

Outcomes and general health-related quality of life among patients medically treated in general daily practice for lower urinary tract symptoms due to benign prostatic hyperplasia

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Abstract

Objective This study's aim was to describe and evaluate outcomes of medical strategies used for lower urinary tract symptoms (LUTS) treatment in general practice and to assess impact of LUTS on patients' general health-related quality of life (HRQoL).

Methods This cross-sectional observational study was conducted by French general practitioners. Eligible patients were males aged ≥ 50 years, diagnosed for at least one year and currently treated for LUTS due to benign prostatic hyperplasia (BPH). Several validated questionnaires were documented by patients to assess severity of LUTS (IPSS), specific quality of life (IPSS-Q8), impact of LUTS (BII), LUTS evolution (VNS) and general HRQoL (EQ-5D).

Results Among 1,098 patients included, 82.7% were treated with monotherapies and 17.3% with combinations. Mean treatment duration was 5.2 ± 3.2 years, and 47.2% of patients had at least one treatment modification since initiation. Patients reported diminished quality of life (IPSS-Q8 ≥ 3) (42.3%), persisting symptoms (IPSS-score ≥ 12) (35.5%), symptoms worsening (VNS-score ≤ -1) (18.8%) and high bother (BII-score ≥ 9) (2.6%). Globally, 52.8% had at least one of these unsatisfactory outcomes. Regarding general HRQoL, mean EQ-5D utility significantly decreased with LUTS severity (mild: 0.90 ± 0.12 ; moderate: 0.81 ± 0.21 ; and severe symptoms: 0.73 ± 0.25 ; $P < 0.001$). As well, all five-dimensions of EQ-5D were significantly altered in patients with moderate-to-severe LUTS (< 0.001), especially 'Pain/Discomfort' and 'Anxiety/Depression'. In multivariate analyses including age and comorbidities, EQ-5D utility index remained negatively associated with each additional unit in the IPSS-score.

Conclusions This study shows that around half of BPH patients medically treated report unsatisfactory outcomes, suggesting consequential unmet medical needs in general practice. Also, moderate-to-severe LUTS significantly impact on general HRQoL.

Article in Memoriam of Richard Olivier Fourcade (1944–2010) who spent a creative life, leaving after himself a great scientific heritage in urology, as well as disciples and followers.

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Introduction

Benign prostatic hyperplasia (BPH) and its lower urinary tract symptoms (LUTS) and complications represent a

considerable health problem in men worldwide, notably in those aged over 50 years. More than half of patients (57%) reporting a history of prostatic treatment have mild LUTS, while 34 and 9% of patients suffer from moderate-to-severe symptoms, respectively [1].

Current BPH management guidelines include several therapeutic strategies [2, 3]. Pharmacological treatment is currently recommended for the treatment of men with moderate-to-severe LUTS who prefer to avoid invasive treatment. There are two principal classes of pharmacological therapies for LUTS caused by BPH: α_1 -selective adrenergic receptor antagonists (alpha-blockers) and 5-alpha-reductase inhibitors (5-ARIs). Additionally, herbal medicines are also prescribed to treat LUTS, especially in France and Spain [4].

The increasing recognition of the importance of patient-reported outcomes in BPH diagnosis and management has led to the development of disease-specific questionnaires (i.e., International Prostate Symptom Score, IPSS; and BPH Impact Index, BII) [5]. Additionally, guidelines state that the primary consideration in making treatment decisions and disease assessments about BPH with LUTS should be the health-related quality of life (HRQOL) to measure interference with social activities and decreasing psychological well-being [2, 6]. Inadequate management of LUTS can trigger disease progression and lead to several complications [7]. As a consequence, patient treatment satisfaction and HRQOL assessment seem to be essential criteria to ensure optimal treatment outcomes [8, 9], particularly in French general practice where around nine out of ten prescriptions for LUTS are filled [10].

The main objectives of this observational study were to describe and evaluate outcomes of current medical strategies used for LUTS treatment in daily general practice and to assess impact of LUTS on patients' general health-related quality of life (HRQoL).

Methods

Patients and study design

This observational cross-sectional study was carried out in France between October 2009 and January 2010, with the participation of general practitioners (GPs) belonging to the Longitudinal Patient Database (LPD) observatory. This is a computerized network of GPs who contribute exhaustive anonymous data on patient consultations and treatment to the centralized LPD. The LPD includes records for >1.6 million patients, routinely collected and is a reliable source of information in numerous previous studies in several disease areas [11].

The following criteria were used to recruit patients: aged 50 years or over with a clinical diagnosis of BPH, treatment with one of the following pharmacological classes or their combinations: an alpha-blocker or a 5-alpha-reductase inhibitor or a phytotherapy.

At the end of routine consultation, physicians filled out extra-computerized questionnaires detailing the comorbidities, ongoing medications and examinations. At home, the patient completed anonymous questionnaires.

Patient questionnaires

Four specific and one generic instrument were used to assess treatment outcomes.

The IPSS questionnaire is a validated seven-item urinary symptom scale (0–35) [12] to which was added an eighth disease-specific quality of life question (IPSS-Q8) [3]. The BII is a disease-specific four-item questionnaire (0–13) that measures the overall impact of LUTS on the general well-being of patients [5]. LUTS evolution was evaluated from the patient's perspective using a visual numeric scale (VNS) which range from –5 (extreme worsening) to 5 (extreme improvement) in relation to a 12-month retrospective period.

The last questionnaire, the EuroQOL-five-dimensions (EQ-5D) index, is a well-validated comprehensive tool developed to determine general HRQOL and health states utilities (0–1; i.e., death–perfect health). Each dimension can be answered as no problem, some problem, or severe problem. Utility was calculated using French value set from EuroQOL [13].

Statistical analysis

Descriptive analyses were provided for all variables. Overall group comparisons were done by ANOVA for quantitative data, and the chi-square or Fisher's exact test for qualitative data. All tests were two-sided and considered significant when $P < 0.05$.

The following four unsatisfactory outcomes were pre-identified and described in terms of patient proportion: (i) IPSS-score ≥ 12 : persistent symptoms representing a trigger for inclusion in previous clinical trials [14–16], (ii) IPSS-Q8 ≥ 3 : considered as a threshold for a (new) treatment [2], (iii) BII-score ≥ 9 : level of high bother [17] and (iv) VNS-score ≤ -1 : worsening symptoms.

Utility derived from EQ-5D-index was treated as a quantitative variable. Three linear models of utility as the dependent variable were performed with the following three independent variables: IPSS-score (Model 1), LUTS severity (Model 2) and unsatisfactory outcomes (Model 3). The models were obtained with step-by-step backward selection where each variable with a P -value less than 0.25

in the univariate analysis was entered in the multivariate regression analysis.

Results

Patients flowchart

Overall, 247 physicians recruited patients during the study period. In total, 1,901 eligible patients were identified and 1,098 of them were finally enrolled. Reasons of non-inclusion were non-consent ($n = 757$) and mental/physical impairment ($n = 46$). Out of all the patients enrolled, 718 returned assessable questionnaires whose data were entered into the outcomes analyses. Demographics and characteristics of enrolled patients were comparable with those of the entire population of the LPD database ($n = 15,137$) in terms of age distribution and frequent comorbidities.

Patients' characteristics

The mean age of the 1,098 men was 71.7 ± 8.9 years (median: 72 years; 50–101). A minority of patients was first diagnosed by urologists (12.4%), and the remaining patients were diagnosed by their current general practitioner (Table 1). To date, 4.4 and 6.1% of patients had a former history of AUR and surgery, respectively. A majority of patients had several comorbidities.

LUTS management

The mean follow-up since BPH diagnosis was 6.2 ± 5.1 years, and the mean patient's age was 65.5 ± 8.6 years at the time of diagnosis (median: 65 years; 34–97). To date, the most frequently reported clinical assessments used for BPH diagnosis were informal questioning and digital rectal examination (Table 1). Only 11.7% of physicians used specific LUTS scores in clinical practice and among them, 9.6% stated using specifically the IPSS-score. Although not indicated in that case, both abdominal or transrectal ultrasonography and PSA measurement were commonly used at BPH diagnosis.

The mean treatment duration was 5.2 ± 3.2 years. The overview of medications prescribed is reported in Table 1. The majority of physicians prescribed combination therapies as second-line treatment of LUTS (94.8%). The main reasons of prescription were the following: monotherapy inefficiency (74.4%), LUTS severity (53.8%), preventive measures aimed to avoid complications (23.1%) or invasive treatment (29.5%).

The mean current treatment duration was 2.4 ± 2.5 years (median: 1.8 years; range: 0–10.9) for monotherapies and 1.3 ± 1.5 years (median: 8 months; range: 0–10.5) for

combination therapies. Since their treatment initiation, 47.2% of patients received at least one treatment modification. In 69.3% of patients, these modifications were referred either to a switch to another pharmacological class or to a drug combination.

The mean IPSS-score was 10.3 ± 6.5 points (median: 9 points), while 52.1% and 9.8% of treated patients had moderate and severe symptoms, respectively.

Treatment outcomes

The patient-outcome data issued from questionnaires completed by 718 (65.4%) patients were analyzed globally and for three groups of patients defined by their treatment history: 434 patients (60.4%) with stable treatment (i.e., without treatment modification during last 12-month), 151 patients (21.0%) with recent initiation of treatment (treated less than 12-month) and a third group of 133 patients (18.5%), considered as being in the treatment failure, received at least one treatment modification during the last 12-month. Proportions of unsatisfactory outcomes significantly varied according to patient's treatment history ($P < 0.001$) (Fig. 1).

Among the whole sample, 42.3, 35.5, 18.5 and 2.6% of patients reported diminished quality of life (IPSS-Q8 ≥ 3), persisting symptoms (IPSS-score ≥ 12), symptoms worsening (VNS-score ≤ -1) and high bother (BII-score ≥ 9), respectively. More than half of patients (52.8%) had at least one of those unsatisfactory outcomes.

General HRQOL

All five-dimensions of EQ-5D were significantly different between severity classes (<0.001). Patients with moderate–severe symptoms especially reported some or extreme problems in 'Pain/Discomfort' (66.1–79.7%) and 'Anxiety/Depression' (45.8–53.8%) (Fig. 2).

The mean utility derived from EQ-5D-index results was 0.84 ± 0.19 and was significantly different among severity groups: 0.90 ± 0.12 , 0.81 ± 0.21 , 0.73 ± 0.25 (<0.001) for mild, moderate and severe LUTS, respectively. To determine properly the relationship between LUTS and EQ-5D utility index, an additional approach based on multivariate method was performed (Table 2). This included available variables known to have a potential impact on general HRQOL, such as socio-demographics and comorbidities. In Model 1, each incremental unit of IPSS-score represented a significant decrease in EQ-5D utility index (-0.009 [-0.012 ; -0.007]). Taking patients with mild LUTS as reference, Model 2 showed a significant negative impact on EQ-5D utility index for those patients suffering from moderate (-0.096 [-0.127 ; -0.065])-to-severe LUTS (-0.159 [-0.210 ; -0.107]). In Model 3,

Table 1 Patients' characteristics

	Overall patients <i>n</i> = 1,098*	[50–60] years <i>n</i> = 117	[61–70] years <i>n</i> = 371	[71–80] years <i>n</i> = 417	>80 years <i>n</i> = 191
<i>Diagnosed by</i>					
General practitioner	959 (87.6%)	108 (92.3%)	326 (88.1%)	358 (86.3%)	165 (86.4%)
Urologist	136 (12.4%)	9 (7.7%)	44 (11.9%)	57 (13.7%)	26 (13.6%)
<i>Diagnosis mode</i>					
Questioning	886 (80.7%)	95 (81.2%)	295 (79.5%)	335 (80.3%)	160 (83.8%)
Digital rectal examination	722 (65.8%)	68 (58.1%)	237 (63.9%)	292 (70.0%)	124 (64.9%)
PSA	635 (57.8%)	71 (60.7%)	219 (59.0%)	242 (58.0%)	101 (52.9%)
Ultrasonography	614 (55.9%)	71 (60.7%)	212 (57.1%)	228 (54.7%)	101 (52.9%)
Creatininemy	69 (6.3%)	8 (6.8%)	29 (7.8%)	26 (6.2%)	5 (2.6%)
Urinalysis	56 (5.1%)	8 (6.8%)	22 (5.9%)	16 (3.8%)	9 (4.7%)
Symptom score	40 (3.6%)	4 (3.4%)	15 (4.0%)	15 (3.6%)	6 (3.1%)
Dipstick urine analysis	11 (1.0%)	2 (1.7%)	3 (0.8%)	5 (1.2%)	–
<i>Disease duration</i>					
Mean in years ± SD	6.2 ± 5.1	3.3 ± 2.8	5.0 ± 3.7	6.8 ± 5.3	9.0 ± 6.4
≤5 years	582 (53.0%)	92 (78.6%)	236 (63.6%)	193 (46.3%)	59 (30.9%)
>5 years	516 (47.0%)	25 (21.4%)	135 (36.4%)	224 (53.7%)	132 (69.1%)
<i>BPH-associated comorbidities</i>					
Acute urinary retention	48 (4.4%)	4 (3.4%)	16 (4.3%)	12 (2.9%)	15 (7.9%)
Hypertension	676 (61.6%)	58 (49.6%)	211 (56.9%)	278 (66.7%)	127 (66.5%)
Type-II diabetes	184 (16.8%)	21 (17.9%)	59 (15.9%)	76 (18.2%)	28 (14.7%)
Dyslipidemia	489 (44.5%)	49 (41.9%)	163 (43.9%)	200 (48.0%)	76 (39.8%)
<i>Body mass index</i>					
Mean in Kg/m ² ± SD	27.0 ± 3.9	27.2 ± 3.9	27.2 ± 4.0	27.1 ± 3.9	26.4 ± 3.5
Median	26.5	26.7	26.5	26.6	26.3
<i>Current treatment duration</i>					
Mean duration in years ± SD	2.2 ± 2.4	1.7 ± 2.1	2.0 ± 2.2	2.0 ± 2.2	2.7 ± 2.8
Median	1.6	0.9	1.4	1.8	2.1
<i>Treatment type</i>					
Monotherapies	908 (82.7%)	96 (82.1%)	310 (83.6%)	348 (83.5%)	152 (79.6%)
Alpha-blocker	528 (58.1%)	62 (64.6%)	177 (57.1%)	223 (64.1%)	65 (42.8%)
Plant extract	242 (26.7%)	26 (27.1%)	94 (30.3%)	78 (22.4%)	43 (28.3%)
5-alpha-reductase inhibitor	138 (15.2%)	8 (8.3%)	39 (12.6%)	47 (13.5%)	44 (28.9%)
Combinations	190 (17.3%)	21 (17.9%)	61 (16.4%)	69 (16.5%)	39 (20.4%)
Alpha-blocker + plant extract	94 (49.7%)	11 (52.4%)	27 (44.3%)	39 (56.5%)	17 (44.7%)
Alpha-blocker + 5-alpha-reductase inhibitor	84 (44.4%)	8 (38.1%)	32 (52.5%)	24 (34.8%)	20 (52.6%)
5-alpha-reductase inhibitor + plant extract	11 (5.8%)	2 (9.5%)	2 (3.3%)	6 (8.7%)	1 (2.6%)

* Including two patients for whom data on age were missing

patients presenting at least one unsatisfactory outcome had an EQ-5D utility index significantly altered compared to others (−0.091 [−0.120;−0.063]).

Discussion

Despite medical treatment, this study's results showed that half (52.8%) of the BPH population still had unsatisfactory

outcomes. However, it is not clear whether this is due to the limited therapeutic effect of the available drugs or to their inappropriate use. IPSS-Q8 was the most frequently affected aspect (42.3% of patients). Furthermore, significant differences in those unsatisfactory outcomes were observed according to the treatment history. The highest burden was observed in the 'recent therapeutic failure' group, where 69.2% of patients had at least one of the described criteria.

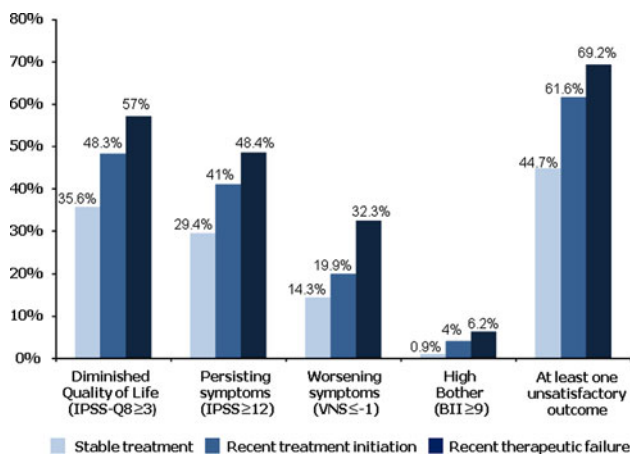


Fig. 1 Outcomes according to treatment history

According to current clinical guidelines, the medical needs of men with LUTS can now be met by general practitioners in a primary care setting [18]. Indeed in our study, patients were diagnosed by GPs and only a small proportion of them (12.4%) by urologists. Diagnostic approaches, mentioned in LUTS management and follow-up, include several clinical assessments as ultrasonography, digital rectal examination and PSA measurement. Guidelines for LUTS management recognize the importance of the assessment of patient health outcomes using LUTS-specific questionnaires [2, 19]. The results of our study suggest that these tools were used only by a small number of physicians who preferred the ‘usual’ informal questioning of patients.

Most patients were treated with monotherapy, frequently with alpha-blockers (58.1%) but also with 5-ARIs in particular among elderly patients. Considering the long natural history of BPH and a well-known correlation of LUTS severity and age, this may be explained by a depletion effect of alpha-blockers leading to a switch to 5-ARI. Potential sexual side effects of 5-ARI may be also more acceptable to older patients. The proportion of prescribed combination therapies was not negligible (17.3%) and may reveal the magnitude of unmet needs with monotherapies. This rate appeared to be consistent with the one previously reported among patients treated by urologists (22.0%) [20]. Differences in mechanisms of action provide additional arguments to use combination therapies (i.e., rapid improvement of symptoms with alpha-blockers and a sustained relief of symptoms with 5-ARIs) [21]. As well, a possible synergistic effect between these two pharmacological classes has been suggested in two randomized clinical trials, the MTOPS study (finasteride–doxazosin) [16] and the recent CombAT study (dutasteride–tamsulosin). Although not evidence based, the combination of phytotherapy and alpha-blockers was prescribed in nearly

half of cases. An additional prescription of alpha-blockers to patients that were already treated with phytotherapy can probably explain this. However, in consistency with clinical guidelines, the combination of α -blockers and 5-ARI was also widely used (44.4%). Initial treatment was modified for 47.2% of patients also indicating unmet medical needs.

The results of this study suggest that all dimensions of patients’ HRQOL measured with EQ-5D significantly decreased with LUTS severity. However, two-dimensions appeared particularly altered: ‘Pain/Discomfort’ and ‘Anxiety/Depression’, suggesting that LUTS profoundly influences the general well-being of patients as shown in previous works [21–28]. As a generic tool, EQ-5D-index allows indirect comparisons with those in other common chronic diseases. For example, in our study, patients with moderate and severe LUTS reported EQ-5D utility index scores similar to patients suffering from chronic obstructive pulmonary disease (0.76 ± 0.21) [26], type-II diabetes (0.79 ± 0.22) [27] or urinary incontinence (0.79 ± 0.22) [28]. An important strength of this HRQOL analysis was its attention to the effects of potential confounders. Although patients with higher symptoms severity were older and more likely to have comorbidities, IPSS-score (Model 1), classes of severity (Model 2) and presence of unsatisfactory outcomes (Model 3) were still significant independent determinants of general HRQOL. These data clearly indicate that the negative impact of LUTS on HRQOL does not appear to be related to other factors such as comorbidities linked to age of patients.

Several limitations should be considered when interpreting the results of our study. Participating GPs were firstly selected at random, but, since participation was voluntary, it is possible that participants may differ from GPs who declined to participate and, as a consequence, leading to a less representative sample. However, the strength of our study was the availability of the LPD database which allowed comparison of included and non-included patients on several characteristics. The study population was also shown to represent the entire disease population on several characteristics (e.g., age and comorbidities).

Our findings provide evidence that unmet medical needs remain high for a large proportion of patients in general practice where many of them continue to receive monotherapy or even aberrant combined treatment. The patient outcomes should be regularly reassessed during their follow-up and considered more carefully at the treatment decision making. As only a limited number of GPs followed scientific clinical directives, developments of advanced guidelines and effective strategies with GPs to optimize BPH medical management and to persuade men with LUTS to present earlier are required to improve patient outcomes.

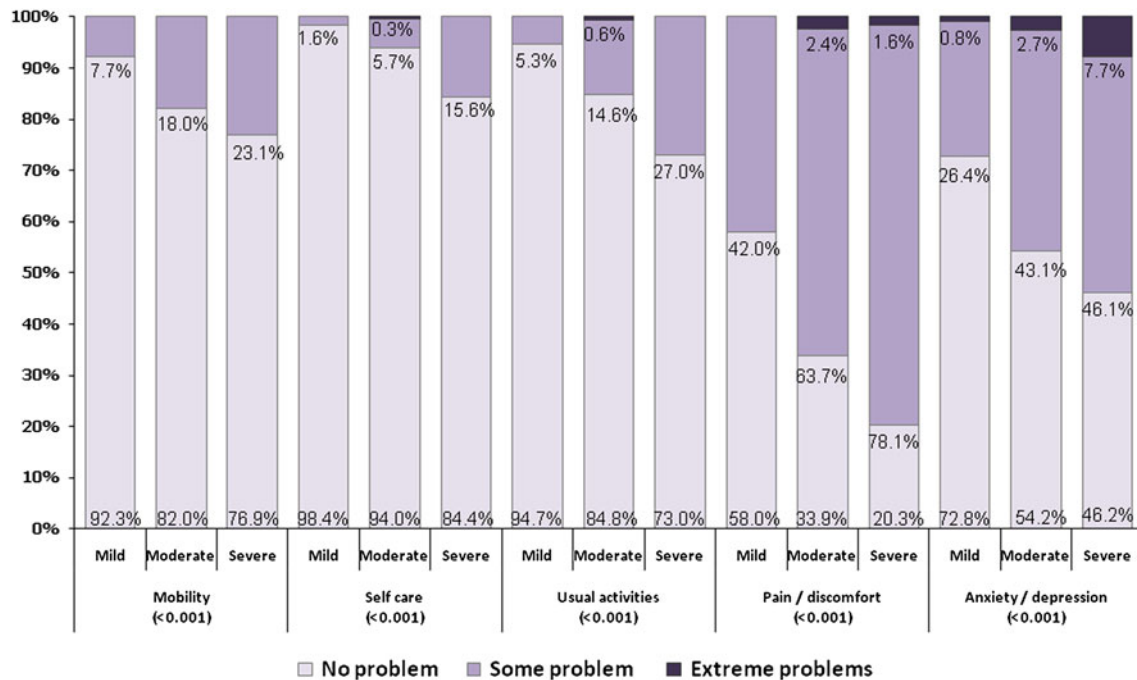


Fig. 2 EQ-5D results by dimension and according to IPSS severity classes: mild (1–7), moderate (8–19) and severe (20–35)

Table 2 Variables significantly associated with general quality of life (EQ-5D utility index scores): results of three multivariate linear regressions

Dependent variable: utility*	Model 1		Model 2		Model 3	
	Coefficient estimation [†]	IC 95%	Coefficient estimation [†]	IC 95%	Coefficient estimation [†]	IC 95%
Intercept	1.096	[0.942; 1.250]	1.349	[1.227; 1.470]	1.315	[1.195; 1.434]
IPSS-score (for one unit increment)	−0.009	[−0.012; −0.007]	–	–	–	–
LUTS severity (mild symptoms as reference)						
Moderate symptoms	–	–	−0.096	[−0.127; −0.065]	–	–
Severe symptoms	–	–	−0.159	[−0.210; −0.107]	–	–
LUTS treatment unsatisfactory outcome (at least one vs. none)	–	–	–	–	−0.091	[−0.120; −0.063]
Others significant variables [‡]						
Age (for one-year increment)	−0.006	[−0.007; −0.004]	−0.006	[−0.007; −0.004]	−0.006	[−0.007; −0.004]
Neuropsychiatric disorders (yes vs. no)	−0.097	[−0.139; −0.055]	−0.097	[−0.139; −0.054]	−0.093	[−0.135; −0.052]
Cardiovascular risk factors (yes vs. no)	−0.035	[−0.067; −0.003]	−0.032	[−0.064; −0.001]	−0.038	[−0.069; −0.006]
Joint diseases (yes vs. no)	NS	NS	−0.036	[−0.072; −0.001]	−0.037	[−0.072; −0.003]

* Utility reflects preference-based health-related quality of life derived from standardized instruments (i.e., EQ-5D) and which values range, by convention, from 1.0 (perfect health) to 0.0 (death)

[†] Coefficients represent changes in utility significantly associated with the following health conditions: presenting one additional unit in IPSS-score (Model 1), moderate or severe symptoms compared with mild symptoms (Model 2) and at least one unsatisfactory outcome compared with none (Model 3)

[‡] Other variables with a *P* value less than 0.25 in univariate analyses but not retained in final multivariate analyses were pulmonary diseases, gastro-intestinal disorders, renal insufficiency, back pain and education

NS not significant

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Conflict of interest ROF and FL have received consultancy fees from GlaxoSmithKline (GSK) with respect to their scientific and medical participation in this study concerning the treatment of BPH. MR has no conflict of interest in this project. ASI, CLF and FEC are employees of Laboratoire GSK who markets dutasteride, a molecule indicated for BPH treatment. EM and ASI received stipends from GSK for data analysis (ASI) or for coordination of the study (EM).

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