Medical management of benign prostatic hyperplasia: Results from a population-based study

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Abstract

Introduction: In men with bothersome lower urinary tract symptoms (LUTS), medical treatment usually represents the first line. We examined the patterns of medical management of benign prostatic hyperplasia (BPH) in the Montreal metropolitan area, within the context of a case control study focusing on incident prostate cancer.

Methods: Cases were 1933 men with incident prostate cancer. Population controls included 1994 age-matched men. In-person interviews collected sociodemographic characteristics and medical history, including BPH diagnosis, its duration, and type of medical treatment received. Baseline characteristics were compared by the chi-square likelihood test for categorical variables and by the students t-test for continuously coded variables.

Results: Overall, 1120 participants had history of BPH; of those 53.7% received medical treatment for BPH. Individuals with medically treated BPH, compared to individuals with medically untreated BPH, were older at index date [mean: 66.9 vs. 64.9 years, p<0.001)] and at diagnosis of BPH [mean: 62.3 vs. 60.3 years, p<0.001]. They also had a longer duration of BPH-history [mean: 4.7 vs. 4.0 years, p=0.02]. Regarding medical treatment, monotherapy was more often used than combination therapy [87.6% vs. 12.4%, p<0.001]. Alpha-blockers (69.9%) were most commonly used as monotherapy, followed by 5alpha-reductase inhibitors (5ARIs) (26.6%). Alpha-blockers plus 5ARIs were the most common combination therapy (97.3%).

Conclusions: Despite evidence from randomized, controlled trials for better efficacy with use of combination therapy, monotherapy consisting of alpha-blockers or 5ARI, in that order, is most frequently used. Additionally, 5ARI use was more common than previously reported (27% vs. 15%).

Introduction

BPH is the leading cause of LUTS in men older than 40 years.[1] In men with bothersome LUTS and who desire treatment, medical treatment usually represents the first line. American and Canadian guidelines recommend the use of alpha-adrenergic receptor blocking agents (alpha-blockers) and 5alpha-reductase inhibitors (5ARIs), either as monotherapy or combination therapy. Anti-cholinergic agents and phosphodiesterase-5 inhibitors were recently suggested as add-ons or alternatives.[2,3] To the best of our knowledge, trends of prescribing patterns for BPH medication in Canada have not been defined at population level. Only two Canadian studies review the topic without providing statistical data on the patterns of use of BPH medication.[4,5] Based on lack of Canadian data, we rely on a case-control study design to describe the contemporary practice patterns for medical management of BPH in the Montreal metropolitan area and compare it to the literature.

Methods

Study population

All analyses were based on data from the population-based case-control study PROtEuS (Prostate Cancer and Environment Study), which was conducted in predominantly French-speaking Montreal men, between 2005 and 2012, as previously described.[6-8] In brief, cases were men with histologically confirmed, newly diagnosed prostate cancer who were actively ascertained through pathology departments across seven of nine French hospitals in the Montreal metropolitan area between 2005 and 2009. The ascertainment covered >80% of all cases diagnosed in the base area. Concurrently, population controls without prostate cancer diagnosis at the time of the interview were randomly selected from Quebec's French permanent electoral list and were frequency matched to cases by age (five-year intervals). Both cases and controls had to be Canadian citizens, residents of Montreal metropolitan area, and aged <76 years at diagnosis or recruitment (index date).

Study participants represented 79.4% of eligible cases and 55.5% of eligible controls. Reasons for non-participation among cases and controls were refusal (94% and 86%, respectively), unable to trace (3% and 11%, respectively), death with no proxy respondent available (2% and 1%, respectively), and language barrier (1% for both groups). Additionally, 1% of eligible controls were too sick to participate with no available proxy. The protocol was approved by Ethics Committees of all participating institutions. All subjects provided informed consent.

Data collection

In person interviews, performed in a single patient encounter, collected detailed information about sociodemographic characteristics (ancestry, family income, educational level, lifestyle factors) and medical history, including number of physician visits per year, timing of last prostate cancer screening (digital rectal exam and/or prostate-specific antigen [PSA] tests) in the last five years prior to index date.

Of relevance to the current analysis, the questionnaire focused on absence or presence of BPH-history ("Had you ever been diagnosed with BPH?" If yes, "How old were you when you were first diagnosed with BPH?"). Based on the interval between BPH diagnosis and index date, BPH history was classified as: a) any BPH history (regardless of its timing prior to index date) and b) non-concurrent BPH history (defined as BPH diagnosis at least one year prior to index date). The questionnaire also addressed BPH medication exposure ("Did you take medication/s for this disease? If yes, which medication/s?", "How old were you when you started taking BPH medication/s?" and "How old were you when you stopped taking BPH medication/s?"). Combination therapy was defined as the concurrent use of two or more classes of BPH medications.

Statistical analysis

The chi-square was used to test for significance of difference in proportion and the students t-test was used to test for significance of difference in means. All tests were two-tailed and p values <0.05 were considered statistically significant. All statistical analyses were performed using RStudio v0.98.953 (R Project for Statistical Computing, *www.R-project.org*).

Results

Overall, 3927 men in the case-control study (PROtEuS) were included. Of those, 137 provided no information on BPH status, which resulted in 3790 evaluable participants (1834 prostate cancer cases and 1956 controls). Our study focused on individuals who reported BPH diagnosis (1120 out of 3790 participants, 29.6%). Of 1120 participants with self-reported BPH diagnosis, 601 (53.7%) received medical treatment. The proportions of medically treated men differed between cases and controls [338 out of 717 cases (47.1%) vs. 263 out of 403 controls (65.3%), respectively; p=0.002]. (Fig.1).

Compared to individuals with medically untreated BPH, individuals with medically treated BPH were older at index date (mean: 66.9 vs. 64.9 years, p<0.001), as well as at diagnosis of BPH (mean: 62.3 vs. 60.3 years, p<0.001). Medically treated men also had longer duration of BPH his-

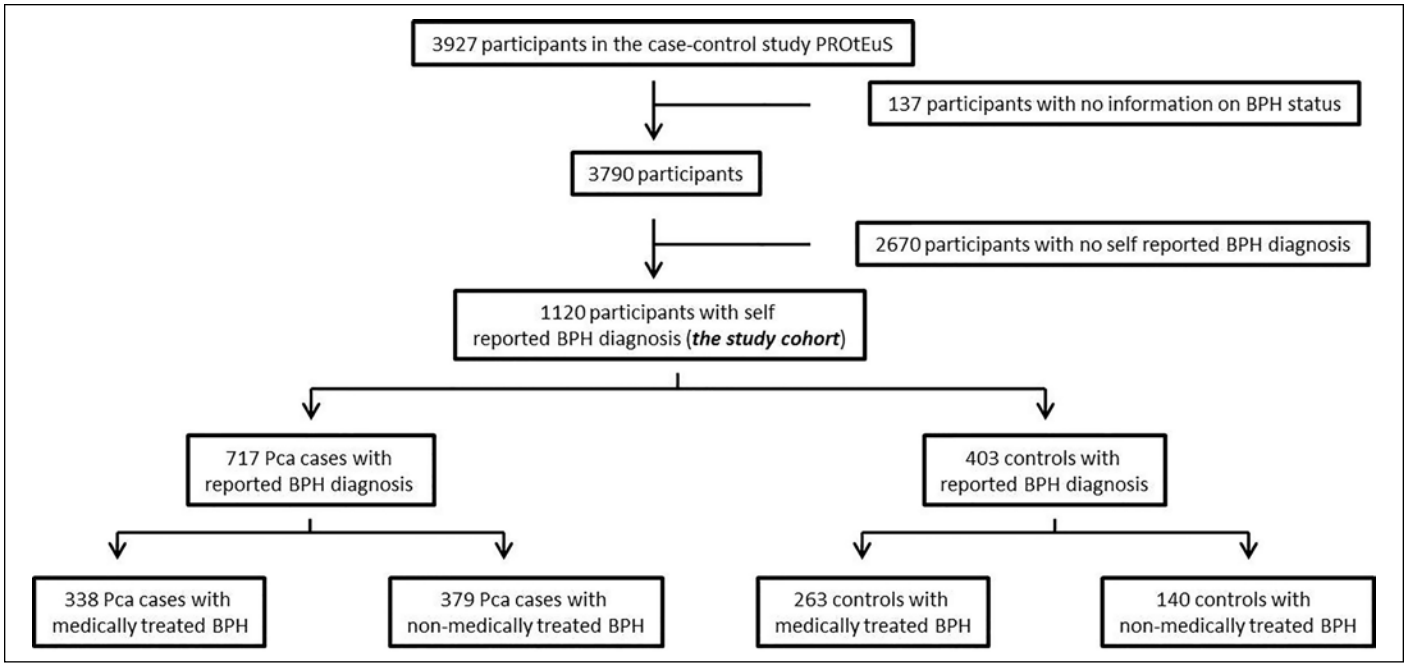

Fig. 1. Flow chart of patient selection.

tory (mean: 4.7 vs. 4.0 years, p=0.02), lower annual family income (income <$50 000 CAD/year: 318 (52.9%) vs. 220 (42.4%), p<0.01)), and reported more frequent annual physician visits (more than one physician visit per year: 552 (91.5%) vs. 424 (82%), p<0.001)) (Table 1). No meaningful differences in the distribution of those results were recorded after stratification according to case vs. control status except for age at index date (mean: 65.9 vs. 68.1 years, p<0.001).

Detailed information concerning the number of BPH medications and medication classes were available for 460 of 601 (76.5%) individuals with medically treated BPH. Monotherapy was more frequently reported as initial therapy than combination therapy (87.6% vs.12.4%, p<0.001). After stratification according to case vs. control status, monotherapy was more frequently reported by cases than controls (91.2% vs. 82.7%, p=0.02) (Table 2).

Of monotherapy types, alpha-blockers (69.9%) were most frequently reported, followed by 5ARIs (26.6%), phytotherapy (2.3%) and anti-cholinergics (1.2%). Of combination therapy types, alpha-blockers plus 5ARIs (97.3%) were most frequently used, followed by 5ARI plus anti-cholinergics (2.7%). Analyses after stratification according to case vs. control status showed virtually the same results (Table 2). Sub-analyses exclusively focusing on individuals with non-concurrent BPH history failed to result in clinically meaningful differences (data not shown).

Discussion

BPH is the leading cause of LUTS in men >40 years.[1] It is a major public health issue, especially in industrialized countries with aging populations.[9,10]

Table 1. Patients characteristics of 1120 individuals with BPH symptoms, stratified according to medically treated and medically untreated BPH patients

	Total	Medically treated BPH	Not medically treated BPH	*p* value
Total, n	1120	601	519	
Age				
Mean (median)	66 (67)	66.9 (68)	64.9 (65)	<0.001
Range	62–71	64–72	61–70	
Age at BPH-diagnosis, mean (median)	61.4 (62)	62.3 (63)	60.3 (61)	<0.001
BPH-duration, years, mean (median)	4.4 (2)	4.7 (3)	4 (2)	0.02
Ancestry, n (%)				0.3
European	983 (87.8)	527 (87.3)	456 (88.2)	
Black	58 (5.2)	33 (5.5)	25 (4.8)	
Asian	20 (1.8)	13 (2.2)	7 (1.4)	
Other	56 (5.0)	30 (5.0)	26 (5.0)	
Unknown	3 (0.3)	0 (0.0)	3 (0.6)	
Educational level, n (%)				0.5
Elementary	235 (21.0)	135 (22.4)	100 (19.3)	
High school	319 (28.5)	167 (27.7)	152 (29.4)	
College	187 (16.7)	104 (17.2)	83 (16.1)	
University	378 (33.8)	196 (32.5)	182 (35.2)	
Other (unknown, missing)	1 (0.1)	1 (0.2)	0 (0.0)	
Annual family income, n (%)				<0.001
<$50 000	538 (48.0)	318 (52.9)	220 (42.4)	
≥$50 000	480 (42.9)	233 (38.8)	247 (47.6)	
Other (refusal, do not know, missing)	102 (9.1)	50 (8.3)	52 (10.0)	
Annual physician visits (frequency), n (%)				<0.001
<1 visit/year	142 (12.7)	50 (8.3)	92 (17.8)	
≥1 visit/year	976 (87.1)	552 (91.5)	424 (82.0)	
Unknown	2 (0.2)	1 (0.2)	1 (0.2)	
Timing of last PSA/DRE testing, n (%)				0.9
≤2 years	1076 (96.1)	576 (95.8)	500 (96.3)	
>2 years	28 (2.5)	19 (3.2)	9 (1.7)	
Never screened	4 (0.3)	0 (0.0)	4 (0.8)	
Unknown	12 (1.1)	6 (1)	6 (1.2)	

BPH: benign prostatic hyperplasia; DRE: digital rectal examination; PCa: prostate cancer; PSA: prostate-specific antigen.

Medical treatment of BPH is a success story; it resulted in a dramatically decreased number of transurethral resections of the prostate.[11] Except for absolute contraindication for medical management (renal insufficiency due to BPH, urinary retention refractory to medical treatment), medical treatment is the standard of care for men with bothersome LUTS in Western countries. Relative contraindications for medical management include failure of medical treatment, bladder stone(s), recurrent urinary tract infections, and persistent gross hematuria due to BPH.[3] The rationale for combination therapy in medical management of BPH hinges on pivotal randomized, placebo-controlled trials.[12,13] These showed that combination therapy (doxazosin and finasteride) is superior to monotherapy in terms of clinical progression, e.g. acute urinary retention, urinary incontinence, renal insufficiency, or recurrent urinary tract infection.[12] Similarly, combination therapy with tamsulosin and dutasteride vs. monotherapy decreased the risk of acute urinary retention, BPH-related surgery, clinical progression, and symptoms deterioration in men with baseline prostate volume ≥40 ml and PSA ≥1.5 ng/ml.[13]

Few studies examined the patterns of BPH medication use with focus on the number and type of agents used.[9,10,14-17] Moreover, no Canadian study addressed this topic with respect to actual treatment patterns. Based on this unmet need, we completed a detailed analysis of BPH-medication use in the metropolitan Montreal area. Our data originated from a case-control design described elsewhere.[6,7]

Several important findings were identified:

First, prevalence of self-reported BPH-diagnosis was 29.1%. This finding is similar to previously reported rates of moderate to severe LUTS that ranged from 26% in 40- to 49-year-old men to 45% among septuagenarians).[18-21]

Second, we found that medically treated BPH patients (601 individuals) were older and had longer duration of BPH history than their untreated counterparts. This result confirms the pivotal effect of age in the diagnosis and management of BPH.[1]

Third, we showed that individuals with annual family income <$50 000 CAD are more frequently treated with BPH medications than others. This implies that lower income does not represent a barrier to BPH medication access. Concurrently, it's important to note that individuals with a lower family income were older (≥65 years) (data not shown).

Fourth, men with medically treated BPH visited their physicians more often than others (more than one visit per year: 91.5% vs. 82%). This finding may be considered obvious, however, it was not previously reported.[9,10,14,16]

Fifth, with regard to agents used in monotherapy setting, alpha-blockers were the most commonly used drug class in the medical management of BPH. The rate in our study was 69.9% vs 60–90% in other studies.[9,10,14,16,17] 5ARI represented the second most frequently used form of medical management of BPH. Its rate was 27% vs. to 10–15% in previous reports from Europe and the U.S.[9,14,16,17] This finding reflects the adoption of results of clinical trials indicating that 5ARI have greater effectiveness in delaying BPH progression, especially in older men.[12,13] It is also of interest to note that nine patients (2.3%) received phytotherapy alone, a practice that dose not reflect guideline recommendations; however, this proportion is lower than previously reported in other studies (17–30%).[10,14] It is important to note that none of the above studies focused on Canadian patients.

Last but not least, we found that monotherapy still has the upper hand (87.6%), despite strong evidence from randomized, placebo-controlled trials supporting the benefit of combination therapy (alpha-blocker plus 5ARI) when symptom control, disease progression, and risk of BPH-surgery are the endpoints of interest.[12,13] Our results regarding the rate of monotherapy treatment are in agreement with reports from Europe and the U.S., where monotherapy was the most common treatment modality (80–90%).[9,14,16]

Our study has several strengths, for example large sample size, detailed information on use of BPH medications (drug classes, concomitant use of multiple medications, etc.), in-

Table 2. Pattern of medical treatment in 601 men with medically treated BPH, stratified according to case and control status

	Overall	Controls	Cases	*p* value
Total, n (%)	601 (100)	263 (65.3)	338 (47.1)	0.002
Initial therapy, n (%)				0.02
Monotherapy	403 (87.6)	163 (82.7)	239 (91.2)	
Combination therapy	57 (12.4)	34 (17.3)	23 (8.8)	
Drug class of monotherapy at initial therapy, n (%)				0.40
Alpha-blocker	276 (69.9)	109 (68.1)	167 (71.4)	
5ARI	105 (26.6)	44 (27.5)	60 (25.6)	
Anti-cholinergic	5 (1.2)	1 (0.6)	4 (1.7)	
Phytotherapy	9 (2.3)	6 (3.8)	3 (1.3)	
Drug class of combination therapy, n (%)				0.04
Alpha-blocker + 5ARI	73 (97.3)	45 (97.8)	28 (96.6)	
Alpha-blocker + anti-cholinergic	2 (2.7)	1 (2.2)	1 (3.4)	

5ARI: 5-alpha reductase inhibitor; BPH: benign prostatic hyperplasia; PCa: prostate cancer.

person interviews and its population-based design. The latter allows for both detailed and comprehensive coverage of BPH cases in the general population.

Our study also has limitations. The first relates to possible reporting errors in BPH status and timing. These variables were based on self-reports of physician diagnoses. We have no direct way to ascertain BPH reports. Nevertheless, in 93% of cases that were reported as not having a history of BPH, we could not find mention of BPH in the medical records of prostate cancer diagnosis. For recruitment purposes, the study was presented to subjects as a non-specific study focusing on prostate diseases. This may have sensitized both cases and controls to report prostate-related conditions, including BPH. It may also have enhanced the participation of eligible controls with BPH, resulting in a selection bias. However, 21% of controls reported BPH history, which is in agreement with reported prevalence rates among Canadian men.[22]

It is important to consider that our study comprised only men aged 72 years or less. This finding restricts, to some extent, the generalizability of our findings, since many men treated for BPH are older than our upper age limit. That said, several studies focusing on medical management of BPH relied on a similar age distribution to ours. For example, Hollingsworth et al focused on North American patients of whom 77.2% were age 70 years or younger,[16] Cindolo et al examined Italian patients whose age averaged were from 71.6–72.3 years,[9] Lukacs et al described a French cohort of medically treated BPH patients whose age averages were between 68 and 70 years,[14] and Nichol et al reported on a North American cohort in which 67.3% of patients were aged 74 years or less.[15] In consequence, the age distribution of our cohort is somewhat younger than most reports; however, our age distribution remains appropriate for the pathology and is comparable to other studies.

Finally, the clinical details, such as PSA and prostate volume, were unavailable. Toxicity and causes of stopping medications were also unknown.

Conclusion

Monotherapy consisting of alpha-blockers or 5ARIs, in that order, is more frequently used in comparison to combination therapy. Additionally, the use of 5ARI as a monotherapy was more commonly identified than in previous reports (27% vs.15%).

Competing interests: The authors declare no competing financial or personal interests.

This paper has been peer-reviewed.

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