Twelve-month medication persistence in men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia

J. S. Koh, K. J. Cho, H. S. Kim, J. C. Kim

SUMMARY
Aims: This study aimed to assess patients’ baseline characteristics and provider factors influencing the continuation of medication for 12 months in patients who were newly diagnosed with benign prostatic hyperplasia (BPH). Methods: This study was conducted in patients with newly diagnosed lower urinary tract symptoms (LUTS)/BPH (age ≥ 40) who received either one or a combination of the two pharmacological classes of drugs (alpha-blockers or 5-alpha-reductase inhibitors) from January 2008 to January 2010. Patient demographics and clinical data were assessed from the electronic patient records and telephone surveys. Persistence was defined as continuation of all BPH medications prescribed at the start of the first treatment. Logistic regression analysis was used to evaluate the association between 12-month persistence and patient or provider factors. Results: Of the 789 newly diagnosed LUTS/BPH patients, 670 (84.9%) were included in the study. Twelve-month persistence for LUTS/BPH medication was 36.6%. Independent predictors of 12-month medication persistence included larger prostate volume, higher prostate specific antigen, having an adequate income and a good patient–doctor relationship. Important reasons for discontinuation were resolved symptoms (31.1%), no improvement in symptoms (23.7%) and adverse events (20.0%). Conclusions: About two-thirds of newly diagnosed LUTS/BPH patients discontinued medications within 1 year of starting treatment. We found several potential patient and provider factors associated with persistence, which could be exploited to increase continuation of treatment in future clinical settings.

What’s known
The effectiveness of treatment with alpha-blockers and 5-alpha-reductase inhibitors or their combination has been shown to significantly reduce symptoms and/or progression of benign prostatic hyperplasia (BPH). Although the continued use of prescribed medication is very important, medication use commonly declines over time, leading to potentially avoidable lower urinary tract symptoms (LUTS)/BPH related complication. Therefore, it is important to investigate factors associated with LUTS/BPH medication persistence.

What’s new
This present study is unique in correlating persistence not only with demographic data and subjective symptoms of LUTS/BPH patients, but also with objective clinical data and provider factor. Twelve-month medication persistence was very low and 74% of newly diagnosed LUTS/BPH patients discontinuing treatment within 1 year. The chance of medication persistence was highest for patients with larger prostate volume, higher prostate specific antigen, an adequate income and a good patient–doctor relationship.

Introduction
Benign prostatic hyperplasia (BPH) is a progressive disease in ageing men and a common cause of lower urinary tract symptoms (LUTS) (1,2). The prevalence of BPH increases from approximately 50% at 60 years to 90% in men older than 85 years (3). Treatment options for BPH/LUTS are watchful waiting, phytotherapy, pharmacological therapy and minimally invasive surgery. Over the past two decades, treatment of symptomatic BPH has shifted markedly from surgery to drug therapy (4).

Two classes of drugs, alpha-blockers and 5-alpha-reductase inhibitors, have been widely used in the management of LUTS/BPH, and they have been shown to significantly reduce symptoms and/or progression of BPH in a substantial number of randomised clinical trials (5–9).

Although the continued use of prescribed medication is key to improving patient outcome, medication use commonly declines over time, leading to potentially avoidable acute urinary retention, BPH related surgery, urinary tract infection, stone formation, neurogenic bladder, and renal insufficiency. Information on longitudinal medication use and the reasons for medication discontinuation in LUTS/BPH patients are limited. Prior studies have identified multiple barriers to long-term continuation of medications including having only one type of symptom, normal prostate specific antigen (PSA), younger age, and lower chronic disease score (10). However, there has been no systematic study of the association
between medication persistence and symptom severity, objective clinical data [e.g. prostate volume, maximum flow rate ($Q_{\text{max}}$), post-void residual (PVR)], or patient–provider communication which might be more important than the variety of symptoms.

The goal of this study was to measure LUTS/BPH medication persistence from the first day of taking a medication up to 12 months in a sample of patients from our hospital. This study sought to determine the 12-month medication persistence and reasons for medication discontinuation, as well as to compare patient baseline characteristics and provider factors between persistent and non-persistent medication use.

**Materials and Methods**

The study was conducted at the Clinical Trials Center of the Catholic University of Korea. The study protocol was approved by the Institutional Review Board.

**Patients and Methods**

This retrospective study was conducted in patients with newly diagnosed LUTS/BPH (age $\geq 40$) who received either one or a combination of the two pharmacological classes of drugs (alpha-blocker or 5-alpha-reductase inhibitor) from January 2008 to January 2010 in our hospital. Reasons for exclusion from the study were: (i) PSA level $> 10$ ng/ml or prostate cancer detected by prostate biopsy or (ii) patients who could not respond because of refusal to answer, illness severity, speech or language deficit, cognitive dysfunction, and/or death. Twelve-month persistence was defined as continuation of all BPH medications prescribed at the start of the first treatment (11,12). The goal of this study was to measure BPH medication persistence. Persistence included switching from the first type of drug to another compound (e.g. tamsulosin to alfuzosin) or the addition of another class of drug (e.g. from an alpha-blocker or 5-alpha-reductase inhibitor monotherapy to combination therapy). Patients were considered non-persistent if they discontinued a medication, regardless of the reasons. Baseline assessments included demographic data (i.e. age, education level, marital status, work, and income status), medical history, International Prostate Symptom Score (IPSS), $Q_{\text{max}}$, PVR, PSA, and prostate volume using transrectal ultrasound. Most patients visited hospital at once per a month and patients who discontinued a medication were asked to select a response that most closely reflected the reason by telephone survey within a month after discontinuation: side-effects, cost, medication not helping, or others. All included patients were asked to provide subjective data on overall satisfaction with communication with their doctor by telephone survey within a month after discontinuation in non-persistent group and 1 year after starting medication in persistent group: ‘excellent’, ‘good’, ‘fair’, or ‘poor’.

**Statistical analysis**

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS version 15.0 for Windows; SPSS, Inc., Chicago, IL). Continuous variables were reported as mean $\pm$ standard deviation and categorical variables were expressed as frequencies with percentages. The Mann–Whitney $U$-test was used for variables to evaluate the associations between 12-month persistence and patient and provider characteristics. A multivariable logistic regression analysis was used to further evaluate the influence of demographic, clinical, and other factors on 12-month persistence and included the following covariates: patients’ baseline characteristics including age, prostate volume, PSA and household income. An additional potential covariate was the provider communication perceptions received by telephone survey responses. The analysis was adjusted for all variables that showed an association with 12-month persistence in the Mann–Whitney $U$-test. A 5% level of significance was used for all statistical testing.

**Results**

Of the 789 newly diagnosed LUTS/BPH patients, a total of 119 patients (15.1%) were excluded for reasons listed in Figure 1, leaving a final sample volume of 670 patients. The overall 12-month persistence for LUTS/BPH medication was 36.6%. Patient variables associated with 12-month persistence are shown in Table 1. Factors associated with 12-month persistence included age ($p = 0.035$), prostate volume ($p < 0.001$), PSA level ($p = 0.007$), having an adequate income ($p = 0.019$), and overall satisfaction with communication with doctor ($p = 0.001$).

The multivariable predictors of 12-month persistence are shown in Table 2. Prostate volume (24–33 cm$^3$: OR 1.73, 95% CI 1.14–2.61; $> 33$ cm$^3$: OR 1.51, 95% CI 1.00–2.26), and PSA (OR 1.72, 95% CI 1.07–2.77) were independent predictors of 12-month persistence. Additional factors associated with 12-month persistence included having an adequate income to meet the needs of the household (OR 0.71, 95% CI 0.51–0.99) and overall satisfaction with communication with doctor (OR 0.50, 95% CI 0.33–0.76). The probability of 12-month persistence was higher in patients with larger prostate volume, higher PSA, higher income, and good patient-doctor relationships.
Of the 670 patients, 425 patients (63.4%) discontinued treatment within 1 year of starting, and among them, 213 patients (31.9%) discontinued treatment within 3 months of starting (Figure 1). Important reasons were resolved symptoms (n = 132, 31.1%), improvement in symptoms (n = 101, 23.7%) and adverse events (n = 85, 20.0%) (Table 3). Of the 670 treated patients, 52 patients (7.8%) switched their first type of drug to another compound within 12 months of starting the first treatment (Figure 2). Patients primarily switched because of adverse events, no improvement in symptoms, or based on recommendations from their doctor.

**Discussion**

This study is unique in correlating persistence not only with demographic data and subjective symptoms of LUTS/BPH patients, but also with objective clinical data such as initial PSA, prostate volume, Qmax, and PVR. We found very low 12-month persistence in medicinal therapy with 74% of patients discontinuing treatment within 1 year, and 31.9% of patients discontinuing treatment within 3 months. This is similar to the results of previous studies evaluating LUTS/BPH medication persistence (10,13,14).

Several baseline factors, such as PSA level and prostate volume predicted long-term persistence. Patients with higher PSA or larger prostate volume were more likely to continue treatment. Higher PSA or larger prostate volume indicates higher risk of disease progression (15), and it appeared that being informed of this risk by doctors may have caused patients to consider their disease in a more serious manner so that persistence increased. On the contrary, patients with normal PSA or smaller prostate volume may have found reassurance in this result and were less motivated to continue treatment (10). Further investigations are needed to support this hypothesis.

The self-reported financial variable was associated with long-term persistence. Participants were asked if their household income adequately met their needs. Those who responded ‘adequately’ or ‘more than adequately’ were 30% more likely to be persistent. Long-term persistence can be influenced by the provider through communication with patients. Persistence decreased by 50% in patients who responded ‘dissatisfied’ in the self-reported satisfaction with communication with their doctor. This finding is not limited to LUTS/BPH and has also been observed in other types of diseases. It appears that a good doctor–patient relationship increases patient persistence (16–18). This factor emerged as the most important among both patient and provider factors to maintain patient persistence. Therefore, doctors always need to be aware that they have to provide proper information on disease and medications in an easily
understandable way for their patients to improve their persistence.

There have been very few studies evaluating factors associated with LUTS/BPH medication persistence. A representative study, ‘The Triumph Project’, investigated the treatment persistence and adherence of 2214 LUTS/BPH patients. Younger patients, patients with only one type of symptom, and patients with less chronic co-morbidity were more likely to discontinue treatment early. Also, although there was no statistical significance, early discontinuation appeared to be lower in patients with storage symptoms than in patients who had voiding symptoms (10). As mentioned by the authors, this study was limited by the lack of an investigation of the association between symptom severity and medication persistence, which may be more important than the variety of symptoms. Our results revealed a tendency of increasing medication persistence with advancing age. However, subjective symptom severity and types of symptoms measured by IPSS did not affect persistence. In other words, symptom severity and types of symptoms in the initial stage of medication treatment do not have a significant effect on the continuation of medication. The reason for this finding is unclear. However, we think that the change of symptoms during therapy might have a bigger effect on persistence than symptom severity or types of symptoms at the first diagnosis. Further studies are necessary to confirm whether this is indeed the case.

We defined 12-month persistence as continuation of all BPH medications prescribed when treatment was first started. However, the goal of this study was to measure BPH medication persistence, and we also included patients in the persistence group if the first type of drug was switched to another compound or another class was added to the first type of drug. Of the 670 patients enrolled in our study, 52 (7.8%) patients switched their first type of drug to another

| Table 1 Patients’ baseline characteristics and 12-month medication persistence |
|---------------------------------|-----------------|-----------------|--------|
| Characteristics                | Persistent (n = 245) | Non-persistent (n = 425) | p-value |
| Mean age (years)               | 63.97 ± 9.01     | 62.24 ± 10.04    | 0.035*  |
| Education level                |                  |                  |        |
| College or above, n (%)        | 76 (31.0)        | 111 (26.1)       | 0.173   |
| Other, n (%)                   | 169 (69.0)       | 314 (73.9)       |         |
| Marital status, n (%)          |                  |                  |        |
| Married                        | 200 (81.6)       | 340 (80.0)       | 0.607   |
| Not married                    | 45 (18.4)        | 85 (20.0)        |         |
| Work status, n (%)             |                  |                  |        |
| Working                        | 155 (63.3)       | 257 (53.4)       | 0.474   |
| Not working                    | 90 (36.7)        | 168 (46.6)       |         |
| Medical history, n (%)         |                  |                  |        |
| Hypertension                   | 54 (22.0)        | 98 (23.1)        | 0.762   |
| Diabetes mellitus              | 36 (14.7)        | 59 (13.9)        | 0.772   |
| Erectile dysfunction           | 79 (32.2)        | 132 (31.1)       | 0.750   |
| IPSS total                     |                  |                  |        |
| Obstructive symptom score      | 16.14 ± 8.65     | 15.75 ± 8.79     | 0.272   |
| Storage symptom score          | 9.40 ± 5.57      | 9.09 ± 5.82      | 0.403   |
| Quality of life                | 7.06 ± 4.16      | 6.65 ± 4.05      | 0.228   |
| Q_max                          | 3.60 ± 1.29      | 3.64 ± 1.27      | 0.577   |
| Post-void residual (ml)        | 12.59 ± 5.47     | 13.02 ± 4.90     | 0.070   |
| Prostate size (g)              | 51.15 ± 59.55    | 48.56 ± 67.81    | 0.086   |
| PSA (ng/ml)                    | 34.97 ± 19.07    | 30.50 ± 17.25    | < 0.001*|
| Income adequately met household needs |                  |                  |        |
| More than adequately or adequately | 144 (58.8)   | 210 (49.4)       | 0.019*  |
| Dissatisfied                   | 101 (41.2)       | 215 (50.6)       |         |
| Overall satisfaction with communication with doctor |                  |                  |        |
| Good or excellent              | 205 (83.7)       | 307 (72.2)       | 0.001*  |
| Fair or poor                   | 40 (16.3)        | 118 (27.8)       |         |

IPSS, International Prostate Symptom Score; Q_max, maximum flow rate; PSA, prostate specific antigen.*Statistically significant.
compound. Since 28 patients among them belonged to the persistence group, we concluded that persistence was maintained in many patients, even with the switch of medication. This finding is very interesting and we are planning to assess the persistence of patients who switched medication in future studies.

As far as we know, this study is the first to assess the correlations of symptom severity, objective clinical data, and medication persistence in LUTS/BPH patients. However, we note that our study had several limitations. First, our findings were based on mainly a retrospective review. Therefore, observations of changes in symptoms with IPSS were not carried out for many patients. Regrettably, we could therefore not assess the persistence based on the change of symptoms after taking medication. Second, the persistence data were obtained through self-reporting or prescription records and not independently audited by pill counts or otherwise validated. If patients failed to refill their prescription, treatment discontinuation could have been underestimated.

Thus, considering the study limitations, a large scale, prospective trial using validated records should be performed to further determine factors influencing LUTS/BPH medication persistence.

### Conclusions

Twelve-month persistence with LUTS/BPH therapy was very low, about two-thirds of newly diagnosed LUTS/BPH patients discontinued medications within 1 year of starting treatment. The chance of medication persistence was highest for patients with larger prostate volume, higher PSA, an adequate income, and a good patient–doctor relationship. These factors may be future targets for increasing medication persistence and further efforts must be undertaken to promote continuation of medication in LUTS/BPH patients.

### Author contributions

Jun Sung Koh: conception and design, statistical analysis and interpretation of data, drafting of the manuscript. Kang Jun Cho and Hyo Shin Kim: conception and design, acquisition of data, administrative technical support. Joon Chul Kim: conception and design, critical revision of the manuscript, supervision.
References

1 Abrams P, Chapple C, Khoury S et al. Evaluation and treatment of lower urinary tract symptoms in older men. *J Urol* 2009; 181: 1779–87.
2 Clifford GM, Logie J, Farmer RDT. How do symptoms indicative of BPH progress in real life practice? The UK experience. *Eur Urol* 2000; 38: 48–53.
3 Wasserman NF. Benign prostatic hyperplasia: a review and ultrasound classification. *Radiol Clin North Am* 2006; 44: 689–710.
4 Elterman DS, Barkin J, Kaplan SA. Optimizing the management of benign prostatic hyperplasia. *Ther Adv Urol* 2012; 4: 77.
5 McConnell JD, Roehrborn CG, Bautista OM et al. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. *N Engl J Med* 2003; 349: 2387–98.
6 Roehrborn CG, Siami P, Barkin J et al. The effects of dutasteride, tamsulosin and combination therapy on lower urinary tract symptoms in men with benign prostatic hyperplasia and prostatic enlargement: 2-year results from the CombAT study. *J Urol* 2008; 179: 616.
7 Lepor H, Auerbach S, Paras-Baez A et al. A randomized, placebo-controlled multicenter study of the efficacy and safety of terazosin in the treatment of benign prostatic hyperplasia. *J Urol* 1992; 148: 1467–74.
8 Goldfischer E, Kowalczyk JJ, Clark WR et al. Hyperplasia on concomitant α1-adrenergic antagonist therapy: results of a multicenter randomized, double-blind, placebo-controlled trial. *Urology* 2012; 79: 873–82.
9 Mobley DF, Kaplan S, Ice K et al. Effect of doxazosin on the symptoms of benign prostatic hyperplasia: results from three double-blind placebo-controlled studies. *Int J Clin Pract* 1997; 51: 282–8.
10 Verhamme KM, Dieleman JP, Bleumink GS et al. Treatment strategies, patterns of drug use and treatment discontinuation in men with LUTS suggestive of benign prostatic hyperplasia: the Triumph project. *Eur Urol* 2003; 44: 539–45.
11 Bushnell CD, Olson DM, Zhao X et al. Secondary preventive medication persistence and adherence 1 year after stroke. *Neurology* 2011; 77: 1182–90.
12 Cramer JA, Roy A, Burrell A et al. Medication compliance and persistence: terminology and definitions. *Value Health* 2008; 11: 44–7.
13 Lukacs B, Leplege A, Thiibault P et al. Prospective study of men with clinical prostatic hyperplasia treated with alfuzosin by general practitioners: 1-year results. *Urology* 1996; 48: 731–46.
14 Roehrborn CG, Oesterling JE, Auerbach S et al. The Hytrin Community Assessment Trial study: a one-year study of terazosin versus placebo in the treatment of men with symptomatic benign prostatic hyperplasia. HYCAT Investigator Group. *Urology* 1996; 47: 159–68.
15 Emberton M, Cornel EB, Bassi PF et al. Benign prostatic hyperplasia as a progressive disease: a guide to the risk factors and options for medical management. *Int J Clin Pract* 2008; 62: 1076–86.
16 Emanuel EL, Dubler NN. Preserving the physician-patient relationship in the era of managed care. *JAMA* 1995; 273: 323–9.
17 Yu KD, Zhou Y, Liu GY et al. A prospective, multicenter, controlled, observational study to evaluate the efficacy of a patient support program in improving patients’ persistence to adjuvant aromatase inhibitor medication for postmenopausal, early stage breast cancer. *Breast Cancer Res Treat* 2012; 134: 307–13.
18 Sawada N, Uchida H, Suzuki T et al. Persistence and compliance to antidepressant treatment in patients with depression: a chart review. *BMC Psychiatry* 2009; 9: 38.