Uro-Technology Journal 2024; 8(3): XX-XX ***XX***
DOI: 10.31491/UTJ.2024.09.XXX

RESEARCH

The effects of 5-ARIs on prostate volume in patients with or without heart failure and benign prostate hyperplasia: prospective, comparative study

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Abstract

Objective: Compare the effects of finasteride and dutasteride on prostate volume in men with or without chronic heart failure (CHF) and benign prostate hyperplasia (BPH).
Materials and Methods: Five hundred and seventy-nine patients were recruited with symptomatic BPH receiving inhibitors of 5-alpha reductase from December 2022 to January 2024. Five hundred and forty-six patients were followed up during 12 months. The study included analysis of four groups of patients: Group I (n = 136) received dutasteride and had chronic cardiac failure; Group II (n = 137) received finasteride and had chronic cardiac failure; Group III (n = 136) received dutasteride and had no chronic cardiac failure; Group IV (n = 137) received finasteride and had no chronic cardiac failure. Prostate volume, PSA level, total IPSS and its voiding and storage subscores, Q_{max}, post-voided residual urine volume (PVR) were evaluated at baseline and after 6 and 12 months. Echocardiography, electrocardiography and brain natriuretic peptide (BNP) testing were performed for diagnosis of chronic cardiac failure in all patients. Statistical significance was set at $P < 0.05$.
Results: The IPSS (total, storage, and voiding symptom) score was significantly decreased after 6 and 12 months of treatment in group III and IV ($P < 0.01$). The reducing of prostate volume was effective in groups III and IV in patients without chronic cardiac failure. There were not statistically significant differences in reducing of prostate volume at 6 and 12 months of treatment in all groups ($P > 0.05$). However, the patients with chronic heart failure had a worse effect of inhibitors 5-alpha reductase on prostate volume. The patients with BNP >100 pg/mL and left ventricular ejection fraction (LVEF) ≤ 40% had the most minimal reducing of prostate volume at 6- and 12-month treatment. In groups III and IV, the postvoid residual urine volume (PVR) and Q_{max} were significantly decreased ($P < 0.05$) at 6 and 12 months of treatment compared with the baseline values. The patients with CHF did not receive any benefits in regarding to PVR, Q_{max} and IPSS score during 12 months of treatment.
Conclusion: Dutasteride and finasteride had no effect on prostate volume in patients with CHF, BNP > 100 pg/mL and with severely abnormal (< 30%) and moderately abnormal (≥ 30% ≤ 40%) LVEF. The patients with BPH and CHF did not receive any benefits in regarding to PVR, Q_{max} and IPSS score improvement after treatment with dutasteride or finasteride.
Keywords: Benign prostate hyperplasia; chronic heart failure; left ventricular ejection fraction; lower urinary tract symptoms; 5-alpha reductase inhibitors

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Received: 17 June 2024 / Revised: 04 July 2024 / Accepted: 09 July 2024 / Published: XX September 2024

Introduction

Benign prostatic hyperplasia (BPH) is one of the most common diseases in aging men and one of the most common causes of lower urinary tract symptoms (LUTS) [1]. The incidence of LUTS/BPH increases with age and reaches more 50% in men by the 60 and 80% in men aged > 70 years. BPH is defined as the abnormal and uncontrolled proliferation of epithelial and stromal cells in prostatic tissue [2-4].The pathogenesis of BPH is complicated and includes the interaction of androgen-dependent (levels of dihydrotestosterone) and androgen-independent (ischemia, oxidative stress, metabolic syndrome, infection, autoimmune reactions, and inflammation) factors [5-7]. Currently, α-blockers (ABs) and/or 5α-reductase inhibitors (5-ARIs) are still the main therapeutic agents for the management of LUTS secondary to BPH [8]. In men suffering from BPH, 5-ARIs are therapeutical option with prostate volume greater than 30–40 mL and duration of treatment longer than 1 year. In the same category patients with BPH, combination of 5-ARIs with ABs is a more effective treatment option for improvement and reduction of disease progression if the profile of adverse effects is favorable [9]. The older men with LUTS and BPH have a high prevalence of cardiovascular disease (CVD) than the general population [10]. The using of ABs is associated with increased risk of adverse cardiovascular events compared with 5-ARIs [11]. In one study, Lusty *et al*. [12] using multivariable competing risk analysis demonstrated that the men treated with 5-ARIs alone appeared to have less cardiac failure than those prescribed ABs, either as ABs alone or as combination therapy. In population-based cohort study, Ayele *et al*. [13] showed that the administration of 5-ARIs in patients with BPH was not associated with an increased risk of hospitalization for stroke, heart failure and myocardial infarction compared with non-use. By literature data, several studies demonstrated that treatment with 5-ARIs in patients with BPH significantly decreased the obstructive LUTS and prostate volume and increased the maximum urinary flow [14, 15]. In our study, we chose the chronic heart failure because one is clinical syndrome underlining many cardiovascular diseases which are closely related to impaired organ perfusion, and accordingly in some extent with prostate hypoxia as well. In this study, we performed comparative analysis of the effects of finasteride and dutasteride on prostate volume in men with or without chronic heart failure (CHF) and BPH during 12 months of treatment.

Materials and methods

Study design and patient population

This open-label, prospective, comparative study included 579 patients with BPH/LUTS who were investigated from December 2022 to January 2024. All participants provided written informed consent (IRB approval number 29052273). The criteria inclusion and exclusion for the study are shown in Table 1. Patients who met the inclusion criteria were assigned into the CHF group (defined as BNP > 100 pg/mL) or non-CHF group (defined as BNP < 100 pg/mL) and then randomly allocated by computer-generated random numbers into the dutasteride 0.5 mg group or finasteride 5 mg group for 12-month of treatment. By the data echocardiography, each group with CHF were divided into three subgroups with left ventricular ejection fraction LVEF < 30%, LVEF ≥ 30% ≤ 40% and LVEF ≥ 40% ≤ 51% for separate analysis of change of prostate volume in patients taking dutasteride 0.5 mg and finasteride 5 mg. For all participants, we conducted history taking, including total IPSS and its voiding and storage subscores; a measurement of serum prostate-specific antigen (PSA); transrectal ultrasonography to assess the prostate volume and abdominal ultrasound investigation for evaluation of post-voiding residual (PVR) urine; uroflowmetry; echocardiography, electrocardiography and brain natriuretic peptide (BNP) testing. The study was performed in according to the principles of the 1964 Declaration of Helsinki and was approved by Institutional Review Board of Central District Hospital Kamenolomni.

Study end-points and assessments

The primary end-point of this study was to determine the effects of dutasteride 0.5 mg and 5 mg finasteride on prostate volume in patients with or without CHF. This parameter was assessed by analyzing changes from baseline in prostate volume at 6 and 12 months. Secondary end-points were to analyze the improvement in total IPSS and its

Table 1. Final items for the treatment satisfaction questionnaire for medication (TSQM).

Inclusion criteria	Exclusion criteria
-The age of men ≥ 50 years -Diagnosis of BPH by history and physical examination -Prostate volume measured by TRUS ≥ 30 cm^3 -IPSS score ≥ 8 (moderate-to-severe symptoms) -Q_{max} ≤ 15 mL/s -Serum PSA level ≥ 1.5 ng/mL -Symptoms of chronic heart failure -Absence of heart failure complications (arrhythmias, pulmonary and hepatic congestion, Pulmonary hypertension, thromboembolism) -BNP levels over 100 pg/mL	-Postvoid residual volume > 250 mL -History of prostate cancer, urethral stricture, pelvic irradiation, recurrent urinary tract infections, carcinoma in situ of the urinary bladder, urinary incontinence. -Previous prostate surgery (TURP, open adenomectomy) -Use of an α1-blocker within 1 month or any previous use of a 5-ARI -Serum PSA level ≥ 10 ng/mL

Note: BPH, benign prostate hyperplasia. BNP, brain natriuretic peptide. TURP, transurethral resection of prostate. PSA, prostate specific antigen. IPSS, International Prostate Symptom Score.

voiding and storage subscores, quality of life (QoL) score, PVR, PSA level and maximum urinary flow rate (Q_{max}) in men with or without CHF at 6 and 12 months.

Statistical analysis

Data are expressed as mean ± standard deviation (SD), and statistical significance was accepted at $P < 0.05$. The Wilcoxon rank sum test and two-sample t-test were conducted to analyze continuous variables, and the chi-square test was used to analyze categorical variables. Statistical analysis was performed with software SPSS 20.0 (SPSS, Chicago IL, USA) and Prism software (version 5.00; GraphPad Instat, San Diego, CA, USA).

Results

Patient demographics and background

Four hundred and seventy-nine men with BPH/LUTS were enrolled for the study from December 2022 to January 2024.During the recruitment period, 30 patients were excluded from the study due to prostate cancer (n = 11), radical prostatectomy (n = 3), pelvic radiotherapy (n = 6) and recurrent urinary tract infections (n = 10). A total of 546 men were followed up for 12 months. Of these, 264 CHF patients and 282 non-CHF patients were randomized to receive dutasteride 0.5 mg or finasteride 5 mg (group I, CHF, dutasteride 0.5 mg; group 2, CHF finasteride 5 mg; group 3, non-CHF, dutasteride 0.5 mg; group 4, non-CHF, finasteride 5 mg). In the group I, 126 patients completed the study and 4 men were withdrawn due to adverse events (AEs). In the group II, 129 men finished the study and 5 patients were withdrawn due to AEs. In the group III, all patients completed the study. In the group IV, 138 finished the study and one patient discontinued because of loss during 12-month follow-up period (Figure 1). Baseline demographic and clinical parameters of the patients are shown in Table 2. There was no statistically significant difference between the four treatment groups in regarding to baseline demographic and clinical parameters. However, there was statistically significant differences between CHF and non-CHF patients in relation to the BNP level and value of LVEF ($P < 0.05$).

Primary endpoint

The long-term follow-up results demonstrate that the prostate volume significantly decreased in patients without CHF in group III and IV during 12 months of treatment. However, the patients with CHF taking both dutasteride 0.5 mg and finasteride 5 mg had no benefits in reduction of prostate volume at 6 and 12 months of treatment (Table

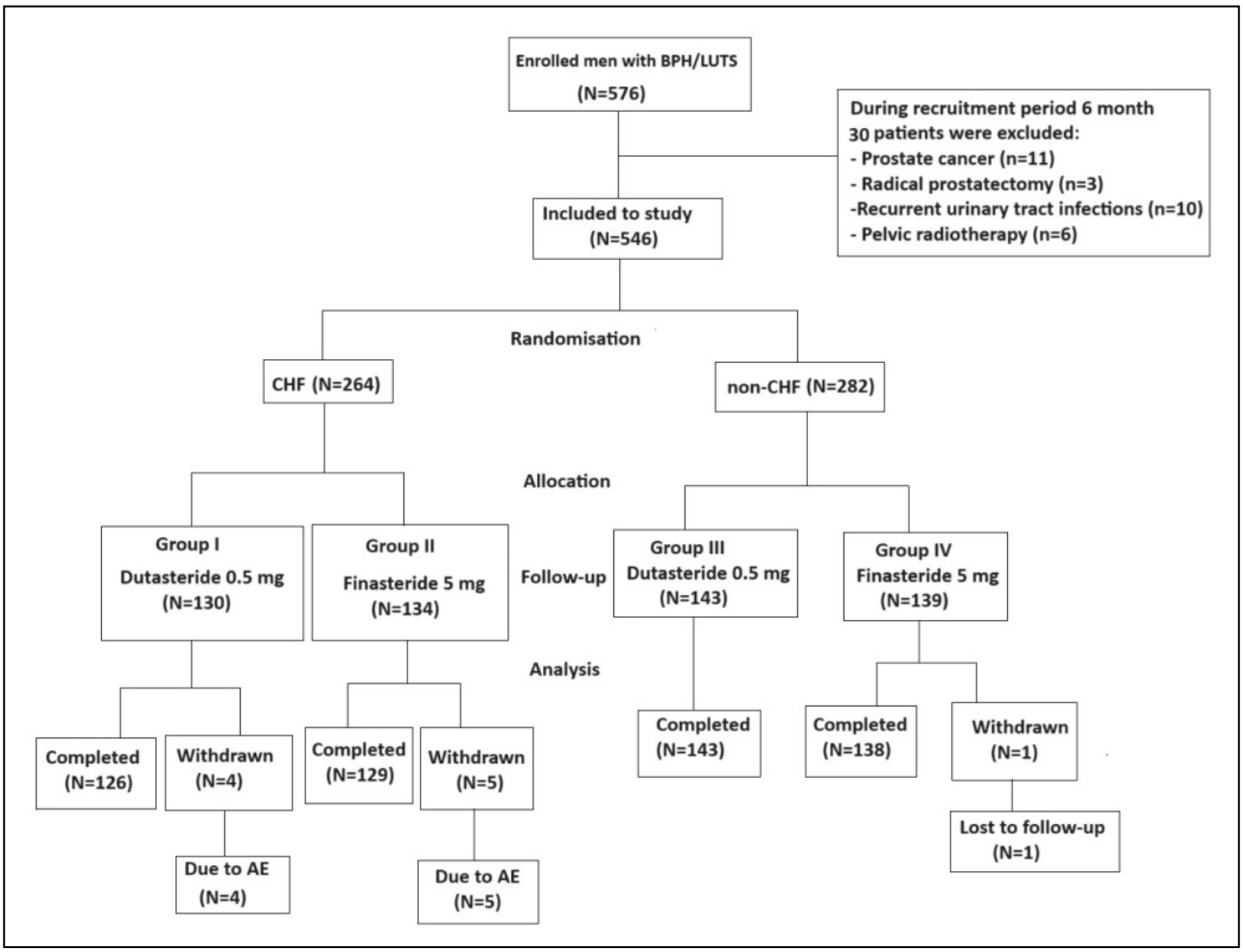

Figure 1. The flow-chart of the study.

Table 2. Patient demographics and baseline parameters in men with BPH/LUTS.

	Chronic heart failure		**Non-chronic heart failure**		***P*-value**
	Group I Dutasteride 0.5 mg	Group II Finasteride 5 mg	Group I Dutasteride 0.5 mg	Group II Finasteride 5 mg	
No. of patient, *n*	130	134	143	139	
Age, years	64 ± 3.4	62 ± 3.9	63 ± 3.6	64 ± 3.7	0.126
Height, cm	169 ± 4	170 ± 3.6	168 ± 4.1	170 ± 3.9	0.457
BMI, kg/m^2	24 ± 3.1	25 ± 3.2	24 ± 3.4	25 ± 3.3	0.321
BNP, pg/mL	690 ± 54	612 ± 65	85 ± 24	81 ± 22	0.012
LVEF, %	37 ± 4.5	38 ± 4.9	67 ± 3.4	65 ± 4.2	0.024
Prostate volume, cc	85 ± 7.9	83± 7.4	84± 8.2	82± 7.7	0.732
PSA, ng/mL	1.5 ± 1.2	1.4 ± 1.3	1.5 ± 1.4	1.6 ±1.4	0.523
PVR, mL	103.5 ± 8.5	104.9 ± 8.7	102.2 ± 7.9	103.4 ± 8.1	0.391
IPSS (baseline)					
Total	20.3 ± 5.7	20.5 ± 6.2	21.2 ± 5.9	20.9 ± 6.4	0.675
Voiding subscore	15.6± 4.1	16.2 ± 4.5	15.9 ± 4.6	16.5 ± 4.8	0.529
Storage subscore	4.7± 1.6	4.3 ± 1.7	5.3 ± 1.3	4.4 ± 1.6	0.734
QoL score	4.5 ± 0.9	4.6 ± 0.7	4.4 ± 0.8	4.5 ± 0.6	0.432
Q_{max} (mL/s)	9.8 ± 2.7	10.1 ± 2.1	9.9 ± 2.3	10.3 ± 2.2	0.589

Note: SD, standard deviation. BMI, body mass index. BNP, brain natriuretic peptide. LVEF, left ventricular ejection fraction. PSA, prostate-specific antigen. PVR, post-void residual volume. IPSS, International Prostate Symptom Score. QoL, quality of life.

3). The subgroup analysis of change of prostate volume in patients with CHF showed that the administration both dutasteride 0.5 mg and finasteride 5 mg in men with severely abnormal (< 30%) and moderately abnormal (≥ 30% ≤ 40%) left ventricular ejection fraction did not have any effects to prostate volume. The men with mildly abnormal (≥ 40% ≤ 51%) LVEF had minimal reduction of prostate volume—10.7 % for A3-subgroup and—10.5% for B3 subgroup at 12-month of follow-up (Table 4). The men with CHF the reduction of prostate volume at 12-month of follow-up was—4.7% for dutasteride 0.5 mg group and—4.8% for finasteride 5 mg group. At the same time, in the patients without CHF, reduction of prostate volume at 12-month was—23.8% and—25.6% for dutasteride and finasteride group, respectively (Table 3).

Secondary endpoints

IPSS and its subscores

A statistically significant improvement ($P < 0.05$) in total IPSS score was observed from baseline in group III and IV without chronic heart failure who received dutasteride 0.5 mg and finasteride 5 mg, respectively mg (Table 5). The mean change from baseline in group III was 7.0 ± 2.0 and 11.0 ± 2.0 for 6 and 12 months of follow-up, respectively. The mean change in group IV was 6.0 ± 3.0 and 10.3 ± 4.0 for 6 and 12 months of follow-up, respectively. The patients with CHF did not have significant improvements in total IPSS and had more pronounced obstructive symptoms during 12 months of treatment compared with patients with normal heart function (Table 5).

PVR

The patients of group III and IV had statistically significant improvement of PVR after 6 and 12 months of treatment ($P < 0.05$). The mean change in PVR from baseline in group III was 42 ± 2.1 mL and 62 ± 3.0 mL for 6 and 12 months of follow-up, respectively. The mean change in PVR from baseline in group IV was 42 ± 2.1 mL and 62

Table 3. Clinical characteristics of the patients.

(A) Chronic heart failure	**Prostate volume (cc)**			
	Baseline	After 6 months of therapy	After 12 months of therapy	*P*-value
Group I Dutasteride 0.5 mg	85 ± 7.9	83 ± 4.5	81 ± 4.2	0.932
Group II Finasteride 5 mg	83± 7.4	81 ± 4.3	79 ± 4.1	0.824
(B) Non-Chronic heart failure	**Prostate volume (cc)**			
	Baseline	After 6 months of therapy	After 12 months of therapy	*P*-value
Group III Dutasteride 0.5 mg	84± 8.2	73 ± 6.5	64 ± 4.9	0.021
Group IV Finasteride 5 mg	82± 7.7	71 ± 6.3	61 ± 4.4	0.015

Table 4. The subgroup analysis of change of the prostate volume in patients with CHF taking dutasteride (**A**) and finasteride (**B**) in depending of value of LVEF (%) during 12 months of follow-up.

(A) Dutasteride 0.5 mg	**Prostate volume (cc)**			
No. of patients (n = 130)	Baseline	After 6 months of therapy	After 12 months of therapy	P-value
A1 subgroup LVEF < 30% (n = 43)	83 ± 4.5	82 ± 4.4	81 ± 4.6	0.876
A2 subgroup (LVEF) ≥ 30% ≤ 40% (n = 44)	84 ± 4.2	83 ± 4.4	82 ± 4.1	0.632
A3 subgroup (LVEF) ≥40% ≤ 51% (n = 43)	84 ± 4.3	79 ± 4.1	75 ± 3.9	0.032
(B) Finasteride 5 mg	**Prostate volume (cc)**			
No. of patients (n = 134)	Baseline	After 6 months of therapy	After 12 months of therapy	P-value
B1 subgroup LVEF < 30% (n = 45)	85 ± 4.4	83 ± 4.3	82 ± 4.5	0.743
B2 subgroup (LVEF) ≥ 30% ≤ 40% (n = 44)	86 ± 4.3	83 ± 4.2	82 ± 4.6	0.812
B3 subgroup (LVEF) ≥ 40% ≤ 51% (n = 45)	85 ± 4.2	78 ± 3.9	76 ± 3.3	0.024

Note: LVEF, Left ventricular ejection fraction.

± 3.0 mL for 6 and 12 months of follow-up, respectively. However, the patients with CHF did not have any improvements in PVR during 12 months of treatment (Table 5).

Q_{max}

The men in group III and IV had a statistically significant increase ($P < 0.05$) in maximum flow rate Q_{max} (mL/s) compared with patients in groups I and II, who had CHF (Table 3). The mean change from baseline in group III was 3.0 ± 0.1 and 5.0 ± 0.3 for 6 and 12 months of follow-up, respectively. The mean change in group IV was 2.0 ± 0.2 and 4.0 ± 0.5 for 6 and 12 months of follow-up, respectively. The men with CHF had no significant improvement in maximum flow rate Q_{max} (Table 5).

PSA level

The PSA level had decreased by 50% in all group and there were not statistically significant differences between the four groups after 6 and 12 months of treatment (Table 5).

Discussion

This study was conducted to compare the effects of 5-ARIs (dutasteride 0.5 mg and finasteride 5 mg) on prostate volume in men with BPH with or without concomitant chronic heart failure. The results demonstrate that both treatment options improved LUTS after 12 months in terms of total IPSS and its subscores in patients with normal heart function. In addition, PVR and Q_{max} were significantly improved in men without concomitant chronic heart failure after 12 months of treatment. At the same time, the men with concomitant CHF had more pronounced obstructive LUTS even at 12-month of treatment. Furthermore, the

Table 5. Comparison of the treatment outcomes at the follow-up assessment and mean changes in values from baseline to 6 months (**A**) and 12 months (**B**) in four groups of patients.

(A)	**Chronic heart failure**		**Non-chronic heart failure**		***P*-value**
	Group I Dutasteride 0.5 mg	Group II Finasteride 5 mg	Group III Dutasteride 0.5 mg	Group IV Finasteride 5 mg	
PSA, ng/mL	0.5 ± 0.4	0.7 ± 0.3	0.8 ± 0.5	0.7±0.4	0.523
PVR, mL	100.4 ± 7.5	101.9 ± 7.7	60.2 ± 5.8	62.4 ± 5.1	0.014
IPSS (baseline)					
Total IPSS	18.3 ± 5.7	18.5 ± 5.2	14.2 ± 3.9	14.9 ± 3.4	0.023
Voiding subscore	14.6± 3.1	14.2 ± 3.5	10.9 ± 2.6	10.5 ± 2.8	0.018
Storage subscore	3.7± 2.6	4.3 ± 1.7	3.3 ± 1.3	4.4 ± 0.6	0.453
QoL score	3.5 ± 0.6	3.6 ± 0.5	2.4 ± 0.8	2.5 ± 0.4	0.032
Q_{max} (mL/s)	10.8 ± 2.2	10.7 ± 2.6	12.9 ± 2.4	12.3 ± 2.4	0.010
(B)	**Chronic heart failure**		**Non-chronic heart failure**		***P*-value**
	Group I Dutasteride 0.5 mg	Group II Finasteride 5 mg	Group III Dutasteride 0.5 mg	Group IV Finasteride 5 mg	
PSA, ng/mL	0.4 ± 0.1	0.3 ± 0.2	0.4 ± 0.3	0.5 ± 1.4	0.782
PVR, mL	100.1 ± 8.5	102.9 ± 8.7	40.2 ± 4.9	43.4 ± 4.1	0.026
IPSS (baseline)					
Total IPSS	17.3 ± 4.7	17.6 ± 5.2	10.2 ± 2.9	10.3 ± 2.4	0.014
Voiding subscore	13.6± 2.1	13.2 ± 2.5	7.9 ± 1.6	7.5 ± 1.8	0.029
Storage subscore	3.7± 2.6	4.4 ± 2.7	2.3 ± 1.3	2.8 ± 0.6	0.014
QoL score	3.4 ± 0.5	3.5 ± 0.6	1.9 ± 0.5	1.7 ± 0.4	0.038
Q_{max} (mL/s)	11.1 ± 2.4	10.9 ± 2.8	14.9 ± 2.6	14.3 ± 2.7	0.004

men with CHF had higher values of PVR and lower Q_{max} at 6 and 12 months of treatment. In the current recommendations of the European Association of Urology (EAU), use of 5-ARIs is indicated in patients with enlarged prostate > 40 cc and moderate to severe LUTS [16, 17]. The main effect of 5-ARIs is associated with induction of apoptosis of epithelial cells in the prostate gland leading to prostate size reduction of about 18-28% and a decrease in circulating PSA levels of about 50% after 6 to 12 months of therapy [18, 19]. Gittelman *et al*. reported that dutasteride decreased a prostate volume by 26.2% from baseline to 48 months in men with prostate volume of 40 cc or greater [20]. Jeong *et al*. demonstrated that a prostate volume was reduced by 24.5% in finasteride-treated group and by 26.1% dutasteride-treated group after 12 months of treatment [21]. In one of the long-term clinical studies was found that finasteride therapy to reduce prostate volume by approximately 27% compared to baseline after 36 months of treatment [22].

In the present study, the patients with BPH and without concomitant chronic heart failure had a similar reduction of prostate size—23.8% for dutasteride 0.5 mg and—25.6% for finasteride 5 mg after 12 months of treatment. However, the men with concomitant CHF had a different pattern of reduction of prostate volume in depending of value of the LVEF. The patients with severely abnormal (< 30%) and moderately abnormal (≥ 30% ≤ 40%) LVEF had no effect on prostate volume during 12 months of treatment. In contrast, the men with mildly abnormal (≥ 40% ≤ 51%) LVEF had a minimal reduction of prostate volume by 10.7% for dutasteride group and by 10.5% for finasteride group at 12-month of follow-up. In large population-based study Ayele *et al*. demonstrated that the use of 5-ARIs was not associated with an increased risk of hospitalization for cardiovascular diseases such as heart failure, stroke, myocardial infarction in men with BPH [13]. In another study, Hsieh *et al*. reported that the long-term use of 5-alpha-reductase inhibitors did not increase the risk of cardiovascular events in men with BPH [23]. In cross-sectional study, Russo *et al*. demonstrated an increase of more than five-fold of having a Framingham CVD risk score of ≥ 10% in men with BPH and moderate-severe LUTS [24]. The diverse effects of 5-ARIs on prostate volume in current study can be explained by hemodynamic differences in patients with or without concomitant CHF. In study, Chen *et al*. demonstrated resistive indexes of the periurethral arteries have a positive correlation with the cardiovascular risk factors. In addition, they reported that the periurethral artery resistive index positively correlated with both prostate and transitional zones volumes [25]. In context of BPH, the increase in the resistive index indicates to vascular resistance suggesting about relationship between underperfusion of prostate and cardiovascular disease. Anatomically, the diameter of periurethral arteries is smaller than the other branches of the prostatic vessels and its resistive index is susceptible parameter to hemodynamic changes. Several studies have demonstrated that cardiovascular risk factors may cause enlargement of the prostate volume by causing chronic prostatic ischemia [26, 27]. In our study, we demonstrate that administration of 5-ARIs in men with CHF did not improve BPH-related LUTS and does not affect prostate volume in patients with severely abnormal (< 30%) and moderately abnormal (≥ 30% ≤ 40%) LVEF. Elsherbini *et al*. reported that preoperative 5-ARI is not associated with any clinically significant different perioperative or functional outcomes for GreenLight photovaporization of prostate (PVP) using the XPS-180W system. Thus, they demonstrate that there is no role for the initiation or discontinuation of 5-alpha reductase inhibitors prior to GreenLight PVP [28]. Thus, such category of patients' needs minimal-invasive surgical treatment for achievement of improvement of LUTS and good quality of life considering all operative-related risk factors.

Conclusions

Dutasteride and finasteride had no effect on prostate volume in patients with CHF, BNP > 100 pg/mL and with severely abnormal (< 30%) and moderately abnormal (≥ 30% ≤ 40%) LVEF. The patients with BPH and CHF did not receive any benefits in regarding to PVR, Q_{max} and IPSS score improvement after treatment with dutasteride or finasteride. Accordingly, the patient with severe LUTS and concomitant chronic heart failure need minimal-invasive surgical treatment considering all operative-related risk factors due-to ineffectiveness of 5-ARIs for reducing of prostate volume.

Declarations

Availability of data and materials: Not applicable.

Financial support and sponsorship: None.

Conflicts of interest: Krakhotkin DV, Chernylovskiy VA, Francesco Greco, Aly M Abdel-Karim and Ali Serdar Gözen are members of the editorial board of *Uro-Technology Journal*. The authors declare that they have no conflicts and were not involved in the journal's review or decision regarding this manuscript.

Ethical statement: This study was approved by the Institutional Review Board of Central District Hospital Kamenolomni. All patients were informed of the procedures and provided written informed consent.

Consent for publication: Not applicable.

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Cite this article as: Krakhotkin DV, Chernylovskyi VA, Greco F, Abdel-Karim AM, Gözen AS, Korplyakova AG, *et al*. The effects of 5-ARIs on prostate volume in patients with or without heart failure and benign prostate hyperplasia: prospective, comparative study. *Uro-Technology Journal*, 2024, 8(3): XX-XX. doi: 10.31491/UTJ.2024.09.XXX