# Improvements in benign prostatic hyperplasia–specific quality of life with dutasteride, the novel dual 5α-reductase inhibitor

**M.P. O'LEARY, C. ROEHRBORN*, G. ANDRIOLE†, C. NICKEL‡, P. BOYLE¶ and K. HÖFNER§**

*Department of Surgery, Harvard Medical School, Division of Urology, Brigham and Women's Hospital, Boston, Divisions of Urology, *The University of Texas South-western Medical Center, Dallas, Texas, and †Washington University School of Medicine, St Louis, MO, ‡Department of Urology, Queen's University, Kingston, Ontario, Canada, ¶Division of Epidemiology and Biostatistics, European Institute of Oncology, Milan, Italy and §Department of Urology, Ev Hospital Oberhausen, Oberhausen, Germany*

Accepted for publication 3 April 2003

## OBJECTIVES

To examine the effect of the dual-action 5α–reductase inhibitor dutasteride on benign prostatic hyperplasia (BPH)-specific health status, as measured by the BPH Impact Index (BII), and to identify baseline and treatment risk factors for those most bothered by their BPH symptoms at the end of the protocol.

## PATIENTS AND METHODS

Data were derived from three randomized, double-blind, placebo-controlled, 2-year studies conducted in 4325 men with lower urinary tract symptoms caused by benign prostatic enlargement. Each study comprised a 1-month single-blind placebo run-in period, followed by randomization to oral dutasteride 0.5 mg once daily or placebo for 2 years. Patients eligible for inclusion were consenting men aged ≥50 years with moderate to severe symptoms (American Urological Symptom Index, AUA-SI, score ≥12), a prostate volume of ≥30 mL, a serum prostate-specific antigen (PSA) level of ≥1.5 or < 10 ng/mL, and a maximum urinary flow rate ($Q_{max}$) of ≤15 mL/s. BII scores were recorded at baseline and each study visit. Clinically and statistically significant changes in BII scores from baseline were investigated for each study visit. Logistical regression analysis was used to assess the significance of baseline prostate volume, symptoms, BII item 3, baseline $Q_{max}$, serum dihydrotestosterone, testosterone, PSA, age and weight in predicting the BII score at 2 years.

## RESULTS

Dutasteride, but not placebo, resulted in clinically and statistically significant improvements in mean BII score from 6 months. Of patients with a baseline BII score of ≥5 (greatest symptomatic burden) treatment with dutasteride improved the scores by 2.41, while the scores in placebo-treated patients only improved by 1.64. Dutasteride-treated patients with a baseline BII score of <5 (least symptom burden) had a clinically significant improvement in health status, while placebo-treated patients deteriorated. Regression analysis showed that men with a combination of a baseline BII item-3 score of 3 (bothered a lot) and a high symptom score (AUA-SI ≥20) were more likely to be bothered by their symptoms at the end of the study. Men receiving placebo were also more likely to be bothered at the end of the study than were those receiving dutasteride.

## CONCLUSIONS

Dutasteride treatment is associated with clinically significant improvements in BII score, reflecting improvements in the quality of life of men with BPH. Taken together with previously reported improvements in prostate volume, lower urinary tract symptoms and urinary flow, and diminution of the risk of acute urinary retention and the need for BPH-related surgery, dutasteride offers demonstrable efficacy in the management of BPH.

## KEYWORDS

benign prostatic hyperplasia, dutasteride, health status, quality of life, bother, BPH Impact Index

## INTRODUCTION

BPH with LUTS is a chronic and progressive condition [1]; the progression of BPH involves a worsening of clinical variables, including an increase in prostate volume, deterioration in LUTS and maximum urinary flow rate ($Q_{max}$), greater risks of acute urinary retention (AUR) and BPH-related surgery, and a deterioration in BPH-specific quality of life [1]. Studies of the natural history of BPH show that men with a prostate volume of >30 mL are at greater risk of having AUR [2] and undergoing prostatectomy [3] than men with smaller prostates. Overall, a 60-year-old man has a 23% lifetime risk of AUR [4] and a man aged ≥60 years with an enlarged prostate and obstructive symptoms has a 20-year probability of undergoing BPH-related surgery of 39% [5]. Both prostate volume and serum PSA levels are important predictors of the deterioration in symptoms and $Q_{max}$, the rate of prostate growth, and the risk of AUR and BPH-related surgery [6–10].

Measuring the burden of BPH and the consequences of treatment from the patients' perspectives is recommended as a routine component of managing BPH [11]. This recommendation is in recognition of the finding that the most common symptoms are not always the most bothersome [12]. Furthermore, bother scores appear to be predictive of both healthcare-seeking behaviour and of outcomes after therapy for BPH. The large-scale, longitudinal Olmsted County study concluded that higher bother scores identified more successfully those men who had sought medical care for urinary problems than either symptom severity scores or 'symptom interference with usual activities' scores [13]. Baseline



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*TABLE 1 Mean (SD) absolute changes in BII scores considered to be clinically meaningful for patients with a baseline BII score of <5 (least symptom burden) and ≥5 (significant symptom burden) [19]*

| | Baseline score | |
|---|---|---|
| Improvement | < 5 | ≥ 5 |
| Marked | − 1.4 (0.12) | − 4.6 (0.36) |
| Moderate | − 0.7 (0.12) | − 2.4 (0.25) |
| Slight | 0.1 (0.13) | − 1.6 (0.19) |
| None | 0.4 (0.56) | − 0.7 (0.26) |
| Worse | 1.8 (0.56) | 2.2 (0.71) |

bothersomeness was also found to be the single most important predictor of failure (change to surgery) for patients on watchful waiting [14,15].

The 5α-reductase inhibitors (5ARIs) are known to prevent disease progression in men with BPH by impeding the conversion of testosterone to dihydrotestosterone, the androgen that is considered primarily responsible for hyperplastic growth of the prostate. 5ARIs not only arrest further development of BPH, they also reduce prostate volume in men with enlarged prostates [16,17]. The efficacy and safety of dutasteride, a potent type 1 and type 2 5ARI, has recently been examined in a pooled analysis of three placebo-controlled, 2-year, double-blind clinical trials. Dutasteride treatment was associated with a reduction in serum dihydrotestosterone of >90% by 2 weeks, maintained to the end of the study, with corresponding decreases in prostate volume of 25.7% at 2 years. Dutasteride also provided sustained symptom relief, improved $Q_{max}$, and reduced the risks of AUR by 57% and the need for BPH-related surgery by 48% [17].

The objectives of the present analysis were to examine the effect of dutasteride on BPH-specific health status, in terms of both statistical and clinical significance, and to identify baseline and treatment risk factors for those most bothered by their BPH symptoms at the end of the protocol. Study patients were evaluated using the BPH Impact Index (BII), a fully validated, self-administered BPH-specific health status questionnaire [18].

## PATIENTS AND METHODS

Data were derived from three randomized, double-blind, placebo-controlled, 2-year studies conducted in 4325 men with LUTS caused by BPH. These studies were primarily designed to evaluate the effects of dutasteride compared with placebo on LUTS, and the risks of AUR and need for BPH-related surgery. Two of these studies were conducted in the USA and the third was international.

The methods and results for the primary endpoints and safety analyses were reported previously [17]. Briefly, each study comprised a 1-month single-blind placebo run-in period, followed by randomization to oral dutasteride 0.5 mg once daily or matching placebo for 2 years. Patients eligible for inclusion were consenting men aged ≥ 50 years with moderate to severe symptoms (AUA Symptom Index, AUA-SI, score ≥12), a prostate volume of ≥30 mL, a serum PSA of ≥1.5 or < 10 ng/mL, and a $Q_{max}$ of ≤ 15 mL/s.

Patients completed the BII before any other study procedures at screening, baseline (after the 4-week placebo run-in), and at 1, 3 6, 12, 18 and 24 months. The BII (Appendix) asks four questions that measure the impact of urinary problems on four domains of health: physical discomfort from urinary problems; worry about health because of urinary problems; bothersomeness of urinary symptoms; and limitation of activities of daily living because of urinary problems. The BII has acceptable test-retest and internal consistency reliability, construct and discriminant validity, and responsiveness [18]. It was designed to provide a total score by adding the scores associated with responses to the four questions. The total BII score is from 0 (no symptom burden) to 13 (significant symptom burden), with the first three questions scoring 0–3 and the fourth 0–4. Barry *et al.* [19] established that patients who rated themselves as being 'slightly improved' have a mean decrease of 0.5 points in the BII from baseline. For the purpose of this study therefore, a change of – 0.5 points was considered to be clinically relevant for patients. In a further analysis, Barry *et al.* [19] also examined whether the patients' perception of improvement was influenced by baseline BII score; they showed that for patients with a baseline BII score of <5 and ≥ 5 (the 75th percentiles of scores), a perception of improvement needs to be accompanied by different changes in BII score (Table 1). Thus for patients with a BII score of < 5, a rating of 'slightly improved' is accompanied by only a slight change in BII score (+ 0.1, ± 0.13), whilst for those with a score of ≥ 5, a change of −1.6 points is needed for a 'slight improvement'. In these analyses therefore, both clinically and statistically significant changes in BPH-specific health status were assessed, for the study group as a whole, and for those with the lowest and highest baseline BII scores.

### EFFICACY ANALYSIS

A pooled analysis from the three studies was conducted using the intent-to-treat population, which consisted of all patients randomized to double-blind study treatment who received at least one dose of study treatment. The results were assessed statistically using an 'at-visit' analysis. Treatment groups were compared in terms of the mean change from baseline in BII score at each assessment after baseline using a general linear model with effects for treatment, cluster and baseline BII score. The mean estimates, mean differences and 95% CI of adjusted mean differences were calculated. The reported *P* values corresponded to the pair-wise comparisons between placebo and dutasteride 0.5 mg. All statistical analyses used two-sided tests of significance at $\alpha = 0.05$.

### ANALYSIS OF RISK FACTORS FOR BOTHER AT THE END OF THE STUDY

A logistic regression model was constructed to identify predictors for patients most likely to be bothered at the end of the study. Bother was defined as a score of 3 ('bothered a lot') on the Bothersomeness of Symptoms domain of the BII (item 3): 'Overall, how bothersome has any trouble with urination been during the past month?' Variables included in the logistic regression model were treatment group, baseline prostate volume, AUA-SI, BII item-3, $Q_{max}$, serum dihydrotestosterone, testosterone, PSA, age and weight.

## RESULTS

The baseline demographic characteristics of the study population are outlined in Table 2. The treatment groups were comparable for baseline characteristics. The mean age of participants, 91–92% of whom were Caucasian, was 66 years. Patients in the two treatment groups had comparable AUA-SI scores of 17 and comparable BII scores of 4.05 (2.74) (dutasteride) and 3.98 (2.76) (placebo).

Dutasteride treatment was associated with a significant improvement in mean BII score over placebo from 6 months (Fig. 1). This improvement in health status was sustained to the end of the double-blind study at 2 years. The net improvement from baseline in mean BII score increased from 6 months to 2 years in favour of dutasteride. Placebo-treated patients showed little further improvement compared with baseline from 6 months and deteriorated from 18 to 24 months.

With an adjusted mean change in score from baseline for dutasteride-treated patients of − 0.63 at 6 months decreasing to −1.0 at 2 years, the predefined clinically relevant change from baseline of −0.5 was exceeded in that period. Dutasteride treatment therefore resulted in a clinically relevant improvement in BPH-specific health status from 6 months. The adjusted mean change from baseline for the placebo-treated patients was not clinically relevant at any time.

Using the predefined definition of lower and higher baseline BII scores, placebo-treated patients with a baseline BII score of <5 (least symptom burden) had a deterioration in BII score of 0.51 at 2 years, while dutasteride-treated patients had an improvement of −0.12. For those with a baseline BII score of ≥5 (significant symptom burden), those on placebo had an improvement of −1.64 in BII score at 2 years while dutasteride had an improvement of −2.41.

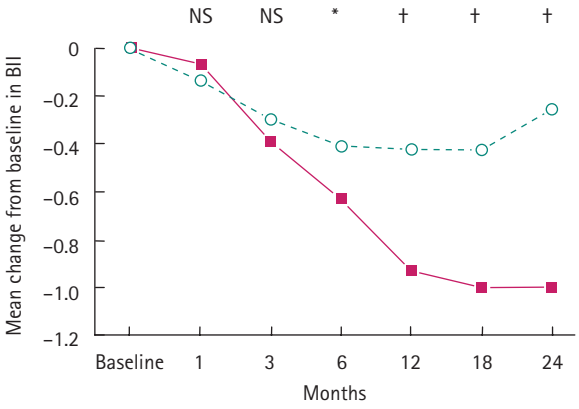


*FIG. 1.*
*Mean change from baseline in BII score in dutasteride- (red squares) and placebo-treated (green circles) patients. *P < 0.005; †P < 0.001.*

| Mean (SD) | Dutasteride 0.5 mg | Placebo |
|---|---|---|
| N | 2167 | 2158 |
| Age, years | 66.5 (7.55) | 66.1 (7.36) |
| Caucasian, % | 91 | 92 |
| Duration of BPH symptoms, years | 5.3 (4.97) | 5.1 (4.60) |
| BPH-specific health status (BII) score | 4.05 (2.74) | 3.98 (2.76) |
| AUA-SI score | 17.0 (6.0) | 17.1 (6.1) |
| $Q_{max}$, mL/s | 10.1 (3.5) | 10.4 (3.6) |
| Prostate volume, mL | 54.9 (23.9) | 54.0 (21.9) |
| Serum PSA, ng/mL | 4.0 (2.1) | 4.0 (2.1) |

*TABLE 2*
*Baseline demographics for the study population by treatment group*

ANALYSIS OF RISK FACTORS FOR BOTHER AT THE END OF THE STUDY

The logistic regression model identified treatment group, a baseline BII item-3 score of 3 (bothered a lot) and baseline AUA-SI score as significant ($P < 0.001$) predictors of bother at the end of the study (Table 3). The combination of these factors was more predictive of which patients would continue to be bothered than any individual factor. Table 3 shows that patients on placebo with a baseline BII item-3 score of 3 and a high symptom score (AUA-SI ≥ 20) were more likely to be bothered by their symptoms at the end of the study.

## DISCUSSION

The progression of BPH involves prostate growth, a deterioration in symptoms and urinary flow, an increase in the risk of AUR and the need for surgery (particularly in high-risk patients), as well as a deterioration in health status that has an important effect on quality of life [16,20–23]. It is this effect on daily activities that drives healthcare-seeking behaviour in men with BPH [13]. Therefore, while it is important to monitor men with BPH using objective measures such as urodynamics or TRUS, it is also necessary to assess baseline, and subsequent changes, in health status.

While the AUA-SI assesses symptom severity, the BII assesses the negative effect of BPH on health status, including the bothersomeness of BPH symptoms. As well being valid, linear regression models show that the BII is a good predictor of general, mental and physical health [18], although it does not specifically measure concern relating to the risk of AUR or surgery. The developers of the BII therefore advocate providing treatment when symptoms have resulted in a significant effect on patients' health status. Because the BII measures this impact, as well as the bothersomeness of symptoms, it is useful for facilitating decision-making about therapeutic interventions.

*TABLE 3 Analysis of risk factors for bother at the end of the study. A BII item-3 score of 3 is 'bothered a lot' and <3 is 'no bother' to 'some bother'*

| Risk factors | N | Dutasteride, % | Placebo, % |
|---|---|---|---|
| BII item-3 = 3: | | | |
| AUA-SI ≥ 20 | 156 | 24 | 44 |
| AUA-SI < 20 | 71 | 9 | 32 |
| BII item-3 < 3: | | | |
| AUA-SI ≥ 20 | 706 | 5 | 14 |
| AUA-SI < 20 | 1891 | 2 | 4 |

Dutasteride is a novel, dual 5ARI that reduces serum dihydrotestosterone by >90% at 2 weeks, significantly reduces prostate volume by 1 month, increases urinary flow as early as 1 month, improves symptoms as early as 3 months in some patients, and reduces the risk of AUR and BPH-related surgery [17]. In

this analysis, dutasteride was also shown to statistically and clinically improve BPH-specific quality of life from 6 months of treatment compared with placebo. Although placebo-treated patients had improvements in BII scores from baseline, they had a deterioration in BII score at 18–24 months, showing the progressive effect of BPH symptoms and worsening quality of life. In contrast, dutasteride treatment was associated with greater and consistent improvements from 6 months to 2 years. It has been argued that the effects of treatment on a clinical variable are only sufficient to warrant changing the patients' management if the change is perceptible to the patients. The improvement in scores from baseline for dutasteride-treated patients met or exceeded a 0.5 point decrease, showing that the improvements in health status were clinically relevant [19]. At no time was the change from baseline for placebo-treated patients clinically relevant.

This study also identified that men with a baseline BII score of <5 (least symptom burden) had a deterioration in BII score after 2 years of placebo treatment. This contrasts with the improvement in BII score with dutasteride in this group. In these patients (the lower 75th percentile) such a change in BII score is associated with a perception of slight improvement [19]. Although both placebo and dutasteride treatment resulted in improvements in BII scores among men with a baseline BII score ≥5 (significant symptom burden), there were more substantial and clinically meaningful improvements with dutasteride. Indeed, whilst the change with placebo (– 1.64) can be classified as a slight improvement, the greater change of –2.41 with dutasteride is classified as a moderate improvement [19]. As might be expected, these data indicate that men who do not have a significant symptom burden benefit from dutasteride treatment, but that those with a significant symptom burden benefit much more.

The BII has also been used in two randomized, double-blind, placebo-controlled studies investigating the efficacy of finasteride, a type 2-selective 5ARI. There were significant differences in favour of finasteride from 9 months in one study [11], and 1 year (in the per-protocol analysis only) in the second [24].

BPH is a common medical problem among older men, and is a major contributor to a reduced quality of life and the consequent psychological sequelae among many ageing men. The growing burden of BPH on an increasingly elderly society defines it as an important public health concern. Furthermore, the understanding from both longitudinal studies and clinical trials that BPH is a progressive disease shows that health status and quality of life, with several other variables, will deteriorate in many men with BPH who remain untreated or are treated inadequately [25].

In conclusion, in this pooled analysis of three 2-year placebo-controlled trials, men receiving dutasteride had sustained, statistically and clinically significant improvements in BPH-specific health status from 6 months compared with men receiving placebo. Dutasteride provides long-lasting improvements in quality of life by reducing worry, discomfort, bother and interference with activities. Patients treated with dutasteride were also less likely to be bothered at the end of the 2-year study than were those treated with placebo. These findings are consistent with improvements in other markers of BPH disease progression, i.e. prostate volume, LUTS, $Q_{max}$, the risks of AUR and the need for BPH-related surgery, already reported with dutasteride in this same cohort of patients [17]. Therefore, dutasteride offers a long-term therapeutic strategy for improving not only clinical measures of BPH progression, but the impact of BPH on daily life. Given the increasingly elderly male population, such a strategy could offer significant improvements in health status to many men in later life.

## ACKNOWLEDGEMENTS

With thanks to Gillian Barnett and Libby Black for their assistance in developing the manuscript.

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Correspondence: Gillian Barnett, GlaxoSmithKline Research and Development, Global Health Outcomes, Middlesex, UK.
e-mail: gillian.s.barnett@gsk.com

Abbreviations: **$Q_{max}$**, maximum urinary flow rate; **AUR**, acute urinary retention; **5ARI**, 5α-reductase inhibitor; **BII**, BPH Impact Index; **AUA-SI**, AUA Symptom Index;

## APPENDIX

Questions in the BII.

1. Over the past month, how much physical discomfort did any urinary problems cause you?

2. Over the past month, how much did you worry about your health because of any urinary problems?

3. Overall, how bothersome has any trouble with urination been during the past month?

4. Over the past month, how much of the time has any urinary problem kept you from doing the kinds of things you would usually do?