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Platinum Priority – Benign Prostatic Hyperplasia
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Does Prostate Size Predict the Development of Incident Lower Urinary Tract Symptoms in Men with Mild to No Current Symptoms? Results from the REDUCE Trial

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Abstract

Background: It has been shown that increased prostate size is a risk factor for lower urinary tract symptom (LUTS) progression in men who currently have LUTS presumed due to benign prostatic hyperplasia (BPH).
Objective: To determine if prostate size is a risk factor for incident LUTS in men with mild to no symptoms.
Design, setting, and participants: We conducted a post hoc analysis of the REDUCE study, which contained a substantial number of men (n = 3090) with mild to no LUTS (International Prostate Symptom Score [IPSS] <8).
Outcome measurements and statistical analysis: Our primary outcome was determination of the effect of prostate size on incident LUTS presumed due to BPH defined as two consecutive IPSS values >14, or receiving any medical (α-blockers) or surgical treatment for BPH throughout the study course. To determine the risk of developing incident LUTS, we used univariable and multivariable Cox models, as well as Kaplan-Meier curves and the log-rank test.
Results and limitations: Among men treated with placebo during the REDUCE study, those with a prostate size of 40.1–80 ml had a 67% higher risk (hazard risk 1.67, 95% confidence interval 1.23-2.26, p = 0.001) of developing incident LUTS compared to men with a prostate size 40.0 ml or smaller. There was no association between prostate size and risk of incident LUTS in men treated with 0.5 mg of dutasteride. The post hoc nature of our study design is a potential limitation.
Conclusions: Men with mild to no LUTS but increased prostate size are at higher risk of incident LUTS presumed due to BPH. This association was negated by dutasteride treatment.
Patient summary: Benign prostatic hyperplasia (BPH) is a very common problem among older men, which often manifests as lower urinary tract symptoms (LUTS), and can lead to potentially serious side effects. In our study we determined that men with mild to no current LUTS but increased prostate size are much more likely to develop LUTS presumed due to BPH in the future. This association was not seen in men treated with dutasteride, a drug approved for treatment of BPH. Our study reveals that men with a prostate size of 40.1–80 ml are potential candidates for closer follow-up.

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1. Introduction

Benign prostatic hyperplasia (BPH) is a common disease in older men, with prevalence as high as 75% in men aged >70 yr, and commonly manifests as lower urinary tract symptoms (LUTS) [1]. As these symptoms can lead to depression and lower quality of life [2,3], as well as more serious side effects such as acute urinary retention and urosepsis [4,5], knowledge of factors that predict LUTS/BPH progression are paramount to prevention.

One potential risk factor for LUTS/BPH progression is an increase in prostate size [6–8]. While there is much controversy about the correlation between prostate size and severity of symptoms [9–11], some studies have found that increasing prostate size is significantly predictive of a higher risk of LUTS/BPH progression in men with pre-existing symptoms [6,7]. Notably, in a secondary analysis of the placebo arm of the Medical Therapy of Prostatic Symptoms (MTOPS) trial, Crawford et al [7] found that prostate size >30 ml predicts an increased risk of LUTS/BPH progression in men with an International Prostate Symptom Score (IPSS) ≥8 [7]. This negative effect of increased prostate size has been shown in other secondary analyses of the placebo arms of clinical trials examining the effect of various BPH treatments. Of note, subjects in these studies had pre-existing LUTS with IPSS ≥8 before enrollment [6–8]. Among men with mild to no LUTS (IPSS <8), one study showed conflicting results with regard to prostate size predicting incident LUTS [11]. Thus, further knowledge of prostate size as a predictor of LUTS/BPH progression in men with mild to no symptoms (IPSS <8) is needed.

To address this gap in the literature, we conducted a secondary analysis of the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial, which was a randomized trial of prostate cancer risk reduction with daily dutasteride (0.5 mg) or placebo. A key strength of REDUCE is the prospective data on prostate size and various BPH parameters for participants who were not specifically selected with prior LUTS, including a substantial proportion of men with mild to no LUTS (IPSS <8) [12]. As enlarged prostates are associated with a higher risk of LUTS/BPH progression in symptomatic men, we hypothesized that men with enlarged prostates with mild to no LUTS are at higher risk of incident LUTS presumed due to BPH.

2. Materials and methods

2.1. Study population

Our study population consisted of men from the REDUCE trial, which was a randomized, double-blind, placebo-controlled study of prostate cancer risk reduction with daily dutasteride (0.5 mg) or placebo [12]. Eligible men were aged 50–75 yr, had serum prostate-specific antigen (PSA) of ≥2.5 ng/ml (50–60 yr) or 3.0 ng/ml (60–75 yr) but ≤10 ng/ml, and one single negative prostate biopsy (6–12 cores) within 6 mo of enrollment. Men were excluded if they had a history of prostate cancer, high-grade intraepithelial neoplasia, atypical small acinar proliferation, prostate volume >80 ml, previous prostate surgery, or IPSS ≥25. Men with IPSS ≥20 who were also on α-blockers or were previously on finasteride or dutasteride were excluded.

Men were required to have a negative prostate biopsy for cancer 6–12 mo before enrollment and a prostate size of ≤80 ml. Participants were followed for 4 yr, with an IPSS obtained at baseline and every 6 mo. We defined incident LUTS as the first report of medical treatment, surgery, or sustained, clinically significant BPH symptoms. Medical treatment included uroselective α-blockers (tamsulosin) and 5α-reductase inhibitors (finasteride). We defined a report of nonspecific α-blocker therapy (doxazosin, prazosin, or terazosin) as BPH if there was concomitant evidence of BPH via either self-reporting of symptoms or one report of IPSS >14 or any two reports of IPSS ≥12 at any time before the report of medication use. Surgical treatments included transurethral prostatectomy, open prostatectomy, urethral balloon dilation, and laser prostatectomy. We defined the onset of clinically significant BPH symptoms as the second report of IPSS >14 [1]. Our rationale was that IPSS of 7–18 is considered moderately symptomatic and most LUTS/BPH clinical trials use IPSS of 12 as an enrollment threshold [13]. Baseline prostate size was measured during the prestudy transrectal ultrasound (TRUS)-guided biopsy and again at the 2- and 4-yr study intervals. As our primary goal was to study men with mild to no LUTS, we excluded 4320 of the 8122 REDUCE efficacy subjects who had baseline IPSS of ≥8 (Fig. 1). We also excluded 538 participants who had previously received medical therapy (α-blockers or 5α-reductase inhibitors) for BPH. In addition, we excluded 39 subjects who met our definition of incident LUTS within 30 d of study enrollment, as this could be attributable to inaccurate reporting of the baseline IPSS. After further excluding subjects with missing data for race (n = 1), body mass index (BMI; n = 41), smoking status (n = 2), diabetes status (n = 1), prostate size (n = 48), or prostate volume >80 ml (n = 38), there were 3090 subjects remaining (Fig. 1).

2.2. Statistical analysis

Our primary aim was to determine the effect of prostate size on progression to incident LUTS among men with mild to no LUTS (IPSS <8)

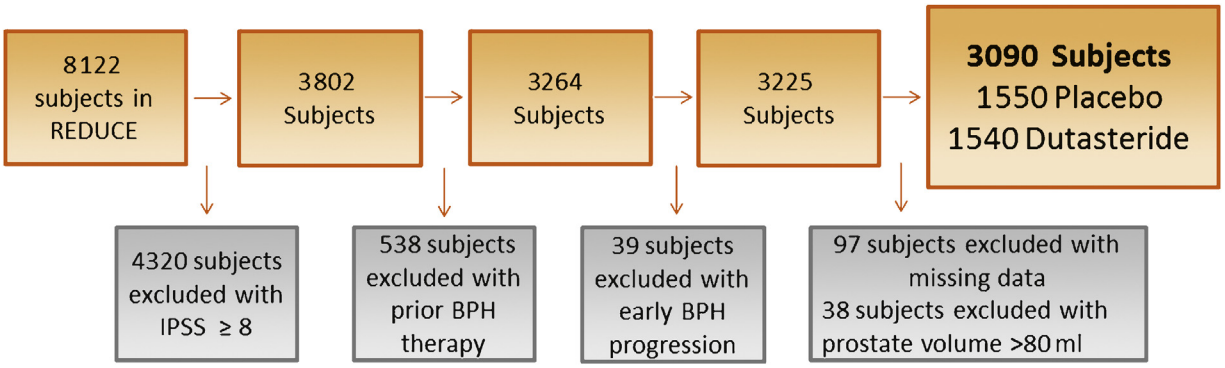

Fig. 1 – CONSORT flow diagram of participants selected from the REDUCE trial.