (p <0.001)	TPV: 42.67 ±4.3	29	TPV: not given absolute values (+2.91% ±0.81) NS	Significant reduction in TPV in phytotherapy vs placebo (p <0.001)
Berges 1995, [64] Moderate Risk	β-sitosterol vs Placebo	Men <75 yo, Qmax <15 ml/s and residual volume 20–150 ml	6 months	83 vs 80	TPV: 44.6 ±19.4	83	TPV:-3.1 ±8.8 (-6.95%) NS	TPV: 48.0 ±27.9	80	TPV:-0.3 ±9.0 (-0.6%) NS	Non-significant change in TPV compared to baseline or between groups
Safarinejad 2005, [65] High Risk	Urtica Diopa vs Placebo	Men 55–72 yo, with LUTS due to BPH	6 months	305 vs 315	TPV: 40.1 ±6.8 PSA: 2.4 ±1.4	287	TPV:-3.8 ±5.94 (-9.47%) (p <0.01) PSA:-0.2 ±1.31 (-8.34%) NS	TPV: 40.8 ±6.2 PSA: 1.8 ±1.4	271	TPV:-0.2 ±5.73 (-0.5%) NS PSA: +0.01 ±1.0 (+1.0%) NS	Significant reduction in TPV in phytotherapy group from baseline (p <0.01)
Bent 2006, [66] Low Risk	Saw Palmetto vs Placebo	Men >49 yo, with moderate to severe LUTS due to BPH, Qmax 8–15 ml/s, PVR <250	52 weeks	112 vs 113	TPV: 34.7 ±13.9 TZV: 13.2 ±10.4 PSA: 1.8 ±1.4	112	TPV: +3.76 ±10.4 (+10.8%) (NP) TZV: +3.26 ±10.9 (+25.3%) (NP) PSA:-0.005 ±0.74 (-0.3%) (NP)	TPV: 33.9 ±15.2 TZV: 12.5 ±11.0 PSA: 1.6 ±1.4	113	TPV: +4.98 ±10.2 (+14.7%) (NP) TZV: +2.01 ±10.7 (+15.1%) (NP) PSA: +0.15 ±0.74 (+8.8%) (NP)	Non-significant changes in prostate size and PSA between groups
Marks 2000, [67] Moderate Risk	Saw Palmetto vs Placebo	Men 45–80 yo, with IPSS >9, PSA <15 ng/dl, Prostate volume >30 ml	24 weeks	21 vs 23	TPV: 58.5 ±6.5 TZV: 32.2 ±6.3 PSA: 2.67 ±0.4	21	TPV: +3.42 ±6.9 (+5.8%) (NS) TZV:-0.92 ±6.3 (-2.9%) (NS) PSA: +0.13 ±0.46 (+4.9%) (NS)	TPV: 55.5 ±5.6 TZV: 27.4 ±4.6 PSA: 4.06 ±0.7	23	TPV: +0.22 ±5.7 (+0.5%) (NS) TZV: +0.42 ±4.7 (+1.5%) (NS) PSA:-0.17 ±0.79 (-4.2%) (NS)	Non-significant changes in prostate size and PSA between groups. Saw palmetto-epithelial contraction in the transition zone (p <0.01)
Ye 2019, [68] Low Risk	Saw Palmetto vs Placebo	Men 50–70 yo, with LUTS due to BPH, IPSS ≤19, Stable sexual life, 2 week BPH medication withdrawal	24 weeks	159 vs 166	TPV: 34.3 ±18.3 PSA: 2.41 ±4.6	150	TPV: +0.77 ±9.4 (+2.25%) (NS) PSA:-0.24 ±1.36 (-9.96%) (NS)	TPV: 34.4 ±22.1 PSA: 1.99 ±2.5	154	TPV:+0.31 ±11.4 (+0.9%) (NS) PSA:-0.01 ±2.3 (-1.0%) (NS)	Non significant change in TPV (p = 0.74) and in PSA (p = 0.289) compared to baseline. No difference between groups
Zhang 2008, [69] High Risk	Flaxseed LIgnan Extractvs Placebo	Men 55–80 yo, IPSS ≥7, Prostate volume ≥30 ml, Qmax 5–15 ml/s, normal kidney function	4 months	25 vs 24	TPV: 46.7 ±3.7	25	TPV:-5.39 ±4.5 (-11.5%) (p<0.01)	TPV: 41.01 ±2.4	24	TPV:-6.6 ±6.1 (-16.1%) (p<0.01)	Significant reduction in TPV from baseline). Non-significant difference between groups

Table 3. *Continued*

Study Description					Results						
					Active medication			Placebo			
Author (yr), [ref] (RoB overall rating)	Comparison	Main inclusion criteria	Study duration	Randomized patients (N) in each arm	Baseline mean (mls), ±SD	Total No. of patients (N) Analysed	Mean change from baseline, ±SD) (p value) (% mean change ±SD, p value)	Baseline mean (mls), ±SD	Total No. of patients (N) Analysed	Mean change from baseline, ±SD) (p value) (% mean change ±SD, p value)	Outcome
Shi 2008, [70] Moderate Risk	Saw Palmetto vs Placebo	Men 49–75 yo, treatment naïve, LUTS due to BOH, clinical BPH on DRE, PSA ≤4 ng/dl	12 weeks	46 vs 48	TPV: 47.72 ±8.1 PSA: 1.84 ±0.88	46	TPV:-2.08 ±6.12 (-4.4%) NS PSA:-0.05 ±0.78 (-2.7%) (NS)	TPV: 48.38 ±7.4 PSA: 1.9 5 ±1.03	46	TPV:-2.48 ±6.4 (-5.1%) NS PSA:-0.26 ±0.65 (-13.8%) (NS)	Non significant difference between groups in TPV (p = 0.826) and PSA (p = 0.305).
Andersen 1995, [35] Moderate Risk	Finasteride 5 mg vs Placebo	Men age ≤80yo, Qmax 5–15 ml/s, LUTS (2 moderate symptoms), enlarged prostate on DRE, PSA ≤10 ng/dl, PVR ≤150 mls	24 months	354 vs 353	TPV: 40.6 mls PSA: NR	197	TPV: -19.2 ±23.27 (-17.9%) (p <0.01) PSA: -52% (p <0.001)	TPV: 41.7 mls PSA: NR	197	TPV: +11.5 ±23.8 (+11.5%) (p <0.05) PSA: +6% (NS)	Significant difference between groups in TPV (p <0.01) and PSA (p <0.001)
Nickel 1996, [36] PROSPECT Study Low Risk	Finasteride 5 mg vs Placebo	Men age ≤80 yo, Qmax 5–15 ml/s, LUTS (2 moderate symptoms), enlarged prostate on DRE, PSA ≤10 ng/dl, PV R ≤150 mls	24 months	310 vs 303	TPV: 44.1 ±23.5 PSA: not reported	246	TPV:-8.63 ±9.04 (-21.0%) (p <0.05) PSA: -50% (p <0.01)	TPV: 45.8 ±22.4 PSA: not reported	226	TPV: +3.84 ±11.4 (+8.4%) NS PSA: +13.3% (p <0.01)	Siignificant difference between groups (P <0.01) in both TPV and PSA
McConnel 1998, [37] Low Risk	Finasteride 5 mg vs Placebo	Treatment naïve men, Qmax <15 ml/s, BPH on DRE, PSA <10 ng/dl	48 months	157 vs 155 *TVP measurement only in 10% of study population	TPV: 54.1 ±26	130	TPV: -9.72 ± n/a (-18.0%) (p <0.01)	TPV: 55 ±26	119	TPV: +5.5 ±n/a (+14.0%) (p <0.05)	Difference between groups, 32% P <0.001)
Marberger 1998, [38] Moderate Risk	Finasteride 5 mg vs Placebo	Men 50–75 yo, BPH, Qmax 5-15 ml/s, VV >150 ml, LUTS (2 at least symptoms), enlarged prostate on DRE, PSA <10 ng/dl, PVR <150 ml	24 months	1450 vs 1452	TPV: 38.7 ±20.1	890	TPV: -8.1 ±25.6 (-15.3%) (p <0.01)	TPV: 39.2 ±20.2	906	TPV: +1.5 ±19.9 (+8.9%) (p <0.05)	Significant reduction in TPV (p <0.01) from 12th months. Statistical significant difference between groups (p <0.001)
Kirby 1992, [39] High Risk	Finasteride 5 mg vs Finasteride 10 mg vs Placebo	Men 48–87 yo, BPH, Urodynamically proven obstruction	3 months	29 vs 16 vs 21	TPV: 49.7 ±NR PSA: 4.1 ±NR	25	TPV: -2.5 ±27.0 (-4.8%) NS PSA: -1.1 ± n/a (-20.5%) (p <0.05) At 12 months TPV -14.1% and PSA -28%	TPV: 54.3 ±NR PSA: 5.0 ±NR	10	TPV:-1.8 ± 14.4 (-4.22%) NS PSA: -1.0 ±n/a (-6.2%) NS	Statistical significant reduction of PSA (p <0.05) in finasteride arm. No dose related effect at 3 months 10 mg: TPV -3.7&, PSA NS

Table 3. *Continued*

Study Description					Results						
					Active medication			Placebo			
Author (yr), [ref] (RoB overall rating)	Comparison	Main inclusion criteria	Study duration	Randomized patients (N) in each arm	Baseline mean (mls), ±SD	Total No. of patients (N) Analysed	Mean change from baseline, ±SD) (p value) (% mean change ±SD, p value)	Baseline mean (mls), ±SD	Total No. of patients (N) Analysed	Mean change from baseline, ±SD) (p value) (% mean change ±SD, p value)	Outcome
Finasteride group 1993, [40] Moderate Risk	Finasteride 1 mg vs Finasteride 5 mg vs Placebo	Men 40–80 yo, Qmax <15 ml/s, TPV >30 ml, clinical BPO, No infection or neurogenic bladder	12 months	249 vs 246 vs 255	TPV: 47.0 ±20.8 PSA: 5.8 ±6.7	246	TPV: -10.53 ±n/a (-22.4%) (p <0.001) PSA: -2.67 ±n/a (-46.0%) (p <0.001)	TPV: 46.3 ±23.4 PSA: 5.7 ±7.2		TPV: -2.31 ±n/a (-5.0%) NS PSA: -0.11 ±n/a (-2.0%) NS	Significant reduction of TPV and PSA from 3rd month. No change in placebo arm. The effect of 1 mg were similar of 5 mg (TPV -23.6%, PSA-43%). Statistical significant difference between groups (p <0.001). There was great difference on clinical improvement with 5 mg
Tammela 1995, [41] High Risk	Finasteride 5 mg vs Placebo	Ambulatory men, with LUTS due to BPO. Qmax <15 ml/s, Negative history for Prostate cancer	6 months	18 vs 18	TPV: 56.0 ±25.0	18	TPV: -15.0 ±22.6 (-26.1%) (p <0.05)	TPV: 47.0 ±17.0	18	TPV: -2.0 ±18.0 (-4.3%) NS	Statistical significant reduction of TPV (p <0.05) as compared to placebo
Pannek 1998, [42] High Risk	Finasteride 5 mg vs Placebo	Treatment naïve Men 45–78 yo, IPSS ≥9, PSA <10 ng/dl	6 months	24 vs 10	TPV: 36.7 ±17.0 PSA: 3.02 ±2.9	24	TPV: -7.1 ±15.2 (-21.4%) (p <0.01) PSA: -1.53 ±2.52 (-50.7%) (p = 0.005)	TPV: 37.2 ±11.4 PSA: 3.74 ±3.3	10	TPV: -1.0 ±11.9 (-2.7%) NS PSA: -1.03 ±2.96 (-27.3%) (p <0.05)	Statistical significant reduction of PSA from baseline but no difference between groups
Marks 1997, [43] Moderate Risk	Finasteride 5 mg vs Placebo	Treatment naïve Men 45–78 yo, IPSS ≥9, PSA <10 ng/dl	6 months	26 vs 15	TPV: 37.0 ±17.0 PSA: 2.7 ±2.5	26	TPV: -8.0 ±15.1 (-21.0%) (p <0.01) PSA: -1.3 ±2.16 (-49.0%) (p <0.01)	TPV: 37.0 ±10.0 PSA: 3.3 ±3.1	13	TPV: -0.4 ±10.0 (-3.0%) NS PSA: -0.2 ±2.0 (-1.0%) NS	Statistical significant reduction of TPV and PSA in finasteride arm (p <0.01) as compared to placebo. 6% reduction of transitional zone epithelium (p <0.01)
Lepor 1996, [18] Prostate Hyperplasia Study Group Low Risk	Finasteride 5 mg vs Placebo	Treatment naïve men, AUASI score ≥8, Qmax 4–15 ml/s, PVR <300 ml, Clinical BPH, no other obvious cause of LUTS	12 months	306 vs 310 vs 309 vs 305	TPV: 36.2 ± 1.0 PSA: 2.2 ±1.8	252	TPV: -6.1 ±NR (-18.4%) (p <0.001) PSA: -0.9 ±NR (-29.0%) (p <0.001)	TPV: 38.4 ±1.3 PSA: 2.4 ±2.1	264	TPV: +0.5 ±NR (+2.3%) NS PSA: -0.1 ±NR (-4.0%) NS	Statistical significant reduction of TPV and PSA in finasteride arm (p <0.001) from baseline. Statistical significant difference between groups (p <0.001)

Table 3. *Continued*

Study Description					Results						
					Active medication			Placebo			
Author (yr), [ref] (RoB overall rating)	Comparison	Main inclusion criteria	Study duration	Randomized patients (N) in each arm	Baseline mean (mls), ±SD	Total No. of patients (N) Analysed	Mean change from baseline, ±SD) (p value) (% mean change ±SD, p value)	Baseline mean (mls), ±SD	Total No. of patients (N) Analysed	Mean change from baseline, ±SD) (p value) (% mean change ±SD, p value)	Outcome
Gormley 1992, [44] Finasteride study group Moderate Risk	Finasteride 5 mg vs Placebo	Treatment naïve men 40–83 yo, enlarged prostate on DRE, Qmax <15 ml/s, PSA <40 ng/dl, No other cause of LUTS	12 months	297 vs 300	TPV: 58.6 ±30.5 PSA: 3.6 ±4.2	257	TPV: -11.1 ±27.6 (-19.0%) (p <0.01) PSA: n/a (-50%) (p <0.001)	TPV: 61.0 ±36.5 PSA: 4.1 ±4.8	263	TPV: -1.2 ±38.0 (-3.0%) NS PSA: non-significant changes	Statistical significant reduction of TPV and PSA in finasteride as compared to placebo (p <0.001). Drop of PSA from month 3 and then stable
McConnell 2003, [19] MTOPS research group Low Risk	Finasteride 5 mg vs Placebo	Treatment naïve men 50 yo and older, AUASI 8–35, Qmax 4–15 ml/s, No other cause of LUTS	4.5 years	756 vs 768 vs 786 vs 737	TPV: 36.9 ±20.6 PSA: 2.4 ±2.1	551	TPV: -12.0 ±26.6 (-19.0%) (p <0.05) PSA: NR (-50%) (p <0.001)	TPV: 35.2 ±18.8 PSA: 2.3 ±2.0	519	TPV: +8.8 ±36.0 (+24.0%) (p <0.001) PSA: NR (+15%) (p <0.001)	4 years results. Statistical significant reduction of TPV and PSA in finasteride
Roehrborn 2002, [45] pooled analyses 3 different trials Low Risk	Dutasteride 0.5 mg vs Placebo	Treatment naïve men, AUASI score ≥12, Qmax <15 ml/s, PSA 1.5–10 ng/dl, Prostate volume ≥30 mls	24 months	2167 vs 2158	TPV: 54.9 ±23.9 TZV: 26.8 ±17.1 PSA: 4.0 ±2.1	1510	TPV: -14.6 ±13.5 (-25.7%) (p <0.001) TZV: -7.1 ±9.7 (-20.4%) (p <0.001) PSA: -2.2 ±2.0 (-52.4%) (p <0.001)	TPV: 54.0 ±21.9 TZV: 26.8 ±17.4 PSA: 4.0 ±2.1	1441	TPV: +0.8 ±14.3 (+2.0%) p = 0.04 TZV: +1.8 ±11.2 (+5.9%) (p <0.01) PSA: +0.5 ±2.1 (+15.8%) (p <0.001)	Significant difference between groups (p <0.001) TPV and TZV decreased significantly from month 1 and continuing through 24 months
Na 2012, [46] Moderate Risk	Dutasteride 0.5 mg vs Placebo	Men ≥50 yo, clinical BPH, TPV ≥30 ml, AUASI ≥12, Qmax 5–15 ml/s, VV ≥125 ml	6 months	126 vs 127	TPV: 48.2 ±27.7 PSA: 3.33 ±1.9	113	TPV: -7.2 ±11.1 (-17.1%) (p <0.05) PSA: -1.44 ±NR (-43.3%) (p <0.05)	TPV: 42.3 ±16.5 PSA: 3.14 ±1.9	116	TPV: -1.6 ±12.8 (-3.7%) PSA: -0.12 ±NR (-4.0%)	Significant improvements in PSA and TPV in dutasteride group
Tsukamoto 2009, [47] Moderate Risk	Dutasteride 0.5 mg vs Placebo	Men ≥50 yo, clinical BPH, TPV ≥30 ml, IPSS ≥8 m qmax <15 ml/s, VV ≥150 mls, PSA <4 ng/dl	6 months	193 vs 185	TPV: 50.2 ±19.8 PSA: 3.5 ±n/a	184	TPV: -13.6 ±12.8 (-27.0%) (p <0.05) PSA: -42.2% (p <0.05)	TPV: 49.4 ±17.2 PSA: 3.5 ±n/a	181	TPV: -4.94 ±8.7 (-10.0%) (p <0.05) PSA: +12.0 %	Significant improvements in PSA and TPV in dutasteride group
Andriole 2010, [48] REDUCE Study group Moderate Risk	Dutasteride 0.5 mg vs Placebo	Men 50–75 yo, PSA 2.5-10 ng/dl, and had TRUSg prostate biopsy 6 months before enrollemnt	48 months	4105 vs 4126	TPV: 45.7 ±18.2	3299	TPV: -6.7 ±18.3 (-17.5%) (p = NR)	TPV: 45.7 ±18.8	3407	TPV: +3.9 ±18.5 (+19.7%) (p = NR)	Significant change between groups in TPV (P <0.001)

Table 3. *Continued*

Study Description					Results						Outcome
					Active medication			Placebo			
Author (yr), [ref] (RoB overall rating)	Comparison	Main inclusion criteria	Study duration	Randomized patients (N) in each arm	Baseline mean (mls), ±SD	Total No. of patients (N) Analysed	Mean change from baseline, ±SD) (p value) (% mean change ±SD, p value)	Baseline mean (mls), ±SD	Total No. of patients (N) Analysed	Mean change from baseline, ±SD) (p value) (% mean change ±SD, p value)	
Yokoyama 2012, [20] Low Risk	Tadalafil 5 mg vs Placebo	Asian men ≥45 yo, BPH-LUTS, Total IPSS ≥13, Qmax 4–12 ml/s, volume >20 ml, PS	3 months	155 vs 154	PSA: 1.71 ±1.14	153	PSA: +0.13 ±0.59 (p = 0.083) (+7%)	PSA: 1.74 ±1.35	152	PSA: -0.03 ±0.55 (-1%)	Non-significant changefrom baseline. No difference between groups
Roerhborn 2006 [21] ALTESS Study group Low Risk	Alfuzosin vs Placebo	Men ≥55 yo, history of LUTS due to BPH, IPSS ≥13, Qmax 5–12 ml/s, VV ≥150 ml, PVR <350 mls, Prostate volume ≥30 mls, PSA 1.4–10 ng/dl	24 months	759 vs 763	PSA: 3.4 ±2.0	754	PSA: -0.1 ±N/a (-0.6%) NS	PSA: 3.6 ±2.1	761	PSA: +0.2 ±N/a (-3.6%) NS	No significant changes from baseline or between group (p >0.05)
Roerhborn 2006 [22] ALFUS Trial Moderate Risk	Alfuzosin vs Placebo	Men ≥55 yo, history of LUTS due to BPH, IPSS ≥13, Qmax 5–12 ml/s, VV ≥150 ml, PVR <350 mls, Prostate volume ≥30 mls, PSA 1.4–10 ng/dl	3 months	353 vs 175	TPV: 39.3 ±17.9 TZV: 18.0 ±11.7	307	TPV: -0.25 ±8.3 (-2%) NS TZV: -0.8 ±6.8 (-2%) NS	TPV: 36.0 ±18.3 TZV: 16.3 ±12.7	157	TPV: +0.46 ±8.5 (+3%) NS TZV: -0.39 ±8.2 (-5%) NS	None of thedifferences between placebo and alfuzosin was statistically significant
McConnell 2003, [19] MTOPS research group Low Risk	Doxazosin vs Placebo	Treatment naïve men 50 yo and older, AUASI 8–35, Qmax 4–15 ml/s, No other cause of LUTS	4.5 years	756 vs 768 vs 786 vs 737	TPV: 36.9 ±21.6 PSA: 2.4 ±2.1	582	TPV: +10.1 ±36 (+24.0%) (p <0.001) PSA: NR (+13%) (p <0.001)	TPV: 35.2 ±18.8 PSA: 2.3 ±2.0	519	TPV: +8.8 ±36.0 (+24.0%) (p <0.01) PSA: NR (+15%) (p <0.00)	4 years results. Non-significant differences between doxazosin and placebo groups
Turkeri 2001 [23] High Risk	Doxazosin 4 mg vs Placebo	Men with LUTS due to BPH	4 weeks	15 vs 14	TPV: 53.7 ±22.8 PSA: 3.6 ±0.6	15	TPV: -3.3 ±n/a (-6.2%) (p = NR) PSA: -0.47 ±N/a (-13.9%) (p = NR)	TPV: 56.7 ±17.6 PSA: 3.5 ±0.7	14	TPV: -5.7 ±n/a (-10.4%) (p = NR) PSA: +0.4 ±N/a (+10%) (p = NR)	Non-significant differences between groups PSA, but small sample size
Lepor 1996, [18] Prostate Hyperplasia Study Group Low Risk	Terazosin vs Placebo	Treatment naïve men, AUASI score ≥8, Qmax 4–15 ml/s, PVR <300 ml, Clinical BPH, no other obvious cause of LUTS	12 months	306 vs 310 vs 309 vs 305	TPV: 37.5 ±1.1 PSA: 2.2 ±1.9	275	TPV: +0.5 ±NR (+2.0%) NS PSA: -0.4 ±NR (-20.0%) NS	TPV: 38.4 ±1.3 PSA: 2.4 ±2.1	264	TPV: +0.5 ±NR (+2.3%) NS PSA: -0.1 ±NR (-4.0%) NS	No statistical significant difference between groups in TPV and PSA

Table 3. *Continued*

Study Description					Results						
					Active medication			Placebo			
Author (yr), [ref] (RoB overall rating)	Comparison	Main inclusion criteria	Study duration	Randomized patients (N) in each arm	Baseline mean (mls), ±SD	Total No. of patients (N) Analysed	Mean change from baseline, ±SD) (p value) (% mean change ±SD, p value)	Baseline mean (mls), ±SD	Total No. of patients (N) Analysed	Mean change from baseline, ±SD) (p value) (% mean change ±SD, p value)	Outcome
Yokoyama 2012, [20] Low Risk	Tamsulosin 0.2 mg vs Placebo	Asian men ≥45 yo, >6 months history of BPH-LUTS, Total IPSS ≥13, Qmax 4–12 ml/s, Prostate volume >20 ml, PSA <4 or else negative biopsy	3 months	152 vs 154	PSA: 1.75 ±1.60	150	PSA: -0.06 ±0.61 (-4%) NS	PSA: 1.74 ±1.35	152	PSA: -0.03 ±0.55 (-1%) NS	Non significant changes between groups
Lepor 1996, [18] Prostate Hyperplasia Study Group Low Risk	Terazosin plus Finasteride combination vs Placebo	Treatment naïve men, AUASI score ≥8, Qmax 4–15 ml/s, PVR <300 ml, Clinical BPH, no other obvious cause of LUTS	12 months	309 vs 305	TPV: 37.2 ±1.1 PSA: 2.3 ±2.0	277	TPV: -7.0 ±NR (-18.8%) (p <0.001) PSA: +0.9 ±NR (+39.1%) (p <0.001)	TPV: 38.4 ±1.3 PSA: 2.4 ±2.1	264	TPV: +0.5 ±NR (+2.3%) NS PSA: -0.1 ±NR (-4.0%) NS	Statistical significant difference between groups in TPV and PSA. Max TPV and PSA reduction at 26th week, as in finasteride group
McConnell 2003, [19] MTOPS research group Low Risk	Doxazosin plus finasteride vs Placebo	Treatment naïve men 50 yo and older, AUASI 8–35, Qmax 4–15 ml/s, No other cause of LUTS	4.5 years	786 vs 737	TPV: 36.4 ±19.2 PSA: 2.3 ±1.9	574	TPV: -12.1 ±30 (-19.0%) (p <0.001) PSA: NR (-50%) (p <0.001)	TPV: 35.2 ±18.8 PSA: 2.3 ±2.0	519	TPV: +8.8 ±36.0 (+24.0%) (p <0.01) PSA: NR (+15%) (p <0.01)	4 years results. Significant differences between combination and placebo groups in TPV and PSA (p <0.001)
Joo 2012, [57] High Risk	Tamsulosin 0.2 mg vs Tamsulosin 0.2 mg and Dutasteride	Treatment naïve men ≥40 yo, IPSS ≥13, Qmax 4–15 ml/s, VV ≥150 ml, PVR <200 ml, Clinical BPH, no other obvious cause of LUTS	12 months	108 vs 108	TPV: 36.63 ±13.2 TZV: 14.94 ±7.16 PSA: 1.7 ±1.23	95	TPV: +0.38 ±2.1 (+1.0%) NS TZV: +0.24±0.66 (+1.6%) NS PSA: -0.06 ±0.22 (-3.5%) NS	TPV: 37.26 ±13.2 TZV: 15.36 ±7.56 PSA: 1.77 ±1.4	98	TPV: -10.04 ±6.14 (-26.9%) (p <0.05) TZV: -3.03 ±2.32 (-19.7%) (p <0.05) PSA: -0.73 ±0.68 (-41.2%) (p <0.05)	Statistical significant change from baseline (<0.05) in combination group. Integroup comparison p <0.05 inTPV, TZV and PSA
Choi 2016, [58] Low Risk	Tamsulosin 0.2 mg vs Tamsulosin 0.2 mg and Dutasteride	Treatment naïve men ≥40 yo, Prostate volume >30 ml, IPSS ≥13, Qmax 4–15 ml/s, VV ≥150 ml, PVR <200 ml, Clinical BPH, no other obvious cause of LUTS	12 months	59 vs 59	TPV: 40.34 ±1.4 TZV: 16.0 ±1.26 PSA: 1.35 ±0.12	55	TPV: 0.0 ±NR (0%) NS TZV: 0.0 ±NR (0%) NS PSA: +0.17 ±NR (+12.6%) (p <0.05)	TPV: 41.05 ±2.7 TZV: 16.95 ±2.33 PSA: 1.31 ±0.15	46	TPV: -8.0 ±NR (-19.5%), p <0.001 TZV: -3.0 ±NR (-17.7%), p <0.001 PSA: -0.24 ±NR (-18.3%), p <0.001	Statistical significant differences between groups in TPV (p = 0028) and TZV (p <0.001). PSA didn't differ (p = 0.108)

Table 3. *Continued*

Study Description					Results						Outcome
					Active medication			Placebo			
Author (yr), [ref] (RoB overall rating)	Comparison	Main inclusion criteria	Study duration	Randomized patients (N) in each arm	Baseline mean (mls), ±SD	Total No. of patients (N) Analysed	Mean change from baseline, ±SD) (p value) (% mean change ±SD, p value)	Baseline mean (mls), ±SD	Total No. of patients (N) Analysed	Mean change from baseline, ±SD) (p value) (% mean change ±SD, p value)	
Ryu 2014, [61] Moderate Risk	Tamsulosin 0.2 mg vs Tamsulosin 0.2 mg and Serenoa repens 320 mg	Treatment naïve men 50–70 yo, IPSS >10, Qmax 5–15, VV >150 ml, Prostate volume ≥25 ml, PSA <4 ng/dl	12 months	60 vs 60	TPV: 30.2 ±0.67 PSA: 1.1 ±0.16	53	TPV: +0.1 ±0.15 (+1.0%) NS PSA: +0.2 ±0.12 (+18.0%) (p = NR)	TPV: 30.1 ±0.93 PSA: 1.2 ±0.11	50	TPV: -0.7 ±0.27 (-2.0%) NS PSA: +0.2 ±0.12 (+8.0%) (p = NR)	No significant changes between groups in prostate volume (p = 0.096) or PSA (p = 0.521)
Debruyne 2002, [24] PERMAL Study Group Low Risk	Tamsulosin 0.4 mg vs Serenoa repens 320 mg	Treatment naïve men 50–85 yo, IPSS >10, Qmax 5–15, VV >150 ml, Prostate volume ≥25 ml, PSA< 4 ng/dl or negative biopsy if PSA ≥4 ng/dl	12 months	354 vs 350	TPV: 48.0 ±19.0 PSA: 2.7 ±2.2	TPV N: 270 PSA N: 268	TPV: +0.2 ±12.8 (+1.0%) NS (p = 0.75) PSA: +0.2 ±1.6 (+7.4%) NS (p = 0.09)	TPV: 48.2 ±18.0 PSA: 2.5 ±1.9	TPV N: 269 PSA N: 266	TPV: -0.9 ±13.4 (-2.0%) NS (p = 0.75) PSA: +0.2 ±1.4 (+10.0%) NS (p = 0.09)	No significant changes between groups in TPV (p = 0.27) or PSA (p = 0.5)
Sengupta 2011, [25] Moderate Risk	Tamsulosin 0.4 mg vs phytotherapy (MurrayaKoenigii and tribulusterrestris)	Treatment naïve men >50 yo, Clinical BPH, no other obvious cause of LUTS, IPSS >7, enlarged prostate	12 weeks	23 vs 23	TPV: 41.3 ±26.8	21	TPV: -1.4 ±23.1 (-3.4%) NS (p = 0.099)	TPV: 33.5 ±24.1	23	TPV: -1.9 ±13.9 (-5.6%) (p = 0.04 from baseline)	Significant difference TPV between groups (p = 0.037)
Latil 2015, [26] High Risk	Tamsulosin 0.4 mg vs hexamic extract Serenoa repens 320 mg	Treatment naïve men 45–85 yo, BPH related LUTS >12 months, IPSS ≥12, prostate volume 30 ml, Qmax 5–15 ml/s, VV 150-500 ml, PSA ≤4 or negative biopsy	12 weeks	101 vs 102	TPV: 46. 3 ±13.8	86	TPV: -0.53 ±10.5 (-1.0%) NS	TPV: 48.8 ±20.8	83	TPV: -0.99 ±10.9 (-2.0%) NS	No significant changes between groups in prostate volume NS
Pande 2014, [27] Moderate Risk	Tamsulosin 0.4 mg vs Silodosin 8 mg	Treatment naïve men >50 yo, LUTS due to BPH, IPSS >7, low PSA	12 weeks	29 vs 32	TPV: 35.6 ±9.6	27	TPV: -1.0 ±13.5 (-2.8%) NS (p = 0.677)	TPV: 42.0 ±20	26	TPV: -3.6 ±19.6 (-8.6%) NS (p = 0.594)	No significant changes between groups in prostate volume (p = 0.996)

Table 3. *Continued*

Study Description					Results						
					Active medication			Placebo			
Author (yr), [ref] (RoB overall rating)	Comparison	Main inclusion criteria	Study duration	Randomized patients (N) in each arm	Baseline mean (mls), ±SD	Total No. of patients (N) Analysed	Mean change from baseline, ±SD) (p value) (% mean change ±SD, p value)	Baseline mean (mls), ±SD	Total No. of patients (N) Analysed	Mean change from baseline, ±SD) (p value) (% mean change ±SD, p value)	Outcome
Sakalis 2018, [34] Moderate Risk	Tamsulosin 0.4 mg vs Tamsulosin 0.4 mg and Solifenacin	Treatment naïve men >50 yo, storage LUTS due to BPH, IPSS >7, Q3 IPSS ≥, Qmax ≥10, PSA <4 or negative biopsy	6 months	34 vs 35	TPV: 48.9 ±13.6 TZV: 24.4 ±10.2 PSA: 1.36 ±1.0	31	TPV: +3.88 ±14.6 (+9.2%) (p <0.001) TZV: +3.74 ±10.7 (+17.4%) (p <0.001) PSA: +0.26 ±1.0 (+19.1%) (p <0.051)	TPV: 52.6 ±13.0 TZV: 28.4 ±21.4 PSA: 1.9 ±1.6	32	TPV: -5.49 ±16.1 (-9.5%) (p <0.001) TZV: -2.48 ±21.1 (-12.5%) (p <0.001) PSA: +0.2 ±1.5 (+10.5%) (p <0.549)	Significant changes in TPV and TZV in both groups from baselines and in intergroup comparison (p <0.001). Non-significant PSA changes
Safwat 2018, [76] Moderate Risk	Tamsulosin 0.4 mg vs Tamsulosin plus Cholecalciferol 600IU/day	Men with AUA-SI score >7	24 months	193 vs 196	TPV: 55.4 ±13.1 PSA: 0.26 ±0.09		TPV: +3.3 ±3.5 (+5.9%) NS PSA: +0.01 ±0.0009 (+3.8%) NS	TPV: 60.2 ±10.8 PSA: 0.19 ±0.05		TPV: +4.9 ±2.2 (+8.1%) NS PSA: +0.032 ±0.0022 (+16.8%) NS	Non significant changes in TPV (p = 0.098) between groups. Significant difference between groups in PSA (p = 0.044)
Griwan 2014, [99] Moderate Risk	Tamsulosin 0.4 mg vs Naftopidil 75 mg	Men >45 yo, symptomatic BPH, Frequency >8, Nocturia >2, Qmax 5–15 ml/s, IPSS >13	3 months	30 vs 30	TPV: 57.73 ±7.33	30	TPV: -0.04 ±7.37 (-1.0%) NS (p = 0.15)	TPV: 56.81 ±6.45	30	TPV: +0.01 ±6.52 (-1.0%) NS (p = 0.18)	No significant changes between groups TPV or from baseline
Nickel 2011, [49] EPICS Study Moderate Risk	Finasteride 5 mg vs Dutasteride 0.5 mg	Men ≥50 yo, with clinical BPH, AUASI score ≥12, Vol Prostate ≥30 ml, Qmax <15 mls/s, VV ≥125 ml, PVR <250 ml	12 months	817 vs 813	TPV: 52.4 ±19.4 PSA: 4.3 ±2.2	735	TPV: -13.99 ±n/a (-26.7%) (p <0.05) PSA:-2.05 ±n/a (+47.7%) (p <0.05)	TPV: 54.2 ±21.9 PSA: 4.3 ±2.3	719	TPV:-14.2 ±n/a (-26.3%) (p <0.05) PSA:-2.12 ±n/a (+49.5%) (p <0.05)	Non-significant changes between groups (p = 0.776) Greater reductions in men with prostates >40 grs
Jeong 2009, [52] Moderate Risk	Finasteride 5 mg plus a-blocker versus Dutasteride 0.5 mg plus a-blocker	Men ≥50 yo, with moderate to severe LUTS (determined by IPSS), without previous 5ARI treatment but on a blocker, with prostate volume ≥25 ml	12 months Plus 12 months of 5ARI discontinuation	60 vs 60	TPV: 39.78 ±9.3 PSA: 1.83 ±1.19	37	TPV: -9.76 ±8.24 (-24.51%) (p <0.001) PSA: -0.89 ±0.49 (-48.9%) (p <0.001)	TPV: 39.22 ±12.3 PSA: 1.85 ±1.31	40	TPV: -10.25 ±9.98 (-26.11%) (p <0.001) PSA: -0.94 ±0.79 (-50.9%) (p <0.001)	Non significant difference between arms inTPV change (p = 0.568) and PSA changes (p = 0.352). Significant increase of TPV (+11.2% and +8.66%) and PSA (+46.2% and +43.1%) at 12 months after 5ARI discontinuation

Table 3. *Continued*

Study Description					Results						
					Active medication			Placebo			
Author (yr), [ref] (RoB overall rating)	Comparison	Main inclusion criteria	Study duration	Randomized patients (N) in each arm	Baseline mean (mls), ±SD	Total No. of patients (N) Analysed	Mean change from baseline, ±SD) (p value) (% mean change ±SD, p value)	Baseline mean (mls), ±SD	Total No. of patients (N) Analysed	Mean change from baseline, ±SD) (p value) (% mean change ±SD, p value)	Outcome
Carraro 1996, [50] Low Risk	Finasteride 5 mg vs Serenoa repens 320 mg	Clinical BPH, IPSS >6, Qmax 4-5 mls/s, Prostate volume >25 mls, PSA according to predefined prostate volume limits	6 months	545 vs 553	TPV: 44.0 ±20.6 PSA: 3.23 ±3.34	484	TPV: -7.3 ±19.12 (-18.0%) (p <0.001) PSA: -1.23 ±2.9 (-41.0%) (p <0.001)	TPV: 43.0 ±19.6 PSA: 3.26 ±3.41	467	TPV: -1.5 ±20.0 (-7.0%) (p = NR) PSA: -0.04 ±3.7 (-3.0%)(p = NR)	Both treatments reduced prostate size, but the reduction was significantly greater in finasteride arm (p <0.001)
Di Silverio 2005, [78] Moderate Risk	Finasteride 5 mg vs Finasteride 5 mg and Rofecoxib 25 mg	Men 50–80 yo, IPSS >12, Qmax 5–15 ml/s, VV >150 mls, Prostate volume >40 mls and PSA <10 ng/dl	6 months	23 vs 23	TPV: 51.65 ±9.1 PSA: 2.68 ±1.18	23	TPV: -8.83 ±8.35 (-20.2%) PSA: -0.98 ±1.1 (-36.4%) (p <0.001)	TPV: 49.65 ±9.5 PSA: 2.62 ±1.16	23	TPV: -8.79 ±8.93 (-20.1%) (p = NR) PSA: -0.93 ±1.02 (-35.4%) (p <0.001)	Significant changes from baseline in both groups (p <0.001) but insignificant changes between groups
Guzman 2019, [71] Moderate Risk	Phytotherapy (Roystonearegia lipid exctract D-004) 320 mg vs Terazosin 5 mg	Men ≥50 yo, Clinical BPH on DRE and, IPSS 7–19, without prior LUT surgery, PSA <5 ng/dl	6 months	50 vs 50	TPV: 31.4 ±23.2	50	TPV: -3.4 ±21.8 (-10.8%) (p <0.01)	TPV: 29.7 ±19.4	50	TPV: -1.4 ±18.7 (-4.7%) (p <0.01)	Statistical significant reduction in TPV both groups. Non-significant difference between groups
Morgia 2018, [54] SPRITE Study Moderate Risk	Phytotherapy (Serenoa repens + selenium + lycopene) vs Tadalafil 5 mg	Men 50–80 yo, negative DRE for PCa, PSA <4 ng/dl, IPSS ≥12, Qmax ≤15 ml/s, PVR <100 ml	6 months	291 vs 136 Randomization 2:1	TPV: 45.0 ±13.1 PSA: 1.8 ±1.0 median value	276	TPV: -2.0 ±n/a (-4.5%) (NS) PSA: -0.1 ±1.65 (-5.5%) (NS)	TPV: 45.0 ±13.0 PSA: 1.9 ±1.1 median value	128	TPV: 0.0 ±n/a (0.0%) (NS) PSA: -0.06 ±1.1 (-3.1%)(NS)	Non-significant changes from baseline or between groups in TPV and PSA
Ozturk 2011, [56] High Risk	Alfuzosin XL vs AlfuzosinXL + Sildenafil 50 mg	Men >45 yo, with moderate to severe LUTS and ED, IPSS ≥12, QoL ≥3	3 months	50 vs 50	TPV: 47.6 ±30.0 PSA: 1.83 ±1.6	50	TPV: +0.7 ±29.3 (+1.5%) (NS) PSA: -0.04 ±1.5 (-2.2%) (NS)	TPV: 44.8 ±22.2 PSA: 1.4 ±1.4	50	TPV: -1.6 ±22.6 (-3.6%) (NS) PSA: -0.12 ±1.3 (-8.6%) (NS)	No significant differences from baseline or between group comparison in TPV and PSA
Mohanty 2006, [59] High Risk	Tamsulosin 0.4 mg plus Finasteride vs Tamsulosin 0.4 mg plus Dutasteride	Men 40–80 yo, with BPH	6 months	53 vs 53	TPV: 45.4 ±22.5 PSA: 2.3 ±2.2	50	TPV: -8.9 ±20.0 (-19.6%) (p <0.001) PSA: -0.2 ±2.1 (-8.7%) (p <0.001)	TPV: 41.1 ±15.1 PSA: 2.0 ±2.2	50	TPV: -6.0 ±14.0 (-14.6%) (p <0.01) PSA: -0.5 ±1.3 (-25.0%) (p <0.001)	Significant differences from baseline but no difference in intergroup comparison in TPV and PSA

Table 3. *Continued*

Study Description					Results						Outcome
					Active medication			Placebo			
Author (yr), [ref] (RoB overall rating)	Comparison	Main inclusion criteria	Study duration	Randomized patients (N) in each arm	Baseline mean (mls), ±SD	Total No. of patients (N) Analysed	Mean change from baseline, ±SD) (p value) (% mean change ±SD, p value)	Baseline mean (mls), ±SD	Total No. of patients (N) Analysed	Mean change from baseline, ±SD) (p value) (% mean change ±SD, p value)	
Ghadian 2017, [77] High Risk	Ω3 300 m g plus Tamsulosin 0.4 mg plus Finasteride 5 mg versus Tamsulosin 0.4 mg plus Finasteride 5 mg	Men 50–70 yo, with LUTS due to BPH, prostate volume >40 ml, IPSS 8–19	6 months	50 vs 50	TPV: 62.1 ±5.2	50	TPV: -17.1 ±6.0 (-27.5%), (p <0.001)	TPV: 61.4 ±5.6	50	TPV: -9.62 ±5.7 (-15.6%), (p <0.001)	Significant differences from baseline but no difference in intergroup comparison in TPV (p <0.001)
Page 2011, [81] Moderate Risk	Testosterone gel 1% 7.5 gr plus placebo versus Testosterone gel 1% 7.5 gr plus dutasteride 0.5 mg	Men ≥50 yo, at least one symptom of androgen deficiency syndrome, Total testosterone <280 nng/dl, Prostate >30 ml, PSA 1.5–10 ng/dl, PVR <200 ml	6 months	27 vs 26	TPV: 54.2 ±38.1 PSA: 2.9 ±2.9	27	TPV: +4.1 ±38.4 (+7.6%) (p <0.05) PSA: +0.3 ±2.9 (10.7%) (p <0.05)	TPV: 44.4 ±19.8 PSA: 2.1 ±1.3	26	TPV: -5.8 ±19.1 (-13.1%) (p <0.05) PSA: -0.7 ±1.3 (33.3%) (p <0.05)	Significant differences from baseline both TPV and PSA in testosterone plus dutasteride group. Significant difference in intergroup comparison in TPV and PSA (p <0.05)
Kacker 2014, [82] Moderate Risk	Testosterone plus placebo vs testosterone plus dutasteride	Men 40–85 yo, who already receive testosterone therapy, ±LUTS	12 months	11 vs 12	TPV: 57.4 ±29.3 PSA: 2.58 ±1.2	11	TPV: +3.4 ±14.6 (+5.9%) (NS p = 0.530) PSA: +0.21 ±1.1 (+8.2%) (NS p = 0.458)	TPV: 45.0 ±25.4 PSA: 1.98 ±0.8	11	TPV: -6.65±11.0 (-14.7%) (p = 0.018) PSA: -0.46 ±0.81 (42.6%)(p = 0.04)	No significant difference between dutasteride and placebo groups in TPV (p = 0.085) and PSA (p = 0.113)
Yamanishi 2017, [60] DIrecT Study Moderate Risk	Tamsulosin plus dutasteride versus Tamsulosin plus Dutasteride plus imidafenacin	Men 40–89 yo, OAB symptoms (OABS S ≥3), prostate volume ≥30 ml	24 weeks	81 vs 82	TPV: 43.7 ±15.2 PSA: 4.1 ±4.2	72 (TPV) 68 (PSA)	TPV: -9.48 ±n/a (-21.7%) (p <0.05) PSA: -1.88 ±n/a (-47.2%) (p <0.001)	TPV: 44.6 ±18.7 PSA: 3.3 ±2.7	69 (TPV) 64 (PSA)	TPV: -10.07 ±n/a (-22.6%) (p <0.05) PSA: -1.28 ±n/a (-38.8%) (p <0.01)	Significant changes in TPV and PSA from baseline in both groups. Non significant difference between groups in TPV (p = 0.78), PSA (p = 0.113)
Goodarzt 2011, [79] High Risk	Terazosin 2 mg vs Terazosin 2 mg plus Celecoxib 200 mg	Men ≥50 yo, LUTS due to BPH, AUA Symptom scale 7–25, benign DRE	12 weeks	80 vs 80	TPV: 43.4 ±18.9 PSA: 3.54 ±3.6	80	TPV: -0.4 ±4.8 (-1.0%) (NS p = 0.454) PSA: -0.37 2.9 (-10.5%) (NS p = 0.238)	TPV: 44.0 ±19.3 PSA: 3.36 ±2.4	80	TPV: -5.7 ±7.0 (-12.9%) (p <0.001) PSA: -0.59 ±2.1 (-17.6%) (p = 0.013)	Significant changes in Celecoxib group from baseline inTPV and PSA. Significant difference between groups in TPV (p < 0.001) only

Table 3. *Continued*

Study Description					Results						
					Active medication			Placebo			
Author (yr), [ref] (RoB overall rating)	Comparison	Main inclusion criteria	Study duration	Randomized patients (N) in each arm	Baseline mean (mls), ±SD	Total No. of patients (N) Analysed	Mean change from baseline, ±SD) (p value) (% mean change ±SD, p value)	Baseline mean (mls), ±SD	Total No. of patients (N) Analysed	Mean change from baseline, ±SD) (p value) (% mean change ±SD, p value)	Outcome
Jhang 2013, [80] High Risk	Doxazosin 4 mg vs Doxazosin 4 mg plus Celecoxib 200 mg	Men ≥40 yo, LUTS due to BPH, PSA ≥4 ng/dl, IPSS ≥8, Benign DRE	3 months	58 vs 64	TPV: 67.0 ±34.0 PSA: 16.2 ±16.8	37	TPV: +3.7 ±34.8 (+5.5%) NS PSA: -0.2 ±22.4 (-2.0%) NS	TPV: 68.3 ±33.5 PSA: 10.7 ±16.8	45	TPV: -1.0 ±33.0 (-2.0%) NS PSA: -1.82 ±6.1 (-17.0% p < 0.05)	Significant changes in Celecoxib group from baseline in PSA. 22 patients diagnosed with PCa. Non significant difference between group in TPV (p = 0.122), PSA (p = 0.545)
Karami 2016, [28] High Risk	Tamsulosin 0.4 mg vs Tadalafil 20 mg	Men ≥45 yo, IPS S≥12, LUTS due to BPH and ED, PVR <200 ml	3 months	59 vs 60	PSA: 2.3 ±1.9	59	PSA: 0.0 ±0.3 (0%) NS	PSA: 2.5 ±1.8	60	PSA: 0.0 ± 0.1 (0%) NS	No significant changes from baseline or between groups in PSA
Hizli 2007, [29] High Risk	Tamsulosin 0.4 mg vs Serenoa repens 320 mg	Men 43–73yo, LUTS due to BPH, IPSS ≥10, Qmax 5–15 ml/s, PVR ≤150 ml, Prostate volume ≥25 ml, PSA ≤4 ng/ml	6 months	20 vs 20	TPV: 28.6 ±11.6 PSA: 2.1 ±0.9	20	TPV: -1.0 ±2.2 (-3.5%) NS PSA: -0.1 ±0.2 (-5.0%) NS	TPV: 35.2 ±10.3 PSA: 1.9 ±0.9	20	TPV: -0.7 ±2.6 (-2.0%) NS PSA: -0.1 ±0.3 (-1.0%) NS	No significant changes between groups in prostate volume (p = 0.61) or PSA (p = 0.07).
Hizli 2007, [29] High Risk	Tamsulosin 0.4 mg vs Tamsulosin 0.4 mg plus Serenoa repens 320 mg	Men 43–73 yo, LUTS due to BPH, IPSS ≥10, Qmax 5–15 ml/s, PVR ≤150 ml, Prostate volume ≥25 ml, PSA ≤4 ng/ml	6 months	20 vs 20	TPV: 28.6 ±11.6 PSA: 2.1 ±0.9	20	TPV: -1.0 ±2.2 (-3.5%) NS PSA: -0.1 ±0.2 (-5.0%) NS	TPV: 31.2 ±4.2 PSA: 1.7 ±0.7	20	TPV: -0.8± 2.0 (-2.5%) NS PSA: -0.2 ±0.3 (-1.0%) N	No significant changes between groups in prostate volume (p = 0.55) or PSA (p = 0.07)
Lepor 1996, [18] Prostate Hyperplasia Study Group	Terazosin vs Finasteride 5 mg	Treatment naïve men, AUASI score ≥ 8, Qmax 4–15 ml/s, PVR <300 ml, Clinical BPH, no other obvious cause of LUTS	12 months	305 vs 310	TPV: 37.5 ± 1.1 PSA: 2.2 ±1.9	277	TPV: +0.5 ±NR (-13.4%) (p <0.001) PSA: -0.4 ±NR (-18.2%) (p <0.01)	TPV: 36.2 ±1.0 PSA: 2.2 ±1.8	264	TPV: -6.1 ± NR (-16.8%) PSA: +0.9 ±NR (+40.1%) (p <0.01)	Statistical significant difference between groups in TPV and PSA. Significant difference from baseline in finasteride group

Table 3. *Continued*

Study Description					Results						Outcome
					Active medication			Placebo			
Author (yr), [ref] (RoB overall rating)	Comparison	Main inclusion criteria	Study duration	Randomized patients (N) in each arm	Baseline mean (mls), ±SD	Total No. of patients (N) Analysed	Mean change from baseline, ±SD) (p value) (% mean change ±SD, p value)	Baseline mean (mls), ±SD	Total No. of patients (N) Analysed	Mean change from baseline, ±SD) (p value) (% mean change ±SD, p value)	
Lepor 1996, [18] Prostate Hyperplasia Study Group Low Risk	Terazosin vs Finasteride 5 mg plus Terazosin	Treatment naïve men, AUASI score ≥8, Qmax 4–15 ml/s, PVR <300 ml, Clinical BPH, no other obvious cause of LUTS	12 months	305 vs 309	TPV: 37.5 ± 1.1 PSA: 2.2 ±1.9	277	TPV: +0.5 ±NR (-13.4%) (p <0.001) PSA: -0.4 ±NR (-18.2%) (p <0.01)	TPV: 38.4 ±1.3 PSA: 2.4 ±2.1	264	TPV: +0.5 ±NR (+2.3%) NS PSA: -0.1 ±NR (-4.0%) NS	Statistical significant difference between groups in TPV and PSA. Significant difference from baseline in finasteride group
Odusanya 2017, [30] High Risk	Tamsulosin 0.4 mg versus Finasteride 5 mg	Men with LUTS due to BPH and enlarged prostate on DRE	6 months	30 vs 30	TPV: 66.2 ±NR	21	TPV: +6.32 ±NR (+9.5%) (p = 0.17)	TPV: 66.57 ±NR	20	TPV: -6.8 ±NR (-10.2%), (p = 0.49)	Non-significant change from baseline, no significant difference between groups
Odusanya 2017, [30] High Risk	Tamsulosin 0.4 mg versus Tamsulosin 0.4 mg plus Finasteride 5 mg	Men with LUTS due to BPH and enlarged prostate on DRE	6 months	30 vs 30	TPV: 66.2 ±n/a	21	TPV: +6.32 ±n/a (+9.5%) (p = 0.17)	TPV: 55.43 n/a	24	TPV: -8.19 n/a (-11.8%), (p = 0.13)	Non significant change from baseline. Significant difference between groups (p = 0.006)
Morgia 2014, [31] PROCOMB Trial Low Risk	Tamsulosin vs Phytotherapy	Men 55–80 yo, benign DRE, PSA ≤4 ng/ml, IPSS ≥12, prostate volume ≤60 ml, PVR <150 ml	12 months	79 vs 71	TPV: 45.0 ±n/a PSA: 2.1 ±n/a	78	TPV: -1.0 ±NR (-2.2%) NS PSA: -0.09 ±NR (-4.3%) NS	TPV: 43.0 ±NR PSA: 1.94 ±NR	67	TPV: -1.5 ±NR (-3.5%) NS PSA: -0.0 ±NR (0%) NS	No significant changes between groups in TPV and PSA. No significant changes form baseline
Morgia 2014, [31] Low Risk	Tamsulosin vs Tamsulosin plus Phytotherapy	Men 55–80 yo, benign DRE, PSA ≤4 ng/ml, IPSS≥12, prostate volume ≤60 ml, PVR <150 ml	12 months	79 vs 75	TPV: 45.0 ±n/a PSA: 2.1 ±n/a	78	TPV: -1.0 ±NR (-2.2%) NS PSA: -0.09 ±NR (-4.3%) NS	TPV: 45.0 ±NR PSA: 2.11 ±NR	74	TPV: -2.5 ±NR (-5.5%) NS PSA: -0.16 ±NR (7.6%) NS	No significant changes between groups in prostate volume and PSA. No significant changes form baseline
McConnell 2003, [19] MTOPS Low Risk	Doxazosin vs Finasteride 5 mg	Treatment naïve men 50 yo and older, AUASI 8–35, Qmax 4–15 ml/s, No other cause of LUTS	4.5 years	756 vs 768	TPV: 36.9 ±21.6 PSA: 2.4 ±2.1	N = TPV 582 N = PSA 655	TPV: +29.0 ±36 (+24.0%) (p <0.05) PSA: NR (+13%) (p <0.05)	TPV: 36.9 ±20.6 PSA: 2.4 ±2.1	N=TPV 519 N=PSA 631	TPV: -12.0 ±30.0 (-19.0%) (p <0.05) PSA: n/a (-50%) p <0.001	4 years results. Significant differences between groups
McConnell 2003, [19] MTOPS Low Risk	Doxazosin vs Doxazosin plus Finasteride 5 mg	Treatment naïve men 50 yo and older, AUASI 8–35, Qmax 4–15 ml/s, No other cause of LUTS	4.5 years	756 vs 786	TPV: 36.9 ±21.6 PSA: 2.4 ±2.1	N = TPV 582 N = PSA 655	TPV: +29.0 ±36 (+24.0%) (p <0.05) PSA: NR (+13%) (p <0.05)	TPV: 36.5 ±19.2 PSA: 2.3 ±1.9	N=TPV 574 N=PSA 673	TPV: -12.0 ±30.0 (-19.0%) (p <0.05) PSA: NR (-50%) p <0.001	4 years results. Significant differences between groupn and from baseline

Table 3. *Continued*

Study Description					Results						
					Active medication			Placebo			
Author (yr), [ref] (RoB overall rating)	Comparison	Main inclusion criteria	Study duration	Randomized patients (N) in each arm	Baseline mean (mls), ±SD	Total No. of patients (N) Analysed	Mean change from baseline, ±SD) (p value) (% mean change ±SD, p value)	Baseline mean (mls), ±SD	Total No. of patients (N) Analysed	Mean change from baseline, ±SD) (p value) (% mean change ±SD, p value)	Outcome
Kuo 1998, [51] High Risk	Dibenyline vs Finasteride	NP	6 months	71 vs 54	TPV: 27.5 ±16.9	53	TPV: -0.1 ±23.1 (-3.6%)	TPV: 30.9 ±12.9	47	TPV: -7.5 ± 11.5 (-24.3%), (p <0.05)	Significant changes in finasteride group
Roehrborn 2010, [32] Low Risk	Tamsulosin vs Dutasteride	Men ≥50 yo, with LUTS due to BPH, IPSS ≥12, prostate volume ≥30 ml, PSA 1.5–10 ng/dl, Qmax 5–15 ml/s	4 years	1611 vs 1623	TPV: 55.8 ±24.2 TZV: 30.5 ±24.5	989	TPV: +2.57 ±NR (+4.6%) TZV: +5.55 ±NR (+18.2%)	TPV: 54.6 ±23.0 TZV: 30.3 ±21.0	1093	TPV: -15.29 ±NR (-28%) TZV: -8.03 ±R (-26.5%)	Significant change from baseline in dutasteride group. Significant difference between groups in TPV (p <0.001) and TZV (p <0.001)
Roehrborn 2010, [32] Low Risk	Tamsulosin vs Tamsulosin plus Dutasteride	Men ≥50 yo, with LUTS due to BPH, IPSS ≥12, prostate volume ≥30 ml, PSA 1.5–10 ng/dl, Qmax 5–15 ml/s	4 years	1611 vs 1610	TPV: 55.8 ±24.2 TZV: 30.5 ±24.5	989	TPV: +2.57 ±NR (+4.6%) TZV: +5.55 ±NR (+18.2%)	TPV: 54.7 ±23.5 TZV: 27.7 ±20.2	1113	TPV: -14.93 ±NR (-27.3%) TZV: -4.96 ±NR (-17.9%)	Significant difference between groups in TPV (p <0.001) and TZV (p <0.001)
Yokoyama 2012, [20] Low Risk	Tamsulosin 0.2 mg vs Tadalafil 5 mg	Asian men ≥45 yo, >6 months history of BPH-LUTS, Total IPSS ≥13, Qmax 4–12 ml/s, Prostate volume >20 ml, PSA <4 or else negative biopsy	3 months	152 vs 155	PSA: 1.75 ±1.6	143	PSA: -0.06 ±0.61 (-3.5%) NS	PSA: 1.71 ±1.14	137	PSA: +0.13 ±0.59 (8.0%) p = 0.083 NS	Non-significant changes from baseline Small tendency in tadalafil arm without significance. Non-significant changes between groups
Debruyne 1998, [33] Low Risk	Alfuzosin SR vs Finasteride 5 mg	Men 50–75 yo, LUTS due to BPH, IPSS >7, Qmax 5–15 ml/s for VV >150 mls	6 months	358 vs 344	TPV: 41.4 ±25.7 PSA: 3.0 ±2.5	318	TPV: -0.2 ±14.3 (+1.0%) NS PSA: +0. 1 ±2.7 (+3.3%) NS	TPV: 40.9 ±23.5 PSA: 3.4 ±2.5	305	TPV: -4.3 ±15.0 (-10.5%) (p = 0.05) PSA: -1.7 ±1.9 (-50.0%) (p = 0.05)	Significant changes in finasteride group from baseline and in between group comparison for TPV (p <0.001) and PSA (p <0.001)
Debruyne 1998, [33] Low Risk	Alfuzosin SR vs Alfuzosin SR plus Finasteride 5 mg	Men 50-75 yo, LUTS due to BPH, IPSS >7, Qmax 5–15 ml/s for VV >150 mls	6 months	358 vs 349	TPV: 41.4 ±25.7 PSA: 3.0 ±2.5	318	TPV: -0.2 ±14.3 (+1.0%) NS PSA: +0.1 ±2.7 (+3.3%) NS	TPV: 41.1 ±22.6 PSA: 3.1 ±2.7	295	TPV: -4.9 ±12.4 (-11.9%) (p <0.01) PSA: -1.4±1.7 (-45.2%) (p <0.01)	Significant changes in combination group from baseline and in between group comparison for TPV (p <0.001) and PSA (p <0.001)

Table 3. *Continued*

Study Description					Results						Outcome
					Active medication			Placebo			
Author (yr), [ref] (RoB overall rating)	Comparison	Main inclusion criteria	Study duration	Randomized patients (N) in each arm	Baseline mean (mls), ±SD	Total No. of patients (N) Analysed	Mean change from baseline, ±SD) (p value) (% mean change ±SD, p value)	Baseline mean (mls), ±SD	Total No. of patients (N) Analysed	Mean change from baseline, ±SD) (p value) (% mean change ±SD, p value)	
Argirovic 2013, [62] High Risk	Tamsulosin 0.4 mg vs Serenoa repens 320 mg	Men with LUTS due to BPH, Prostate volume <50 ml, IPSS 7–18, QoL >3, Qmax 5–15 ml/s, PVR <150 ml, PSA 1.5–4 ng/ml	6 months	87 vs 97	TPV: 38.6 ±11.6 PSA: 2.1 ±0.9	87	TPV: -1.0 ±0.6 (-2.6%) PSA: -0.1 ±0. 2 (-4.8%)	TPV: 35.2 ±10.3 PSA: 1.9 ±0.9	97	TPV: -0.7± 0.1 (-2.0%) PSA: -0.3 ±1.4 (-15.0%)	No significant changes between groups in prostate volume or PSA
Argirovic 2013, [62] High Risk	Tamsulosin 0.4 mg vs Tamsulosin 0.4 mg plus Serenoa repens 320 mg	Men with LUTS due to BPH, Prostate volume <50 ml, IPSS 7–18, QoL >3, Qmax 5–15 ml/s, PVR <150 ml, PSA 1.5–4 ng/ml	6 months	87 vs 81	TPV: 38.6 ±11.6 PSA: 2.1 ±0.9	87	TPV: -1.0 ±0.6 (-2.6%) NS PSA: -0.1 ±0. 2 (-4.8%)	TPV: 31.2 ±4.2 PSA: 1.97 ±0.7	81	TPV: -0.8 ±0.3 (-2.6%) NS PSA: -0.25 ±0.2 (-14.7%) (NS p = 0.25)	No significant changes between groups in prostate volume or PSA
Braeckman 1997, [72] High Risk	Serenoa repens 320 OD vs Serenoa repens 160 BD	Men <75 yo, LUTS due to BPH, BPE from DRE and TRUS, Qmax 5–15 ml/s, IPSS 12–24, PVR <100 ml, PSA <10 ng/dl	12 months	42 vs 42	TPV: 46.4 ±44.1	33	TPV: -6.7 ±40.5 (-14.5%) (p <0.001)	TPV: 37.6 ±17.6	34	TPV: -3.63± 23.7 (-9.6%) (p <0.001)	Significant difference from baseline in both groups, non-significant difference between groups
Chung 2011, [83] Moderate Risk	Tolterodine plus a blocker plus 5ARI vs a blocker plus 5ARI	Men <70 yo, IPSS >8, IPSS storage Subscore >5, QoL >3, TPV >20 ml, Qmax <15 ml/s, urodynamically confirmed BPH/BOO	12 months	50 vs 87	TPV: 49.2 ±26.3 TZI: 0.46 ±0.13 PSA: 3.44 ±1.55	50	TPV: -9.5 ±22.9 (-19.3%) (p <0.001) TZI: -0.02 ±0.12 (-4.5%) (p <0.039) PSA: -1.44 ±1.61 (-41.8%) (p <0.001)	TPV: 53.3 ±22.1 TZI: 0.47 ±0.15 PSA: 3.9 ±2.06	87	TPV: -9.1 ± 21.8 (-17.1%) (p <0.001) TZI: -0.04 ±0.13 (-12.8%) (p <0.001) PSA: -0.97 ±3.1 (-24..8%) (p <0.013)	Significant difference from baseline in both groups, non significant difference between groups in TPV (p = 0.877), TZI (p = 0.671) and PSA (p = 0.434)
Kosilov 2019, [55] HighRisk	Tadalafil 5 mg versus Tadalafil 5 mg plus Solifenacin 10 mg	ED, LUTS due to BPH, IPSS 8–19, TPV <45 ml, PSA <10 ng/dl	12 weeks	107 vs 107	TPV: 37.4 ±4.8	107	TPV: -2.2 ±4.1 (-5.9%) (NS)	TPV: 42.4 ±6.4	107	TPV: -1.4 ±5.6 (-3.3%) (NS)	Non significant difference from baseline or between groups

Table 3. *Continued*

Study Description					Results						
					Active medication			Placebo			
Author (yr), [ref] (RoB overall rating)	Comparison	Main inclusion criteria	Study duration	Randomized patients (N) in each arm	Baseline mean (mls), ±SD	Total No. of patients (N) Analysed	Mean change from baseline, ±SD) (p value) (% mean change ±SD, p value)	Baseline mean (mls), ±SD	Total No. of patients (N) Analysed	Mean change from baseline, ±SD) (p value) (% mean change ±SD, p value)	Outcome
Allott 2019, [73] post hoc analysis of REDUCE trial Moderate Risk	Subgroup analysis statinsusers vs non statinusers	Men 50–75 yo, PSA 2.5-10 ng/dl, and had TRUSg prostate biopsy 6 months before enrollment	48 months	692 vs 3414	Dutasteride arm Statin users TPV: 45.3 ±18.2 Non-statin users TPV: 45.7 ±22.4	NR	Dutasteride arm Statin users TPV: -6.8 ±18.5 (NR%) (p <0.033) Non-statin users TPV: -5.6 ±23.2 (NR%) (p = NR)	Placebo arm Statin users TPV: 45.2 ±18.8 Non-statin users TPV: 45.7 ±10.7	NR	Placebo arm Statin users TPV: +11.4 ±19.2 (-NR%) (p <0.32) Non-statin users TPV: +12.6 ±24.3 (-NR%) (p = NR)	Statistical significant difference (p = 0.032) in dutasteride group in patients receiving statins over the non-statin users (4.5% smaller prostate). Similan differences between statin and non-statin users in placebo arm (3–3.3%) without statistical significance (p ≥0.18)
Mills 2007, [74] Low Risk	Atorvastatin 80 mg vs Placebo	Men ≥50 yo, IPSS score ≥13, Vol prostate ≥30 ml, Qmax 5–15 ml/s, LDL100–190 mg/dl	26 weeks	176 vs 174	TPV: 48.7 ±19.0 TZV: 21.4 ±15.3 PSA: 2.73 ±2.2	160	TPV: -2.0 ±0.83 (-4.1%) TZV: -0.3 ±0.64 (-12.5%) PSA: -0.1 ±0.08 (-3.6%)	TPV: 50.7 ±19.0 TZV: 22.4 ±13.6 PSA: 2.81 ±2.3	159	TPV: -2.4 ±0.85 (-4.7%) TZV: -0.3 ±0.66 (-13.4%) PSA: 0 ±0.08 (0%)	No significant change from baseline I both groups. non-significant difference between groups in TPV (p = 0.654), in TZV (p = 0.421) and PSA (p = 0.235)
Zhang 2015, [75] Moderate Risk	Atorvastatin 20 mg vs Placebo	Men ≥60 yo, with LUTS due to BPH, TPV >30 ml, IPSS score >7, PSA <4 ng/dl, MetS as defined by NCEP ATPIII criteria	12 months	40 vs 41	TPV: 50.69 ±17.7 PSA: 1.93 ±1.8	40	TPV: -5.91 ±19.5 (-11.7%), (p <0.001) PSA: -0.06 ±1.77 (-3. 1%), (p = NR)	TPV: 47.14 ±16.3 PSA: 2.0 ±1.9	41	TPV: +1.17 ±17.4 (+2.5%), (p = NR) PSA: +0.02 ±1.8 (+1.0%), (p = NR)	Significant changes in TPV in favor of Atorvastatin group as compared to placebo (p <0.01). Non significant changes in PSA between groups or from baseline
Pinggera 2014, [53] Moderate Risk	Tadalafil 5 mg vs Placebo	Men ≥45 yo, with LUTS due to BPH ≥6 months history, Qmax ≥4 to ≤15 ml/s, IPSS ≥13	8 weeks	47 vs 50	mRI: 0.65 ±0.7 mCPI: 77.88 ±28.4 mCPD: 11.73 ±7.4	39	mRI: 0.01 ±0.01 (1.5%) (NS) mCPI: 4.3 ±2.6 (5.5%) (NS) mCPD: 0.36 ±1.3 (3.0%) (NS)	mRI: 0.63 ±0.7 mCPI: 79.16 ±22.9 mCPD: 12.81 ±9.9	45	mRI:-0.01 ±0.01 (-1.6%) NS mCPI: 1.67 ±2.5 (2.1%) (NS) mCPD: 0.39 ±1.2 (3.0%) (NS)	Non-significant changes from baseline in either parameters. Non-significant difference from placebo

AUA-SI score – American Urology Association Symptom Index score; BD – twice daily; BPH – benign prostate hyperplasia; DRE – digital rectal examination; IPSS – international prostate symptom score; LUTS – lower urinary tract symptoms; Non-Sr – other than Serenoa repens; MetS – metabolic syndrome; NR – not reported, NCEP ATPIII – National Cholesterol Education Program Adult Treatment Panel III; NS – non sinificant; OD – once daily; PVR – postvoid residual; Qmax – maximum flow rate; PCa – prostate cancer; PSA – prostate specific antigen; Qmax – maximum flow rate; TPV – total prostate volume, TZI – transitional zone index; TZV – transitional zone volume; Vol – volume; TRUS – transrectal ultrasonography; VV – voided volume; yo – years old

by 3 basic perfusion parameters [53]. There was no information on TPV and TZV changes.
The SPRITE study randomized men to tadalafil 5 mg or phytotherapy [54]. No change of TPV was observed in the tadalafil arm at 6 months. Two trials with high RoB reported a non-significant reduction in TPV from baseline after tadalafil (-5.9%) and sildenafil (-3.9%) treatment [55, 56]. PSA changes as reported in three trials were not significantly different from baseline (-8.6% -0%) [28, 54, 56]. There was no information on TZV or prostate perfusion parameters.

Combination treatment

The 12-month VA-COOP study reported a significant reduction in TPV from baseline (-18.8% or -7.0 ml, p <0.001) after terazosin and finasteride combination compared to non-significant changes in the placebo arm (+2.3% or +0.5 ml) (Table 3) [18]. MTOPS reported a similar reduction in the combination arm (-19% or -12.1 ml, p <0.001), while TPV increased significantly in the placebo arm (+24% or +8.8 ml, p <0.01) [19]. MTOPS reported a 50% PSA reduction, while VA-COOP reported an unexplained 39.1% increase from baseline. There was no information on TZV or prostate perfusion parameters.
Two 12-month studies randomized men to tamsulosin 0.2 mg versus tamsulosin plus dutasteride combination and reported a significant reduction of TPV (-18.8% to -26.9%), TZV (-17.7% to -19.7%) and PSA (-18.3% to -41.2%) in combination arms and no changes in tamsulosin arms [57, 58]. Mohanty et al., compared tamsulosin plus finasteride versus tamsulosin plus dutasteride combination, and found similar TPV changes after 6 months of treatment [59].
Two 6-month RCTs assessed the influence of anticholinergics in prostate morphometric parameters in men with OAB and BPE [34, 60]. A moderate risk trial randomized men to tamsulosin versus tamsulosin plus solifenacin combination [34]. Authors reported a significant reduction of TPV (-9.5% or 5.5 ml, p <0.001), TZV (-12.5% or -2.5 ml, p <0.001) and prostate perfusion (-41%) in the combination arm. Yamahishi et al., randomized men to tamsulosin plus dutasteride alone or with imidafenacin. Both arms significantly improved TPV (-21.7% vs -22.6%) and PSA (-47.2% vs -38.8%), without significant differences between them. Three trials randomized men to tamsulosin monotherapy versus tamsulosin plus Serenoa repens (Sr). No significant differences in TPV or PSA were reported [29, 61, 62].

Phytotherapy

Eight trials randomized men (n = 1608) to phytotherapy versus placebo (Table 3) [63–70]. Four Sr trials reported non-significant changes in TPV as compared to placebo [SMD:0.12(95%CI:-0.03 to 0.27, p = 0.13) (Figure 5) [66, 67, 68, 70]. Non-Sr trials reported significant TPV reduction from baseline up to -16.9% [63, 64, 69]. Two trials reported similar TZV changes to placebo at 52 and 24 weeks respectively [SMD:0.06 (95%CI:-0.18 to 0.30, p = 0.64) (Figure 3) [66, 67]. A small trial reported pronounced epithelial component involution in the transitional zone as compared to baseline (17.8% to 10.7%, p <0.01) in the Sr group [67]. Four trials reported non-significant small effects of phytotherapy on PSA as compared to placebo [SMD: -0.06 (95%CI: -0.21 to 0.10, p = 0.46) (Figure 5) [66, 67, 68, 70]. There was no information regarding prostate perfusion parameters.
Ten trials randomized men (n = 2972) to phytotherapy versus active component [24, 25, 26, 29, 31, 50, 54, 62, 71, 72]. Six RCTs compared Sr to an active comparator and reported non-significant changes in TPV from baseline (-7% to –2% or -2.0 ml to -0.7 ml) [24, 26, 29, 31, 50, 62]. A single trial reported significant TPV change from baseline after Sr 320 mg once daily (-14.5%, p <0.001) or Sr 160 mg twice daily for 12 months (-9.6%, p <0.001) [72]. Two non-Sr trials reported significant reduction in TPV as compared to baseline (-5.6% and -10.8%) [25, 71]. Six trials reported non-significant changes in PSA as compared to baseline or to comparator (-15% to +10% or -0.3 ng/dl to +0.2 ng/dl) [24, 29, 31, 50, 62]. There was no information regarding TZV and prostate perfusion parameters.

Other medications

A post hoc analysis of the REDUCE trial classified men on dutasteride as statin and non-statin users (Table 1) [73, 48]. Authors reported a significant TPV change from baseline (-15.8% or -6.8 ml, p = 0.033) in the statin users' subgroup as compared to the non-statin users. The effect of dutasteride on lowering TPV was roughly 10-fold greater than the statin-associated effect at year 2 (p <0.001) and year 4 (p <0.001) [73]. A 26-week RCT compared atorvastatin 80 mg versus placebo and reported no difference from baseline or between groups in TPV (-4.1% vs -4.7%, p = 0.654), in TZV (-12.5% vs -13.4%, p = 0.421) and in PSA (-3.6% vs 0%, p = 0.235) [74]. In contrast, a 12-month trial reported a significant difference in TPV in favor

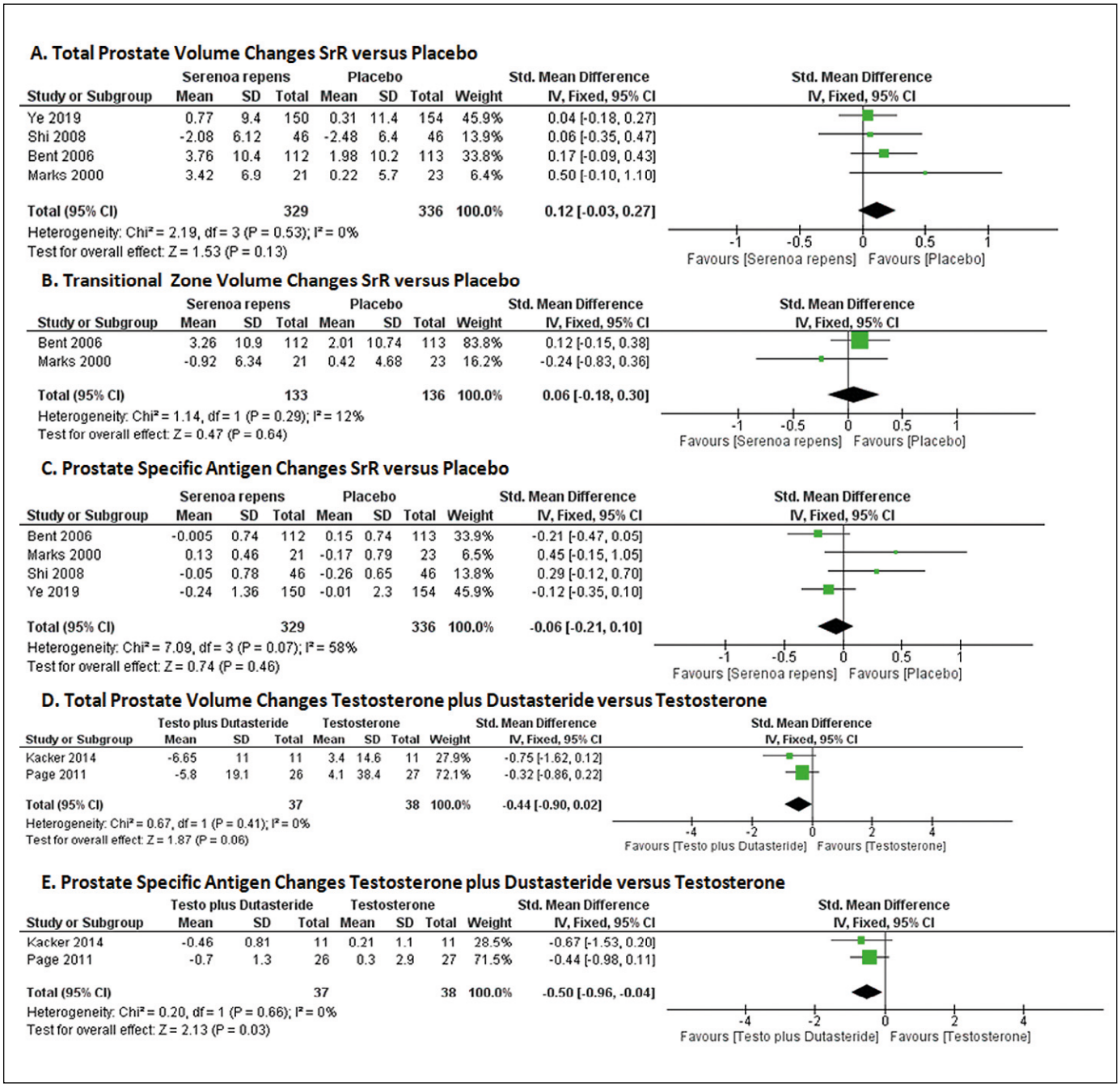

Figure 5. *Meta-analysis of Serenoa repens (Sr) and testosterone effect on prostate morphometric parameters effect in placebo-controlled trials.* **A)** *Forrest plot of the effect of Sr versus placebo on total prostate volume (TPV).* **B)** *Forrest plot of the effect of Sr versus placebo on transitional zone volume (TZV).* **C)** *Forrest plot of the effect of Sr versus placebo on prostate-specific antigen (PSA).* **D)** *Forrest plot of the effect of testosterone plus dutasteride combination versus testosterone monotherapy on total prostate volume (TPV).* **E)** *Forrest plot of the effect of testosterone plus dutasteride combination versus testosterone monotherapy on PSA.*

CI – confidence interval; SD – standard deviation

of atorvastatin group as compared to placebo (-11.7% vs +2.5%, p <0.01), changes which were more pronounced in obese patients compared to normoweight individuals [75].

A single study compared cholecalciferol 600 IU plus tamsulosin versus tamsulosin monotherapy and reported non-significant TPV changes between groups (+8.1% vs +5.9%, p = 0.098) at 24 months [76].

Ω3-fatty acids in combination with tamsulosin and finasteride were non-superior to tamsulosin plus finasteride combination in reducing TPV [77]. Di Silverio studied the effect of rofecoxib 25 mg with finasteride versus finasteride monotherapy and reported comparable reductions in TPV (-20.1% vs -20.2%) and PSA (-35.4% vs -36.4%) at 6 months [78]. They reported an accelerated effect in rofecoxib group. The effect of celecoxib was tested in two studies against terazosin and doxazosin [79, 80]. The first reported that celecoxib reduces significantly TPV (-12.9%) and PSA (-17.6%) and the latter reported a significant PSA change (-17.0%) only. Two RCTs studied the effect of testosterone replacement in TPV and PSA of men with androgen deficiency syndrome [81, 82]. Both studies reported an increase in TPV (+7.6% and +5.9%) and PSA (10.7% and +8.2%) after testosterone supplementation. The co-administration of dutasteride spares prostate from androgenic stimulation since both TPV (-13.1% and -14.7%) and PSA (-33.3% and -42.6%) were reduced significantly. The treatment effect was considered moderate in favor of combination regarding TPV [SMD: -0.44 (95%CI: -0.90 to 0.02, p = 0.06) (Figure 3) and PSA change [SMD: -0.50 (95%CI: -0.96 to 0.04, p = 0.03).

Placebo arm

In phytotherapy trials, the changes in TPV were from -5.1% to +2.91% and in PSA from -4.2% to -1.0% [63–70]. A trial with 12-month follow-up reported +14.7% increase in TPV and +8.8% increase in PSA [66]. In short-term RCTs with α-1 blockers, the changes in TPV and PSA were not significant, ranging from 2.3% to 3% and -4% to +10% respectively. In 5-ARI trials TPV change was reported between -10.0% and -2.7% in 6-month studies, -5.0% to -2.3% in 12-month studies, +2.0% to +14.0% in 24-month studies [18, 19, 35–48]. REDUCE and MTOPS trials, both with long follow-up, reported TPV change +19.7% and +24.0% respectively [48, 19]. The changes in PSA were -6.0% to -1.0%, -5.0% to -2.0% and +6% to +15.8% respectively.

DISCUSSION

Herein, we systematically reviewed the effect of pharmacotherapy on prostate morphometric parameters, namely TPV, TZV, PSA and prostate perfusion. The strengths of this review include the systematic and transparent approach to analyze the evidence base, including the Cochrane review methodology, the adherence to PRISMA guidelines and a-priori written protocol. We also used a comprehensive approach to determine RoB and to include studies with well-defined protocol assessing morphometric parameters.

The weaknesses relate to the limitations of the body of evidence that we analyzed. Based on AHRQ standards, 16 RCTs were considered as low-risk, 31 RCT as moderate-risk and 20 as high-risk. Thirteen out of 28 placebo-controlled trials were considered of moderate-risk. Most trials were powered to assess post-treatment changes in clinical parameters such as relevant questionnaires or flow test. Only 10 RCTs were powered to assess changes in morphometric parameters as a primary outcome. An additional methodological issue relates to the technique used to evaluate prostate parameters. To overcome measurement bias, we included studies that describe in detail the method of volume calculation. Concerning PSA and perfusion parameters, we relied on data provided by each group.

α-blockers do not affect TPV, TZV or PSA. Studies with long-term follow-up report changes similar to placebo, while the observed significant differences from baseline result from physiologic growth. Animal experiments demonstrated that sympathomimetics induce prostate hyperplasia, whereas quinazoline-based α-blockers exert apoptotic effect on human prostate cancer cell cultures [8]. This in vitro effect is not evident in clinical setting [83]. There is evidence that tamsulosin improves prostate perfusion, possibly by the antagonistic action on α1A- and α1D-adrenoceptors of vesical arteries [12, 84]. A single RCT in OAB population reported increased perfusion up to +149%, which was similar to previous findings (+132.8%), hence the beneficial effect of tamsulosin on LUTS [85].

Robust evidence supports the effect of 5-ARIs on TPV, TZV and PSA. Dihydrotestosterone (DHT) induces prostate growth via enhanced proteinosynthesis and reduced apoptotic rates [86]. 5-ARIs reduce TPV, TZV and PSA in at least 85.3% of patients after six to twelve months of treatment [87]. A head-to-head comparison of finasteride and dutasteride showed similar efficacy, but dutasteride effect appears sooner [49, 52]. A pooled analysis of dutasteride trials reports significant changes of TPV starting at 1st month of treatment, as a result of the faster DHT suppression [45, 47]. These changes reach the maximum effect at 12 months and this change is sustained thereafter [18, 19, 35–38, 40, 44]. DHT increases prostatic blood flow via increased expression of VEGF [86]. Finasteride downregulates VEGF and reduces prostate blood flow as early as 7 days after administration [11, 86]. Preliminary literature search on single-arm studies revealed two dutasteride

single-arm trials reporting a reduction in perfusion parameters [88, 89].

Even though there is little evidence, PDE5 inhibitors do not affect TPV, TZV and PSA. Studies on human prostatic tissue strips, suggested that up-regulation of intracellular cGMP by PDE5 inhibition decreases smooth muscle tone and might attenuate prostate cells proliferation [3, 10, 90, 91]. Animal models of chronic pelvic ischemia demonstrated that PDE5 inhibitors increase cGMP levels and improve lower urinary tract perfusion [10]. Using contrast-enhanced ultrasound, an observational study demonstrated improvements in prostate perfusion after tadalafil administration [10, 92]. In men at high-risk for endothelial dysfunction, tadalafil significantly improves flow-mediated dilation of brachial artery as compared to controls [21, 93]. However, these vasoactive effects of PDE5 inhibitors were not evident at clinical level [9, 10, 92, 94, 95]. A single RCT did not report any significant effect on prostate perfusion parameters [53].

The overall effect of phytotherapy on prostate morphometric parameters is ambiguous. Both placebo-controlled and active medication-controlled trials on Sr reported no significant difference from comparators, while non-Sr trial reported a significant reduction in TPV. These trials are characterized by high heterogeneity and poor quality. Conclusions from phytotherapy trials are difficult due to differences in consistency, concentration or extraction techniques. As a result, the biological activity might differ even among studies with same extracts. A recent meta-analysis reported significant reduction in TPV and non-significant increase of PSA after administration of hexanic extract of Sr [96].

Combination treatment is indicated when monotherapy fails to control symptoms. According to European Association of Urology (EAU) guidelines, α-blockers are combined with 5-ARIs to improve residual voiding LUTS or with an anticholinergic for residual storage symptoms [1]. CombAT reported similar TPV changes between combination and dutasteride monotherapy arm (-27.3% vs -28.0%) [32]. TZV changes differ, almost statistically significantly (-17.9% vs -26.5%, $p = 0.052$). In the case of α-blocker with anticholinergic combination the data is limited. A single RCT reported significant reduction in TPV, TZV and perfusion parameters with combination of solifenacin and tamsulosin as opposed to tamsulosin monotherapy [34]. There is no data on the effect of β3-agonists on TPV. Evidence from basic science shows that mirabegron improves bladder wall blood flow and bladder dysfunction through amelioration of pelvic blood flow [97].

Statins reduce TPV, albeit ten times less than dutasteride [73]. Recent evidence shows that atorvastatin has pro-cell apoptotic action, a pro-cellular adhesion effect, a pro-proliferation effect and an anti-inflammatory action via reduction of Interleukin-6 and IGF-1 [75]. Cholecalciferol and rofecoxib did not differ from their comparators. By contrast, celecoxib reduces both TPV and PSA [79, 80]. Testosterone replacement therapy restores DHT levels, thus TPV and PSA do not change further from a saturation point [82]. Dutasteride reduces TPV, PSA in men who receive testosterone replacement therapy, an effect that validates the influence of intraprostatic DHT on morphometric parameters.

A single summary for the effect of medications on prostate morphometric parameters is not possible. The degree of heterogeneity renders inappropriate any formal data pooling. The reasons of heterogeneity were the differences in study design, in follow-up duration, in sample size, in drop-out rates, in the inadequacy of reporting standards and in the forced unilateral regression to the mean (due to inclusion/exclusion criteria other than volume such as uroflowmetry). In addition, a small number of trials were powered enough to detect changes in morphometric parameters while others were characterized as low-quality due to high risk of bias [100]. The placebo response differs surprisingly among trials. A similar effect has been previously described [98]. The relevant mechanisms of this effect are poorly understood.

CONCLUSIONS

A detailed review of the effect of medical therapy on prostate morphometric parameters has been presented. The 5-ARIs show large effect size in reducing TPV as compared to placebo. There is no difference between finasteride and dutasteride but data support an earlier influence of dutasteride on TPV. Quinazolin-based α-blockers are associated with significant TPV changes in 4-year trials which are similar to placebo and represent the natural growth of prostate. Non-Sr phytotherapy appears to reduce TPV in contrast to a non-effect of Sr, but relevant studies suffer from moderate or high risk of bias. PDE5-inhibitors' trials reported non-significant TPV changes. Among other medications, atorvastatin and celecoxib were found to significantly reduce TPV. A large effect on TZV is observed after either 5-ARI monotherapy or after combination treatment with an α-blocker, but the reduction in the latter group is less. PSA changes are significant in patients receiving 5ARI monotherapy or in combination. No other treatment class appears to affect PSA. There is less robust evidence to suggest that tamsulosin improves prostate

perfusion while tadalafil has no effect on clinical perfusion parameters.

CONFLICT OF INTEREST

The authors report no conflicts of interest.

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