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# Cost effectiveness comparison of dutasteride and finasteride in patients with benign prostatic hyperplasia – The Markov model based on data from Montenegro

## Analiza odnosa troškova i efekata finasterida i dutasterida u terapiji benigne hiperplazije prostate – Markovljev model baziran na podacima iz Crne Gore

**Vera Dabanović*, Marina Kostić†, Slobodan Janković†**

***Health Pharmacy Institution of Montenegro "Montefarm", Podgorica, Montenegro;**
**†Department of Pharmacology and Toxicology, Faculty of Medical Sciences, University of Kragujevac, Kragujevac, Serbia**

**Abstract**

**Background/Aim.** Benign prostatic hyperplasia (BPH) is one of the most common disease among males aging 50 years and more. The rise of the prevalence of BPH is related to aging, and since duration of life time period has the tendency of rising the prevalence of BPH will rise as costs of BPH treatment will and its influence on health economic budget. Dutasteride is a new drug similar to finasteride, inhibits enzyme testosterone 5-alpha reductase, diminish symptoms of BPH, reduce risk of the complications and increases quality of life in patients with BPH. But, the use of dutasteride is limited by its high costs. The aim of this study was to compare cost effectiveness of dutasteride and finasteride from the perspective of a purchaser of health care service (Republic Institute for Health Insuranse, Montenegro). **Methods.** We constructed a Markov model to compare cost effectivenss of dutasteride and finasteride using data from the available pharmacoeconomic literature and data about socioeconomic sphere actual in Montenegro. A time horizon was estimated to be 20 years, with the duration of 1 year *per* one cycle. The discount rate was 3%. We performed Monte Carlo simulation for virtual cohort of 1,000 patients with BPH. **Results.** The total costs for one year treatment of BPH with dutasteride were estimated to be 6,458.00 € which was higher comparing with finasteride which were 6,088.56 €. The gain in quality adjusted life years (QALY) were higher with dutasteride (11.97 QALY ) than with finasteride (11.19 QALY). The results of our study indicate that treating BPH with dutasteride comparing to finasteride is a cost effective option since the value of incremental cost-effectiveness ratio (ICER) is 1,245.68 €/QALY which is below estimated threshold (1,350.00 € per one gained year of life). **Conclusion.** Dutasteride is a cost effective option for treating BPH comparing to finasteride. The results of this study provide new information for health care decision makers about treatment of BPH in socioeconomic environment which is actual both in Montenegro and other countries with a recent history of socioeconomic transition.

**Key words:**
**economics, pharmaceutical; prostatic hyperplasia; 5-alpha-reductase inhibitors; cost-benefit analysis; montenegro**

**Astrakt**

**Uvod/Cilj.** Benigna hiperplazija prostate (BHP) jedno je od najčešćih oboljenja kod muškaraca starijih od 50 godina i tesno je povezano sa procesom starenja. S obzirom na to da životni vek ima tendenciju produženja, može se očekivati da će povećanje učestalosti ove bolesti dovesti do povećanja troškova zdravstvene zaštite. Ukoliko se ne leči, BHP ima progresivan tok i dovodi do teških komplikacija. Inhibitori testosterona 5-alfa reduktaze, finasterid i dutasterid, ublažavaju simptome bolesti, povećavaju kvalitet života i snižavaju rizik od komplikacija. Dutasterid u odnosu na finosterid značajno usporava progresiju bolesti i komplikacije, kao što su akutna retencija urina i hirurške intervencije, ali je skuplji od finasterida 2,3 puta. Cilj ove studije bio je da pokaže da li je sa stanovišta odnosa troškova i efikasnosti opravdano finansiranje upotrebe dutasterida od strane Fonda za zdravstveno osiguranje Crne Gore. **Metode.** Studija je sprovedena prema Markovljevom modelu, koji je razvijen na osnovu podataka iz literature o efektivnosti i na osnovu troškova lečenja u Crnoj Gori. Trajanje jednog ciklusa u modelu je jedna godina a vremenski horizont praćenja iznosio je 20 godina. Za troškove i ishode korišćena je perspektiva društva i oni su diskontovani po stopi od 3% godišnje. Urađena je Monte Karlo mikrosimulacija modela sa 1 000 virtuelnih bolesnika. **Rezultati.** Primena dutasterida imala je nešto bolji odnos troškova i kliničke efikas-

**Correspondence to:** Vera Dabanović, Health Pharmacy Institution of Montenegro "Montefarm", 81 000 Podgorica, Montenegro.
E-mail: vera.dabanovic@montefarm.co.me

nosti od finasterida (539,51 €/QALY u odnosu 544,11 €/QALY). Jedna dobijena godina života prilagođena za kvalitet upotrebom dutasterida košta Fond za zdravstveno osiguranje Crne Gore 1 245,68 €, što ukazuje na to da je terapija sa dutasteridom farmakoekonomski isplativa. **Zaključak.** Ova studija pokazala je da u terapiji BHP dutasterid ima bolji odnos troškova i kliničke efikasnosti u odnosu na finasterid, pa je finansiranje dutasterida od strane Fonda za zdravstveno osiguranje Crne Gore farmakoekonomski opravdano.

**Ključne reči:**
**farmakoekonomika; prostata, hipertrofija; 5-alfa-reduktaza inhibitori; troškovi-korist, analiza; crna gora.**

## Introduction

Benign prostatic hyperplasia (BPH) is the most common entity for clinical condition which includes non-cancerous enlargement of epithelial, muscle and stromal tissue of prostatic gland leading to the enlargement of prostatic gland and urinary obstruction [1]. This kind of disease is related to aging [2], and the results of the observational study The Baltimore Longitudinal Study of Aging indicate that the prevalence of BPH rises with aging; the prevalence of BPH is 25%, 50% and 80% in men who are 40–49 years old, 50–59 years old and 70–79 years old, respectively [3]. Since there is the tendency of prolongation of lifetime period [4], the prevalence of BPH will be higher in near future in the USA as well as in European countries and Montenegro, too [5, 6]. The rise of the prevalence of BPH with the tendency of prolongation of life time period will result in higher costs of treatment of BPH and its greater impact on health economic budget in near future. In the USA, BPH is ranked with high prevalence beside other diseases as hypertension, hyperlipidemia etc. among male which indicates the importance of socioeconomic influence of BPH on health economic budget [7].

Clinical features of BPH can reduce quality of life of patients [8], especially if BPH is left untreated when progressive form of BPH can occur with complications as urine retention (acute and complete), urine incontinence, recurrent urinary tract infection, nephrolithiasis, bladder diverticulitis, hematuria and renal insufficiency [1]. The main therapeutic strategy for patients with BPH according to European Association of Urology (EAU) depends on the phase of BPH [9]. In the early stages of disease "watchful waiting" is recommended and in the later progressive form of BPH the main therapeutic strategy is the use of different class of medications: alpha adrenergic blockers which reduce dynamic part of prostatic obstruction and facilitate urination, but do not change the progression of disease, 5-alpha reductase inhibitors which diminish prostatic enlargement, as well as complications of BPH and phytotherapeutics [1]. In the final stage of the disease, the surgical treatments are only therapeutic options since patients in this phase of BPH do not respond to medications and disease has great impact on quality of life of patients.

The effectivness of 5-alpha reductase inhibitors has been proved through the results of numerous clinical studies which indicate that the use of these medications in patients with BPH reduces its symptoms, improves the quality of life of patients, diminishes progression of disease and the rate of serious complications such as urinary retention and development of conditions which need surgical treatment. In Montenegro, two different 5-alpha reductase inhibitors have been registered, finasteride which blocks type 2 isoenzyme of 5-alpha reductase, and dutasteride which inhibits both type 1 and type 2 isoenzymes of 5-alpha reductase. The results of recent clinical trials have shown that dutasteride in comparison to finasteride significantly reduces progression of BPH [10, 11], as well as the rate of severe complications of BPH such as acute urinary retention and development of the late phase of BPH which needs surgical treatment [12]. Yet, the use of dutasteride is limited by its high costs: the costs of dutasteride are 2–3 times higher than the costs of finasteride. Finasteride is a part of the list of drugs which is funded by the Health Insurance Fund of Montenegro while dutasteride is not [13].

The aim of this study was to compare cost-effectiveness of finasteride and dutasteride in patients with BPH in actual socioeconomic environment of Montenegro.

## Methods

For the purpose of this research, we conducted cost-effectiveness analysis of dutasteride versus finasteride in patients with BPH, using Tree Age Pro software and constructing Markov model.

The main therapeutic strategies in our model were: oral treatment with finasteride in the dosage regimen of 5 mg/day and oral treatment with dutasteride in the dosage regimen of 0.5 mg/day in patients with BPH. Dose regimens for finasteride and dutasteride were in compliance with actual clinical guidelines for BPH treatment [1]. For both therapeutic options virtual patients were in one of the following health states which represents chronic course of BPH, with the possibilities of moving to another health state at the end of the model cycle: mild BPH, moderate BPH, severe BPH, acute urinary retention (AUR), transurethral prostatic resection (TURP), repeated transurethral prostatic resection (TURP1) and death outcome, like in a study by Ismalia et al. [14] (Figure 1). A time horizon was estimated to be 20 years due to chronic course of BPH, and the duration of one cycle was one year.

All symptoms of severity of BPH in our study were valued according to the International Prostate Score System (IPSS) (Table 1). Acute urinary retention is an acute complication of BPH which needs urgent placement of urinary catheter. A virtual cohort of patient with BPH from every health state in the model can move to the AUR state and if catheterization completes successfully they move into the previous health state, and if catheterization completes unsuccessfully patients need surgical treatment and move to the TURP state, since TURP is the most commonly used surgical treatment. If IPSS does not reduce by 50% and more after

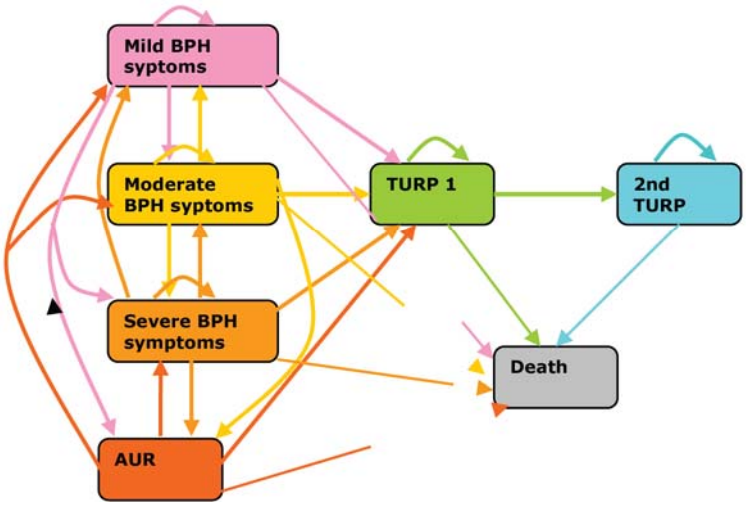


**Fig. 1 – Health states in the Markov model for benign prostatic hyperplasia (BPH).**
**TURP – transuretheral prostatic resection (1, 2 – the number of repeated operations).**

**Table 1**

**Symptoms of benign prostatic hyperplasia according to the values of International prostate score system**

| Score | Symptoms |
|---|---|
| 0–7 | Mild |
| 8–19 | Moderate |
| 20–35 | Severe |

performed TURP, virtual patients stay in the TURP state. In our research patient could stay in TURP stay for two cycles.

For every health state of both therapeutic strategies we estimated effectiveness from the available pharmacoeconomic literature. The effectiveness of finasteride and dutasteride was valued through quality adjusted life years (QALY) for every health state in the model, and it was estimated from the available pharmacoeconomic literature [15–18] (Table 2).

chaser of health care service (Republic Institute for Health Insurance of Montenegro). For therapy with finasteride as well for dutasteride in patients with BPH direct and non-medical costs were included in the model – costs of: medications, inpatient and outpatient services (general practice and urology specialist examinations, hospitalizations, laboratory services, diagnostic procedures, surgical procedures, treatment of AUR, treatment in emergency care services, home visiting medical services and patients transport). The afor-

**Table 2**

**Values for quality adjusted life years (QALY) in all health states of the Markov model**

| Health state | Quality of life | | |
|---|---|---|---|
| | Therapy with dutasteride | Therapy with finasteride | Reference |
| Mild BPH | 0.89 | 0.84 | 15,16 |
| Moderate BPH | 0.76 | 0.71 | 15,16 |
| Severe BPH | 0.69 | 0.64 | 15,16 |
| AUR | 0.17 | 0.17 | 17 |
| TURP1 | 0.668 | 0.668 | 18 |
| TURP2 | 0.594 | 0.594 | 18 |

**BPH – benign prostate hyperplasia; AUR – acute urinary retention; TURP – transurethral prostatic resection (1, 2 – the number of repeated operations).**

Initial and transition probabilities were estimated from the available pharmacoeconomic studies and they are shown in Table 3 [19–31]. For both therapeutic options initial probabilities were the same.

For every health state and for both therapeutic options in the model we estimated costs from the perspective of purmentioned costs of care have been shown to be substantial in prostatic carcinoma and associated disorders [32, 33]. All costs were estimated from randomly chosen patients with BPH, who were treated in General Hospital in Nikšić, Montenegro from January 1, 2012 to December 31, 2012. All costs were expressed in Euros. The costs of medications were estimated

**Table 3**

**Initial and transition probabilities used in the Markov model**

| Probabilities | Therapy with dunasteride | Therapy with finastride | References |
|---|---|---|---|
| Initial and transition probabilities for the states | | | |
| Mild BPH | 0.55 | 0.55 | 19–24 |
| Moderate BPH | 0.35 | 0.35 | 19–24 |
| Severe BPH | 0.074 | 0.074 | 19–24 |
| AUR | 0 | 0 | |
| TURP1 | 0 | 0 | |
| TURP2 | 0 | 0 | |
| Death | 0 | 0 | Data calculated by model |
| Transition probabilities for model | | | |
| Mild BPH → Mild BPH | 0.96 | 0.95 | Data calculated by model |
| Mild BPH → Moderate BPH | 0.01 | 0.012 | 10, 11, 25 |
| Mild BPH → Severe BPH | 0 | 0 | 10, 11, 25 |
| Mild BPH → AUR | 0.0066 | 0.0103 | 12, 26 |
| Mild BPH → TURP1 | 0.0037 | 0.009 | 12, 26 |
| Mild BPH → Death | 0.017 | 0.017 | 6 |
| Moderate BPH→ Mild BPH | 0.27 | 0.22 | 10, 11, 25 |
| Moderate BPH→Moderate BPH | 0.70 | 0.74 | Data calculated by model |
| Moderate BPH→ Severe BPH | 0.01 | 0.012 | 10,11,25 |
| Mild BPH→ AUR | 0.0051 | 0.0079 | 12, 26 |
| Mild BPH→ TURP1 | 0.0037 | 0.009 | 12, 26 |
| Mild BPH→ Death | 0.01 | 0.01 | 6 |
| Severe BPH → Moderate BPH | 0.07 | 0.06 | 10, 11, 25 |
| Severe BPH → Mild BPH | 0.16 | 0.13 | 10, 11, 25 |
| Severe BPH → Severe BPH | 0.75 | 0.78 | Data calculated by model |
| Severe BPH → AUR | 0.0036 | 0.0057 | 12, 26 |
| Severe BPH → TURP1 | 0.0067 | 0.0164 | 12, 26 |
| Severe BPH → Death | 0.002 | 0.002 | 6 |
| AUR → Mild BPH | 0.009 | 0.008 | 12, 26, 27 |
| AUR → Moderate BPH | 0.031 | 0.027 | 12, 26, 27 |
| AUR → Severe BPH | 0.17 | 0.15 | 12, 26, 27 |
| AUR → TURP1 | 0.649 | 0.674 | 12, 26, 27 |
| AUR → Death | 0.141 | 0.141 | 29 |
| TURP1 → TURP1 | 0.97 | 0.97 | Data calculated by model |
| TURP1 → TURP2 | 0.0195 | 0.0195 | 30 |
| TURP1 → Death | 0.0065 | 0.0065 | 31 |
| TURP2 → TURP2 | 0.99 | 0.99 | Data calculated by model |
| TURP2 → Death | 0.0065 | 0.0065 | 31 |

**BPH – benign prostate hyperplasia; AUR – acute urinary retention; TURP – transurethral prostatic resection (1, 2 – the number of repeated operations).**

on maximal drug prices which were valid in Serbia in June 2013 [34], since in Montenegro this kind of document is not available, and costs of medical services were estimated from the Republic Institute for Health Insurance (RIHI) Tariff Book [35]. All costs and effects were discounted for 3% and willingness to pay was estimated on 1,350.00 Euros *per* one gained year of life [36]. We performed Monte Carlo simulation where a randomly chosen patient from virtual cochort of patients with BPH runs through each scenario in the model and the results expressed as incremental cost effectiveness ratio (ICER) in Euro/QALY. For both therapeutic options we calculated mean costs and mean effects and summarized them also as ICER. In order to check robustness of the model results we peroformed one way sensitivity analysis, decreasing the price of dutasteride by 50%.

## Results

The total costs of each health state in the model were calculated for both therapeutic options in the model and the results showed the difference in the costs of finasteride and dutasteride (Table 4).

Using the cost effectiveness calculation method we compared total costs *per* QALY for the therapy with dutasteride and the one with finasteride in the patients with BPH. The total costs with dutasteride *per* one year *per* patient was estimated to be 6,458.00 ± 3,726.62 € and for that period total effectiveness with dutasteride was estimated to be 11.97 ± 3.85 QALY while under the same conditions treatment with finasteride required 6,088.56 ± 4,866.8 € *per* 11.19 ± 3.50 QALY (Table 5).

The distribution of ICERs calculated by Monte Carlo simulations (using a cohort of 1,000 virtual patients) for total costs *per* QALY is shown in Figure 2. For therapeutic option dutasteride the calculated ICERs (with finasteride as baseline comparator) for the majority of virtual patients fall on the right side of willingness-to-pay line, which indicates that dutasteride is a cost effective therapeutic option in patients with BPH in socioeconomic enviroment of Montenegro. The

**Table 4**

**Total costs for each health state in the model for finasteride and dutasteride in the patients with benigh prostate hyperplasia (BPH)**

| Therapeutic strategies → Health states in model ↓ | Cost (€) | |
|---|---|---|
| | finasteride | dutasteride |
| Mild BPH | 248.01 | 363.45 |
| Moderate BPH | 305.34 | 403.55 |
| Severe BPH | 355.11 | 466.61 |
| AUR | 529.73 | 564.51 |
| TURP 1 | 1013.20 | 1013.20 |
| TURP 2 | 2026.40 | 2026.40 |

**AUR – acute urinary retention; TURP – transurethral prostatic resection (1, 2 – the number of repeated operations).**

**Table 5**

**Results of Monte Carlo simulation**

| Parameters | $\bar{x} \pm SD$ | Minimum value | Median | Maximum value |
|---|---|---|---|---|
| Dutasteride | | | | |
| costs (€) | 6,458.00 ± 3,726.62 | 0 | 6,328.81 | 32,420.05 |
| clinical effectiveness | 11.97 ± 3.85 | 0 | 13.90 | 14.63 |
| Finasteride | | | | |
| costs (€) | 6,088.56 ± 4,866.81 | 0 | 4,374.29 | 32,420.05 |
| clinical effectiveness | 11.19 ± 3.50 | 0 | 1.61 | 13.76 |

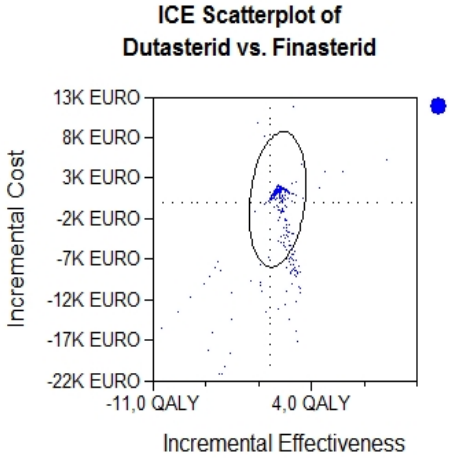


**Fig. 2 – The distribution of incremental cost-effectiveness ratios (ICE) for dutasteride comparing to finasteride in the patients with benign prostate hyperplasia.**

value of ICER for dutasteride comparing to finasteride in patient with BPH was estimated to be 1,245.68 €/QALY which was below the estimated treshold of 1,350.0 €.

In order to check robustness of our results we decreased the price of dutasteride by 50% performing one-way sensitivity analysis. The results of sensitivity analysis indicate that with the decreasing price of dutasteride by 50% the value of ICER decreases too with the value of 483.72 €/ QALY. Distribution of ICER under the conditions of decreasing price of dutasteride by 50% is shown in Figure 3.

## Discussion

The results of our research indicate that the use of dutasteride in the patients with BPH comparing to finasteride requires a slight increase of funding (369.44 €) but provides 11.97 ± 3.85 QALY which is higher comparing with finasteride used under the same conditions providing 11.19 ± 3.5 QALY. The difference between these therapeutic options in costs is minimal (369.44 €), but still lower in the dutasteride group where one QALY requires investment of 539.51 €, while in the finasteride group one QALY requires investment of 544.11 €. In the research that compared dutasteride to placebo and finasteride in socioeconomic environment of Poland [37] dutasteride was a cost-effective therapeutic option, with lower costs providing more gained years of life (1.092 gained years) without complications of BPH as prostatic carcinoma and surgical interventions.

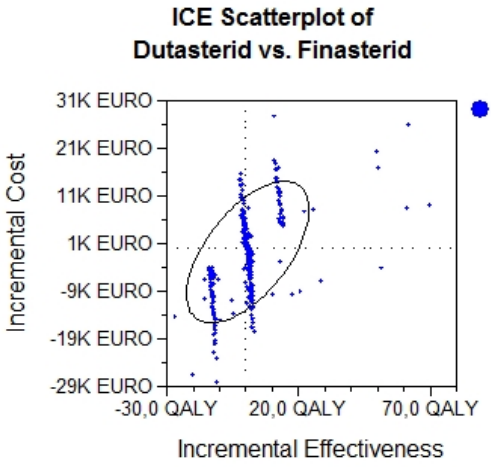


**Fig. 3 – Distributions of the incremental cost-effectiveness ratio (ICE) for dutasteride comparing to finasteride in the patients with benign prostate hyperplasia, with the decreasing price of dutasteride for 50%.**

We could have expected a better cost-effectiveness position of dutasteride in our research if prices of medical services and drugs in socioeconomic sphere of Montenegro had

been similar to socioeconomic conditions in developed countries in the European Union [38]. In the Balkan region, except in Albania, there is a legacy of the health care system based on socialism and insurance. In the recent period, in the Balkan region there has been a tendency of appearing more integrated strategies for social protection, but very often they have not been carried out to the end, while the monitoring and evaluation of the implementation has been poor. In the context of the economic crisis, conflict and low levels of social security contributions, public spending on social protection are faced with major problems and disadvantages of the funds in the region. Balkan countries fall into the high-middle income countries with the gross national income of $ 3,809 in Albania, to $ 22,169 in Slovenia, in 2012 the age or annually for health care *per* capita stands relatively small amount (in 2012 the age $ 561 in Serbia, Bosnia and Herzegovina, $ 447, $ 1942 Slovenia, Montenegro, $ 493, $ 516 to Bulgaria, Macedonia $ 327, $ 908 Croatia, Poland, $ 854, $ 228 and Albania, Rumania $ 420). Health systems in these countries are state-owned, and the prices of health services are determined and controlled by the state health insurance funds [39].

Since the prices of medical services are determinated by the Republic Institute for Health Insurance of Montenegro and drug prices are controlled by drug producers, the socioeconomic environment of Montenegro is characterized with lower prices of medical services than in the EU and with the similar values for prices of drugs. For example, the TURP state in our model has the highest total costs, and the average price of this procedure in the United Kingdom is 7.5 times higher than in Montenegro (6,128£ or 7,650 €) [40] while the price of finasteride is 14,94 £ (18,64 €) and of dutasteride 29,77 £ (37,14 €) [41] which is approximately 2 to 2,6 higher than in Montenegro. The difference in costs of BPH treating complies also with private practice where costs of surgical treatment of BPH is 2.5 time higher than in state hospitals. All these discrepancies make specific socioeconomic sphere which can blur real cost effectiveness position of drugs as dutasteride is.

On the other side, in the Republics of Serbia and Montenegro the price of dutasteride differs from the price of finasteride (18.13 € and 7.90 €, respectively) which is dissimilar in countries of EU. In Germany total month costs of treatment with finasteride and dutasteride are the same [42], and in Poland a difference between costs of dutasteride and finasteride is lower than in Montenegro [43]. Dutasteride was registred as Avodart® and its generic copies will be available on the drug market in November 2015. After that period we can expect that the price of dutasteride and costs of BPH treating with dutasteride will be lower which has already been shown with finasteride and its generic copies.

According to the World Health Organization a therapeutic option could be considered as cost-effective if its ICER in comparison with the standard therapy (costs *per* quality-adjusted life year gained) is under one, two or three multiples of average gross national income *per capita* for that country [34]. Our results indicate that the value of ICER for dutasteride comparing to finasteride is 1,245.68 € *per* one quality adjusted life year, which is below the estimated threshold of 1,350.00 €, and favors dutasteride as cost-effective therapeutic option comparing to finasteride in patients with BPH in socioeconomic environment of Montenegro. The results of Dardzinski et al. [44] point out that including dutasteride on the list which is financed by the National Institute for Health Insurance in Poland will result in reduction in costs as well as decreasing risk for prostatic cancer and development of complications of BPH which need surgical treatments.

This study has a few limitations. We chose to use data about effectiveness of dutasteride in patients with BPH from the available clinical trials since we had no "real" data from patients in Montenegro. An underlying issue of patient compliance affecting the treatment success rates was difficult to assess due to objective nature of modeling approach and therefore we decided to omit it from further analysis [45]. We chose that patients in our model could undergo only in TURP because it is the most frequently surgical intervention among these patients with frequency estimated from the available literature. Since adverse reactions of dutasteride are minimal and similar to finasteride, we chose not to incorporate them in our model, but we corrected the value of QALY for both therapeutic options with estimated frequency for adverse reactions. This assessment was based on the assumption of patient perceived quality of life [46]. Since the perspective in our study was the one of a purchaser of health care service (Republic Institute for Health Insurance, Montenegro) only the direct costs were included in our model.

## Conclusion

Our results indicate that dutasteride is a cost-effective therapeutic option comparing to finasteride in patients with benign prostate hyperplasia (BPH) in socioeconomic environment of Montenegro. Since the differences considering costs and effects between dutasteride and finasteride are minimal, finasteride should still be a part of the list of drugs which is financed by the Republic Institute for Health Insurance. Our results provide new information for health care decision makers about treatment of BPH in socioeconomic environment which is actual both in Montenegro and other countries with recent history of socioeconomic transition.

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