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HEALTH ECONOMIC EVALUATION OF CHRONIC

UROLOGIC DISEASES

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PhD THESIS

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SHORT SUMMARY

In my thesis I provide analysis of the health economic aspects of chronic prostatic diseases including benign prostatic hyperplasia, bladder cancer, female and male urinary incontinence, lower urinary tract symptoms and overactive bladder syndrome.

Due to the ageing of the population the prevalence and social burden of these diseases increase substantially. These diseases already at present have major cost impacts and the related costs are expected to rapidly increase further in the near future. The disease incidence within the specified age groups appears to be fairly constant, however due to the increasing life expectancy of the population and to the more and more effective therapeutic agents, the total number of patients rise significantly.

The costs rise constantly since these chronic diseases are long-lasting and require ongoing medical care. Due to the constantly increasing patient number and social burden these issues receive special attention in more and more developed countries. Some countries develop "ageing strategies" and health economic research of ageing is in the mainstream of health economic research. Substantial data are required in order to make adequate health policy decisions and to find sustainable finance solutions.

Little is known about the epidemiology and social burden of chronic urologic diseases in Hungary which makes adequate decision-making in health policy and finance remarkably difficult.

In order to come to know the social burden we need to be aware of the epidemiology of these diseases including the number of new cases (incidence), the total patient number (prevalence), the number of patients in the subgroups important from disease severity aspects (since the costs are related to disease severity), the direct and indirect costs associated with the disease and the quality of life implications of the disease.

These pieces of information are necessary in order to assess the real social importance of the diseases and to calculate the budget impact and cost-effectiveness of the newer and newer and more and more expensive therapies which is an obligation of the social security system and is also essential to develop a sustainable health care finance system.

The research published in the thesis includes the health economic evaluation of several chronic urologic diseases since we need to compare these results. In order to make ranking possible for health policy and financing purposes it is necessary to know the number of patients with the diseases concerned, the direct and indirect costs and the implications on quality of life and work i.e. the social burden. The aims and the hypotheses set for the specific diseases under investigation differed with consideration to the characteristics of the field and the available Hungarian and international literature, so did the methodology applied differ as well.

The research results published in the thesis previously were not available either in Hungary or in the wider region; furthermore we have successfully found and published several results for the first time in the literature. The research results fill a knowledge gap and can be of use for promoting decision making in health policy and finance.

LIST OF ABBREVIATIONS

AUR   Acute urinary retention

BC   Bladder cancer

BCI   Bladder Cancer Index

BMI   Body Mass Index

ICD   International Classification of Diseases

BPH   Benign prostatic hyperplasia

EQ-5D   Generic health status questionnaire (formerly: EuroQol)

IBE   Hungarian Organisation of Patients with Incontinence (acronym based on the Hungarian equivalent: Inkontinencia Betegegyesület)

ICS   International Continence Society

I-PSS   International Prostate Symptom Score

LUTS   Lower Urinary Tract Symptom

MÁESZ   Comprehensive Hungarian Health Promotion Screening Programme (acronym based on the Hungarian equivalent: Magyarország Átfogó Egészségvédelmi Szűrőprogramja)

MUT   Hungarian Association of Urology (acronym based on the Hungarian equivalent: Magyar Urológusok Társasága)

OAB   Overactive Bladder Syndrome

OECD   Organisation for Economic Co-operation and Development

OEP   National Health Insurance Fund of Hungary (acronym based on the Hungarian equivalent: Országos Egészségbiztosítási Pénztár)

QALY   Quality Adjusted Life Year

WPAI   Work Productivity and Activity Impairment questionnaire

1. INTRDUCTION

The evaluation of ageing associated diseases and conditions represent a prominent research area in the field of health economic research. The life expectancy at birth increased significantly in the majority of the countries (Figure 1), for example between 1960 and 2009 in Hungary the life expectancy increased by 6 years (Figure 2). (OECD, 2017)

Figure 1 Life expectancy at birth (2014
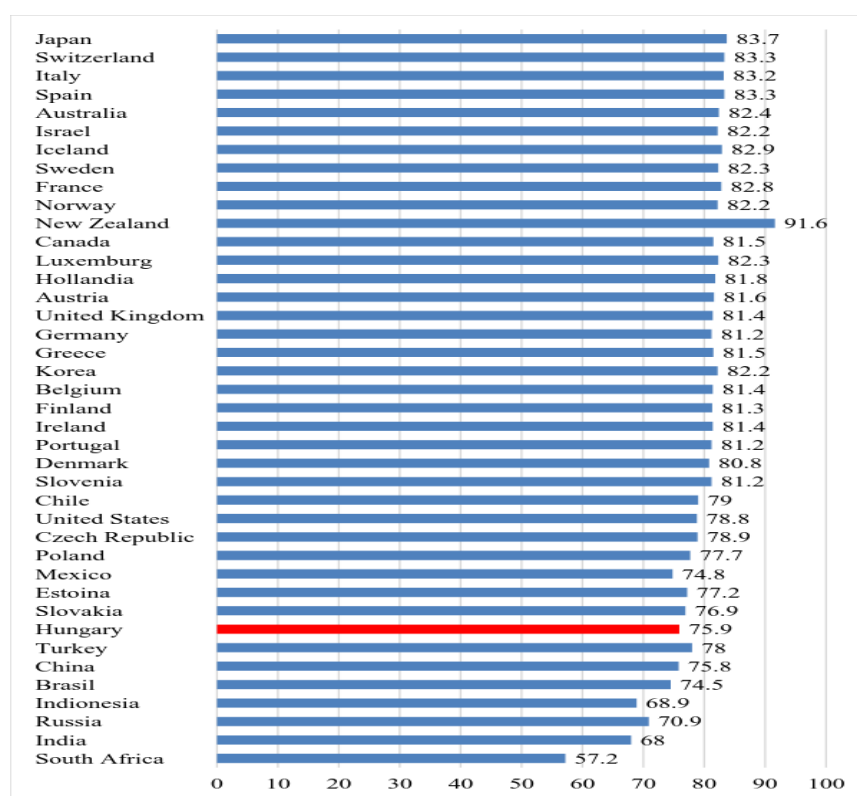
Source: (OECD, 2017)

Figure 2 Life years gained (1960-2009)
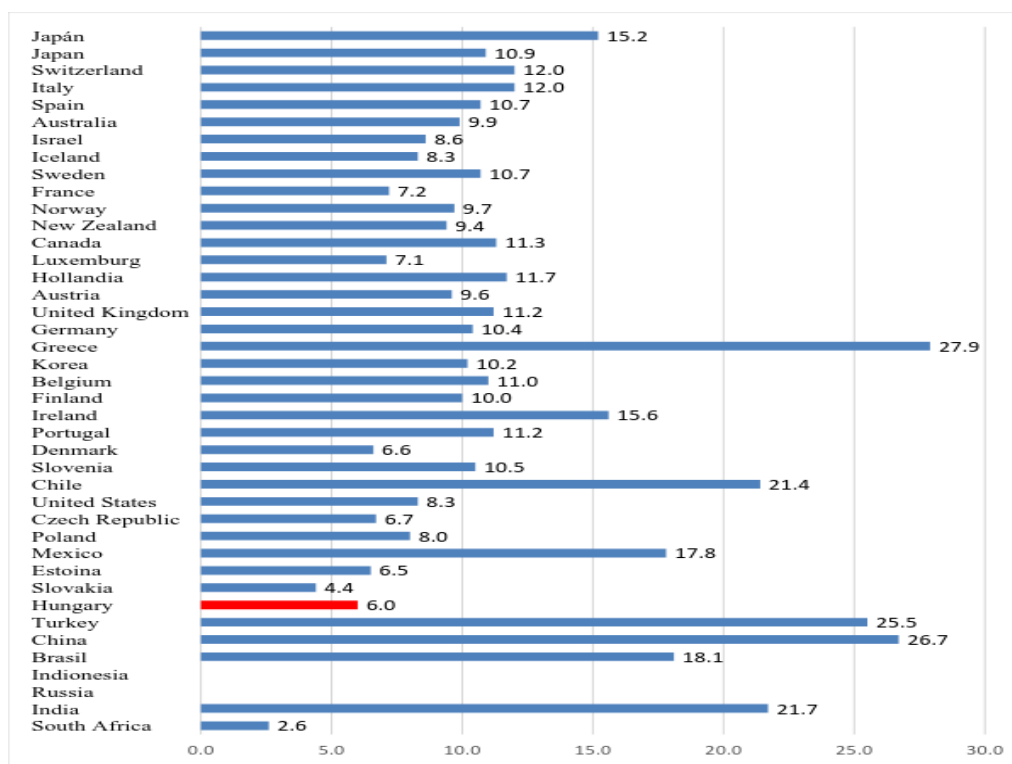
Source: (OECD, 2011)

The society is ageing; the age group of 70+, 80+ individuals is growing and the changes of the Hungarian population pyramid clearly reflect this fact (Figure 3 and Figure 4). The most important predictor of age related diseases is the age; therefore the expected number of patients in the future can be estimated based on the demographic trends and the epidemiologic characteristics of the diseases. These diseases already at present have a high prevalence, which is expected to increase significantly based on the demographic trends.

Benign prostatic hyperplasia is one of these diseases that already at present causes and is expected to keep causing a significant social burden in the future as well. Based on

literature data the disease affects 25% and 50% of individuals aged 55 and 75 years, respectively (Riesz, 2006). In 2012 the number of patients with BPH was between 350 – 415 thousands in Hungary and this number is expected to increase by 20-25 thousands by 2020. (Rencz 2012; KSH [acronym for Hungarian Central Statistical Office in Hungarian] 2011)

These diseases include prostate cancer, in the case of which 75% of the newly diagnosed cases affect individuals over 65 and the incidence of which is 3500 patients per year in Hungary. (Gajdácsi et al., 2011) These diseases include cancers in general including cancers of the bladder and other urologic diseases e.g. overactive bladder syndrome, male and female urinary incontinence. (Hungarian Ministry of Human Capacities – State Secretariat for Health Care, 2016)

Figure 3 Hungarian population by sex and age group, as of 1 January 2017 (thousands persons) (N= 9 690 388 persons)
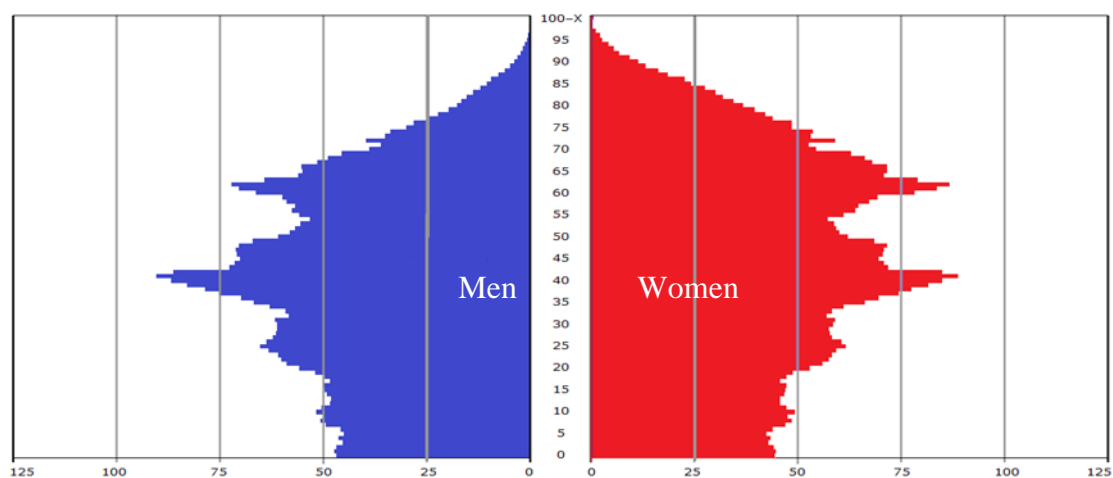
Source: (KSH, 2017)

Figure 4 (Expected) number of the Hungarian population by sex and age group, as of 1 January 2030 (thousands persons) (N= 9,690,388 persons)

Source: (KSH, 2017)

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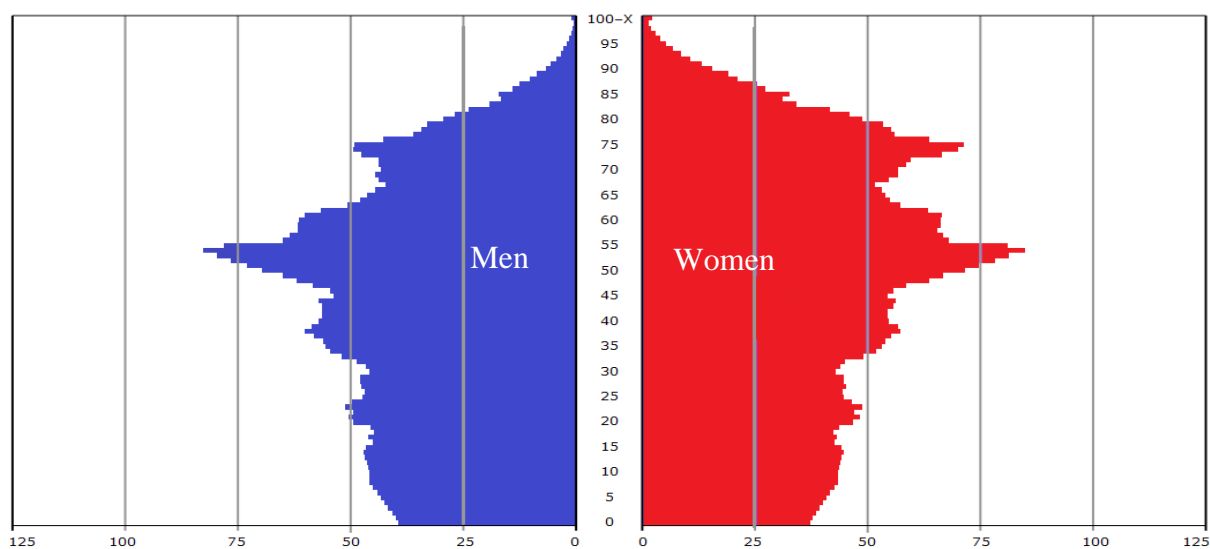
Assessing the actual and the expected future burden of disease in the case of these diseases is crucial and fundamentally important from health policy and finance aspects.

Prior to my research no such data or only very limited data were available in the field of urology in Hungary. Assessing the cost of illness, the burden of disease are the most widely used types of health economic evaluations. The burden of disease studies live on the assumption that the cost demonstrated in the assessment represent the amount of money that can be considered as profit if the problem is successfully solved i.e. the disease is avoided. The method is widely used, primarily in promotion of health policy decision making. (Gulácsi, 2012)

In my research projects I evaluated the burden of disease in chronic urologic diseases that are associated with significant social burden in ageing societies.

Chapter 2 of the PhD thesis contains short description of the important terms and methods used in the thesis and of the diseases under evaluation.

From Chapter 3 onwards chapters include the following subchapters (numbering applies for second-level headings):

- Subchapters #"1" (Subchapters 7.1, 8.1, 9.1):

Assessing social burden and cost of illness in patients with benign prostatic hyperplasia:

-the relevant international and national literature was reviewed[1]

-the cost of illness was assessed in a questionnaire based cross-sectional survey in patients treated for benign prostatic hyperplasia[2]

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[1] Kovács Á (2015): Cost of illness in benign prostatic hyperplasia: a review. Society and Economy, 37, 4, pp. 531–542. doi: 10.1556/204.2015.37.4.7
[2] Rencz F, Kovács Á, Brodszky V, Gulácsi L, Németh Z, Nagy GJ, Nagy J, Buzogány I, Böszörményi-Nagy G, Majoros A, Nyirády P (2015): Cost of illness of medically treated benign prostatic hyperplasia in Hungary. International Urology and Nephrology, 47, 8,

-the quality of life was assessed based on responses obtained in a questionnaire based study in patients with benign prostatic hyperplasia using generic and disease specific questionnaires[3]

- Subchapters #"2" (Subchapters 7.2, 8.2, 9.2): **Cost of illness in patients with bladder cancer in Hungary**

- out-of-pocket healthcare expenditure, especially the medication expenses of patients with bladder cancer were assessed by analysing the database of the National Health Insurance Fund of Hungary

- Subchapters #"3" (Subchapters 7.3, 8.3, 9.3): **Epidemiology of male and female urinary incontinence and lower urinary tract symptoms in Hungary**

- the epidemiology of female urinary incontinence was evaluated in a questionnaire based survey in 2011[4][5][6][7]

- Subchapters #"4" (Subchapters 7.4, 8.4, 9.4): **Health economic evaluation of the treatment of overactive bladder syndrome**

pp. 1241-1249. doi: 10.1007/s11255-015-1028-7.treated benign prostatic hyperplasia in Hungary. Int Urol Nephrol, 47(8):1241-1249. DOI 10.1007/s11255-015-1028-7

[3] Kovács Á. (2017): A gyógyszeresen kezelt jóindulatú prosztata-megnagyobbodásban szenvedő betegek életminősége Magyarországon; keresztmetszeti felmérés hat urológiai centrumban. Magyar Urológia, [accepted for publication]

[4] Kovács Á, Vártokné Hevér N, Tóth A, Pálffi B (2012): A női vizeletinkontinencia epidemiológiája Magyarországon; kérdőíves vizsgálat. Magyar Urológia, XXIV, 4, pp. 15-22.

[5] Majoros A, Sipos A, Kovács Á, Nyirády P (2014): A női vizeletinkontinencia és urogenitális prolapsusok sebészi kezelésének hazai gyakorlata. Magyar Urológia, XVI, 3, pp. 132-133.

[6] Sipos A, Kovács Á, Nyirády P, Majoros A (2015): A női vizeletinkontinencia és urogenitális prolapszusok sebészi kezelésének hazai gyakorlata. Magyar Nőorvosok Lapja, 78, 1, pp. 38-45.

[7] Kovács Á, Vártokné Hevér N, Tóth A, Pálffy B (2013): Férfiak alsó húgyúti tüneteinek gyakorisága Magyarországon - egy nyílt kérdőíves vizsgálat eredményei. Magyar Urológia, XXV, 1, pp. 22-26.

-health economic evaluation was conducted in the field of overactive bladder treatment[8,9]

-literature review was conducted in order to review and analyse the health economic literature on the therapy of overactive bladder syndrome

[8] Brodszky V, Ecseki A, Gulácsi L, Kovács Á, Romics I, Majoros A, Rubliczky L, Simon Zs (2008): A solifenacin (Vesicare®) magyarországi alkalmazása hiperaktív hólyag szindrómában; egészség-gazdaságtani elemzés. IME, VII, 9, pp. 30-36. .
[9] Domján Zs, Kovács Á, Buzogány I (2015): A hiperaktív hólyag kezelése kismedencei prolapsusok esetében. Magyar Urológia, XXVII, p. 119.

2. SHORT INTRODUCTION TO THE IMPORTANT METHODS AND TERMS USED IN THE THESIS AND TO THE DISEASES UNDER EVALUATION

2.1 Methods used in the thesis

The methods used in the thesis are described below.

2.1.1 Quality of life surveys

The most important features of the generic and disease specific questionnaires used for the research are summarised below.

2.1.1.1 EQ-5D Generic health status questionnaire

The EQ-5D questionnaire is suitable for measuring generic quality of life related to health and can be used in any disease (Euroqolgroup, 1990, Péntek, 2012, Péntek, 2014). The questionnaire measures the actual health state of the individual. It comprises two systems: EQ-5D descriptive system where 3 different answer levels can be provided in 5 dimensions each. The 5 dimensions are the following: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The 3 possible answer levels are: no problems, some problems, and extreme problems/inability. The other system used in the questionnaire is the visual analogue scale used to measure the health state (EQ-VAS). The scale ranges between 0-100 where 100 equals to the "Best imaginable health state" and 0 to the "Worst imaginable health state", respectively. (The 5-level EQ-5D version was introduced, hence the 3 answer level version was renamed EQ-5D-3L, whereas the

new version is named EQ-5D-5L. EQ-5D-3L is hereinafter referred in the thesis as EQ-5D.)

The health conditions captured by the descriptive system of the EQ-5D can be converted to a utility score reflecting preferability of the given health profile from social aspects (population-based utility scores developed by time trade-off method). The utility score set developed in the United Kingdom is the one that is used most frequently in Hungary, the population-based reference values were produced with this set as well (Baji et al., 2015, Rencz et al., 2016). The utility scores derived from the EQ-5D questionnaire are used most often in the health economic (cost-effectiveness) evaluations to calculate quality adjusted life year (QALY).

2.1.1.2 Disease specific questionnaires

Three of the disease specific questionnaires were used in the research; the International Prostate Symptom Score (I-PSS), the Patient Perception of Bladder Condition (PPBC) questionnaire and the Severity of urgency scale for patients with symptomatic overactive bladder (PPIUS). The questionnaires are available in validated Hungarian language version as well.

The I-PSS questionnaire (see Annex 1) were developed specifically for assessing the health state of patients with benign prostatic hyperplasia (BPH), while the other two questionnaires assess the presence and severity of overactive bladder syndrome (see Annex 2) which may be of concern for patients with BPH as well. The I-PSS questionnaire comprises 7 questions concerning voiding and storage symptoms over the last 1 month, and 1 question concerning the quality of life. Patients may provide their answer to each question by scoring between 0-5 depending on whether the given symptom

is not present at all (equals to 0) or is present almost always (equals to 5). The total score therefore may be 35. Disease severity is expressed in 3 levels as follows: symptoms are mild if the score ranges between 0-7, moderate between 8-19 and severe between 20-35, respectively. In the PPBC questionnaire the patient may choose from 6 possible answers to the question "Which of the following statements describes your bladder condition best at the moment?", while the Urgency scale asks the patients to rate the degree of urgency on a 5-point scale. 0, if there was no urgency, 4, if the degree of urgency was the maximum possible and the patient even leaked before arriving to the toilet. The results obtained with the I-PSS questionnaire are described in details in my thesis; the other two questionnaires were not introduced into the routine clinical practice in Hungary for assessing the health state, establishing the diagnosis and selecting the therapy for patients either with BPH or overactive bladder syndrome. Calculation of disease burden and costs are available as well.

2.1.2   Calculation of disease burden and costs

Burden of disease and cost of illness studies became widely used to promote health policy and finance decision making procedures. In these studies the hypothesis is that the social burden (cost, impaired quality of life, work absenteeism and other consequences) demonstrated manifests as benefit in case the given problem is successfully solved (disease avoided, cured). Often the aim of a cost calculation is to quantify the cost of illness (burden of disease). The aim of the cost calculation is to evaluate the costs associated with the diseases and healthcare during which the direct medical cost, the direct non-medical costs and the indirect costs all need to be taken into account. (Gulácsi et al., 2012, Gulácsi et al., 2006)

The cost calculation procedure comprises the following phases:

- identification of the relevant resource (cost) items,

All costs should be considered in the analysis irrespective of by whom these costs are specifically incurred and where (in which sector) these costs are realised within the society.

- measurement of the resources identified

When measuring the resources, utilisation of the individual items should be analysed. The analysis may be conducted from the society's perspective during which all relevant resource items must be taken into account regardless at which level and in which "cash register" of healthcare these cost incur or if they incur outside of the healthcare sector. The travel costs, the out-of-pocket medication expenses of patients and the costs related to work absenteeism may need to be reviewed. The analysis may be performed from the service provider's perspective as well, in which case use of e.g. hospital, outpatient clinic or general medical practice databases may suffice per se.

- determination of the value of the resources (expressed in monetary terms).

In this phase the unit price of resources should be determined; then the value of resource can be assessed provided that the quantity used is known.

The costs can be classified into the following categories: direct medical costs, direct non-medical costs and indirect costs.

The cost categories evaluated in our research were the following:

Direct medical costs

The direct medical resources are those that are directly required to perform the medical intervention. For example:

- specialist and general practitioner visit costs due to the disease over the last 1 year

- diagnostic tests, examinations performed due to the disease

- costs of medications and medical devices applied due to the disease

- cost of in-hospital care

Direct non-medical costs

The direct non-medical resources are the ones that are necessary to perform the medical intervention. This category includes costs such as:

- travel/transport cost related to the medical care

- cost of informal care

Indirect costs

This category includes costs such as:

- patients staying away from work due to the illness.

In the case of chronic diseases this cost category may represent 40-60% of the total cost.

2.1.3 Short description of the diseases included in the thesis

2.1.3.1 Benign prostatic hyperplasia

Benign prostatic hyperplasia (BPH) manifesting in lower urinary tract symptoms is one of the most common urologic conditions with a prevalence of 10-46% in patients over 40. (Speakman et al., 2015) Ageing – the main risk factor for developing BPH – is a major social concern, particularly for social security, pension systems, and financing and provision of healthcare services. (Shrestha, 2000) By 2050, there will be 58 million people over 65 living in the European Union. (European Commission, 2008) Healthcare expenditure in the current 27 EU member states is projected to rise from 7.1% to 8.4% of GDP between 2010 and 2060 which is clearly attributable to the effect of the ageing population on healthcare spending. European Commission, (2012)

Ageing-associated diseases, such as BPH, type 2 diabetes, dementia, osteoporosis, arthritis, pemphigus, bladder cancer and prostate cancer, have become major cost drivers of healthcare financing. (Brodszky et al., 2009, Érsek et al., 2010, Hevér et al., 2015, Péntek et al., 2008, Rencz et al., 2014a, Rencz et al., 2014b, Rencz et al., 2015a, Taub&Wei, 2006) Due to the increasing life expectancy, the demographic ageing observed in the developed countries and the high prevalence of BPH, a growing number of men use health care services because of BPH symptoms. (Boncz et al., 2014, Rencz, 2012) Funding the rising demand for healthcare is a major challenge for societies and economies, particularly in times of recession when countries struggle to comply with austerity measures. The treatment of BPH typically depends on the disease severity and the main options include watchful waiting (i.e. regular follow-up without applying any specific therapy), pharmacotherapy and a number of surgical procedures. However, the costs may vary dramatically, therefore, the economic evaluation of the above treatment modalities are very useful to facilitate cost-effectiveness in health policy decision-making and elimination of the existing system deficiencies. (Taub&Wei, 2006)

In countries with well-established health technology assessment agencies the economic evaluations are key elements of healthcare decision-making. (Gulácsi&Péntek, 2014, Gulácsi et al., 2014a, Gulácsi et al., 2014b) As the number of patients, hence the costs increase continuously, a literature review is deemed an appropriate starting point to explore and understand the economic burden imposed by BPH.

2.3.1.2 Bladder cancer

The summary on bladder cancer is cited from our published review paper. (Kovács - V. Hevér, 2016)

Bladder cancer is estimated to affect app. 2.7 million patients globally. (Yeung et al., 2014) Thereby bladder cancer is the 9th and 5th most common malignant disease in the world and in Europe, respectively. In 2012 in Europe 151,000 new and 55,400 lethal bladder cancer cases were registered. (Cancer Research UK, 2015)

Epidemiology of bladder cancer

Bladder cancer is categorised into two main categories: the non-invasive (confined to the bladder mucosa) and muscle-invasive (involving the muscle layer of bladder) bladder cancers. Prognosis and treatment of the two categories differ significantly. (Egészségügyi szakmai irányelvek tára 2015)

In Hungary data on bladder cancer is collected by the Hungarian National Cancer Registry and currently the database currently available covers the period between 2001 and 2011. (Hungarian National Cancer Registry) In Figure 5 and 6 the number of new patients reported with diagnosis of benign neoplasm of bladder (International Classification of Disease - ICD D30.3) and malignant neoplasm of bladder (ICD C67) between 2001 and

2011 are shown by gender, respectively. It can be noted that the newly diagnosed cases of benign bladder neoplasm rose to nearly 4-fold by 2011 compared to 2001 (283 cases as compared to 73 cases) while the increase in the number of reported patients with malignant bladder cancer was lower over the 10-year period (almost 1.5-fold increase, increase from 2,301 to 3,025 in the number of patients). The rate of new malignant cases compared to the cases diagnosed as benign are several fold: the number of new patients reported with diagnosis of malignant bladder cancer was 32 times and 11 times higher in 2001 and in 2011, respectively.

The number of men diagnosed with malignant bladder cancer was more than double of the respective number in women in each year of the period evaluated. The rate of diagnosed benign neoplasm cases were also higher in men with the exception of year 2001, however the extent of gender difference was lower than in the case of reported malignant disease. Nevertheless, a remarkable fluctuation can be noticed in the number of patients with malignant disease over the observed 11-year period. (Figure 6)

Figure 5 Number of new patients reported with diagnosis of benign neoplasm of bladder (ICD D30.3) between 2001 and 2011
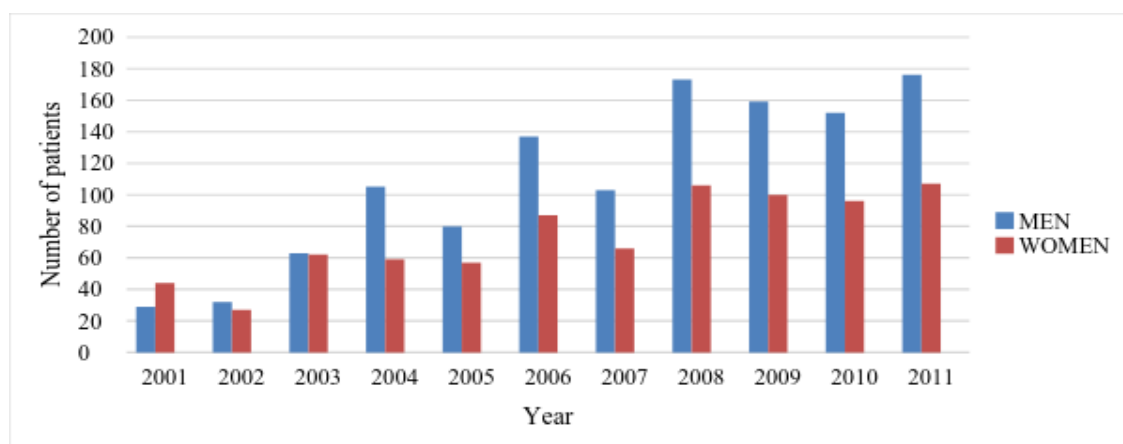
Source: Hungarian National Cancer Registry D30.3 data 2001-2011.

Figure 6 Number of new patients reported with diagnosis of malignant neoplasm of bladder (ICD D30.3) between 2001 and 2011
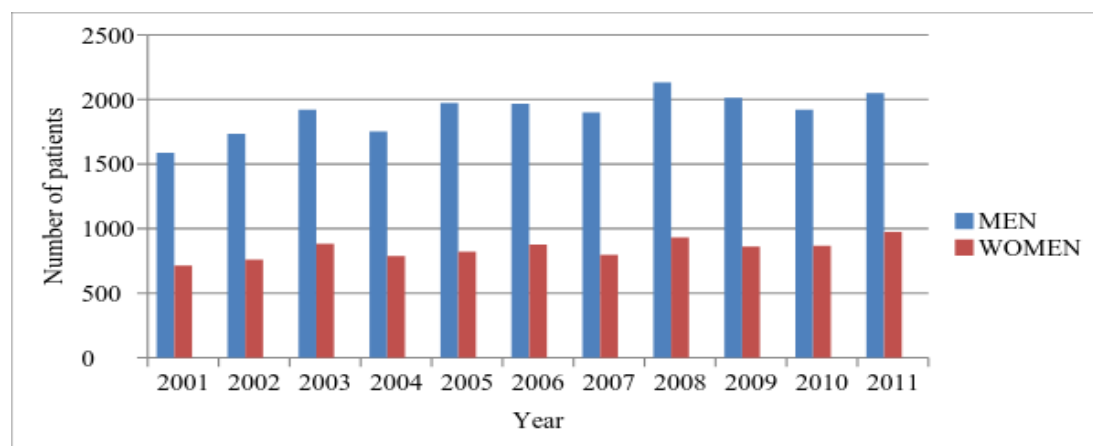
Source: Hungarian National Cancer Registry C67 data 2001-2011.
[http://www.oncol.hu/rakreg/stat2]

With respect to the annual incidence (year 2011), the number of new malignant bladder cancer cases per 100,000 inhabitants increased with age in men up to 84 years (Figure 7). A sharp increase in incidence can be observed in the age group of 50-54 then the incidence rises constantly with age up to the age group of 80-84. Moreover, the incidence stagnates in women over 70 hence the rise in overall incidence is due to diseases of men. The highest incidence is observed in the age group of 80-84 and over 85. The incidence in children and young adults is negligible (total of 4 patients were reported in the age group 0-24) and shows mild gradual increase over 25 years (total of 130 patients were reported in the age group 25-49).

Figure7 New cases of malignant bladder cancer by age groups in Hungary in 2011
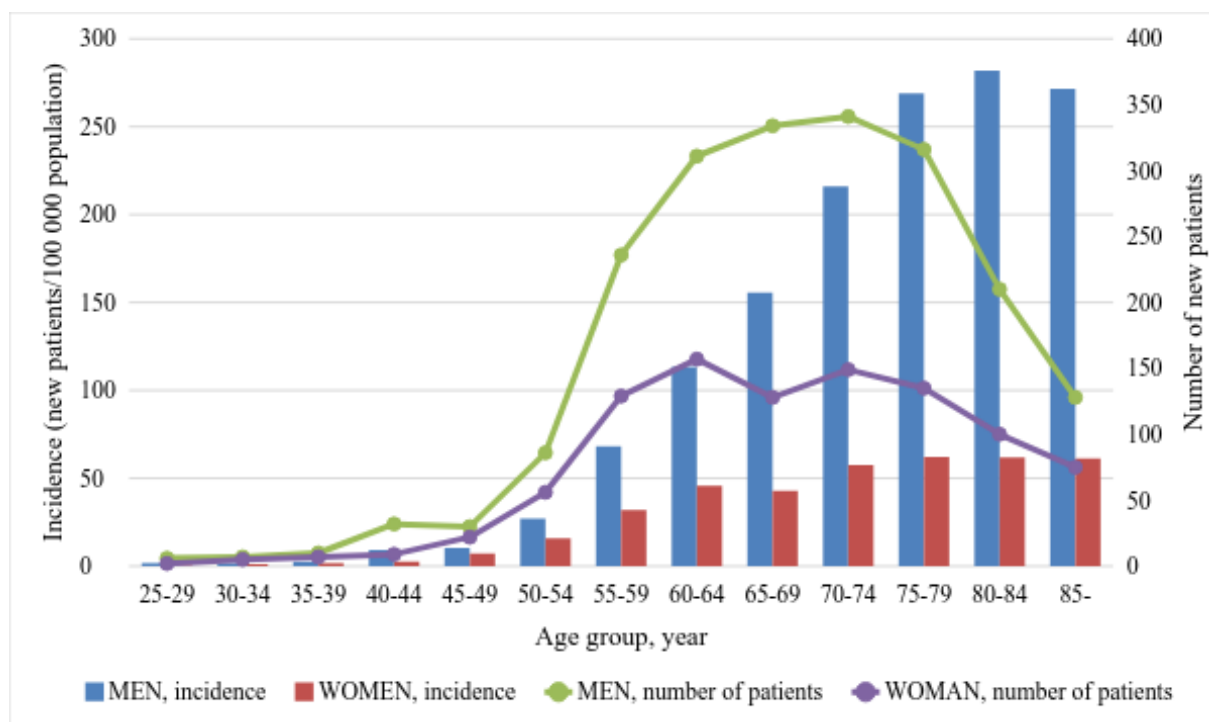
Source: Hungarian National Cancer Registry C67 data 2011. [Population: Eurostat database, 2011]

As to the geographic distribution by counties, 34.4% of new patients with the diagnosis of malignant bladder cancer (incidence) were reported from Budapest and Pest county (total of 1,040 patients/100,000 inhabitants). With respect to the remaining counties it can be noted that in the majority of the Eastern counties the number of new malignant diseases is above 100: Bács-Kiskun 175 (33.54 / 100,000 inhabitants), Borsod-Abaúj-Zemplén 177 (25.36 / 100,000 inhabitants), Hajdú-Bihar 143 (24.5 / 100,000 inhabitants), Szabolcs-Szatmár-Bereg 119 (20.78 / 100,000 inhabitants), Jász-Nagykun-Szolnok 134 (33.97/ 100,000 patients), while the number of cases was below 100 in several Western counties: Vas 81 (31.59 / 100,0000 inhabitants), Veszprém 87 (24.53 / 100,000

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inhabitants, Zala 86 (30.25 / 100,0000 inhabitants). However, the above Western-Eastern tendency cannot be generalised as the lowest number of new patients, 38 (10.33 / 100,000 inhabitants) was reported from Békés county (located in the Eastern part of Hungary) whereas in Győr-Moson-Sopron county (located in the Western part of Hungary) the respective number, 156 (35.99 / 100,000 inhabitants) was higher than in the surrounding counties. (KSH, 2013)

Based on the patient numbers the male / female ratio among the patients with malignant bladder cancer ranged between 1.6 (0.42 patients / 100,000 inhabitants) and 3.0 (0.99 patients / 100,000 inhabitants) in Baranya and Komárom-Esztergom counties, respectively.

In 2011 the incidence per county data ranged between 10.6 and 42.9 patients/100,000 inhabitants (Békés county and Budapest, respectively), the average incidence was 29.4 patients/100,000 inhabitants taking both sexes together. Higher than average incidence was found in Budapest, in Bács-Kiskun, Győr-Moson-Sopron, Heves, Nógrád, Somogy, Jász-Nagykun-Szolnok and Vas counties, whereas the incidence was apparently low in Békés county compared to other counties. The average male/female incidence ratio was 2.4 across the counties with the lowest (1.8) and highest (3.3) male/female incidence being reported from Vas and Komárom-Esztergom counties, respectively. (Hungarian National Cancer Registry C67 data; 2011 and KSH Population registry 2011)

2.1.3.1 Urinary incontinence

Voiding or storage dysfunction due to a condition or disease occurs to almost everyone at some point during their life. Definition of incontinence using the definition of the International Continence Society (ICS) from 2002 is as follows: "Any involuntary loss of urine through the urethra." (Abrams et al. 1988) Hampel et al reviewed the results of 48 incontinence prevalence studies published between 1954 and 1995. (Hampel et al., 1997)

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Results obtained in various epidemiological studies applying three different definitions were compared based on which the average prevalence in women and men were found to be 14.0-40.5% and 4.6-15.0%, respectively. (Banyó et al., 2004)

Epidemiology of urinary incontinence

Data on the prevalence of female urinary incontinence are available from research projects conducted by several authors in Hungary. In 2003 the INKO Panel (Hungarian equivalent: INKO Fórum) in co-operation with the Hungarian health visitor network conducted an epidemiological survey interviewing 36,000 ladies over the age of 18. (Lipcsey et al., 2003)

The survey results were in line with the international prevalence data, female urinary incontinence including occasional loss of urine affects 11-36% of women participating in the surveys. By extrapolation of data the number of women with urinary incontinence in Hungary is estimated to be 600,000.

The surveys conducted in Hungary, similarly to international studies, used different methods and definitions. Not all publications include detailed description of the methods and definitions, therefore assessing the validity of results and making comparison with national and international data requires caution. At the initiative and supported by the INKO Panel Banyó conducted a survey in the female population of Pápa and surroundings. (Banyó, 2000) The data published in November 2000 showed an incontinence prevalence of 4-38% in the specific age groups. (Banyó et al., 2004)

Between 2003 and 2004 further three publications became available in Hungary by Lipcsey et al (Lipcsey et al., 2003) and Matányi et al. (Matányi et al., 2004) demonstrating the results of the epidemiological survey conducted in the female Hungarian population. Thirty-six percent of the subjects considered themselves incontinent. (Lipcsey et al.,

2003, Lipcsey et al., 2004, Matányi et al., 2004) The surveys revealed that in the majority of the cases (in 89% and 94%) the symptoms are not severe. (Lipcsey et al., 2004, Péntek et al., 2012) Results of the epidemiological surveys showed that some sort of therapy was applied in app. 32% of the urinary incontinence cases, however no further details were available in this regard. (Banyó, 2000)

Between 2011-2012 a total of 5 outpatient departments treating patients with incontinence (4 urology and 1 gynecology outpatient departments) conducted a survey among patients with overactive bladder syndrome. The aim was to evaluate the quality of life and burden of disease in those affected. The questionnaire, which included the King Health Questionnaire (KHQ) and the EQ-5D, was completed by 61 patients. The average age was 57.7 years and the average time from onset of overactive bladder syndrome was 6.6 years. Eighteen (30%), 33 (54%) and 10 (16%) patients rated their life style healthier, just as healthy and less healthy compared to others, respectively. Furthermore, this was the first study to provide data on the quality of life and fitness for work of Hungarian patients with OAB. (Péntek et al., 2012)

Urinary incontinence primarily affects women but the incidence rises with age in both sexes. Many people are affected by this disease in Hungary as well, the disease entities associated with incontinence has become endemic. (Brodszky et al., 2008, Majoros et al., 2012). This huge prevalence impose a massive burden on both the society and the patient since only a subgroup of patients has access to adequate curative therapy. While the number of patients with anti-incontinence devices rises constantly in Hungary some of the available and effective treatment options (magnetic therapy, pelvic floor exercises) (Aranyné Molnár et al., 2011, Majoros et al., 2009) are either not financed or available only in restricted number and sites (Tot Secure, Argus sling, artificial urinary sphincter). (Bajory et al., 2009, Bajory&Pajor, 2009, Bajory&Pajor, 2010) In cases when the adequate treatment option is both available and accessible (transobturator tape placement - TOT, tension-free transvaginal tape - TVT or surgery in the case of overflow incontinence due to BPH) often the inadequate patient evaluation or inadequate patient

referral systems are responsible for patients confining to use devices and losing their chance to get cured. (Bajory et al., 2008, Deák et al., 2006b, Deák et al., 2006a, Deák et al., 2010)

2.1.3.4 Overactive bladder syndrome

Overactive bladder syndrome (OAB) also called as urge incontinence may be caused by several urologic, gynecologic and neurologic disorders, other structural abnormalities and some less frequent etiologies. A wide range of different etiologic factors may result in urge incontinence / overactive bladder syndrome. A common feature of these factors is that these all impair the patient's quality of life and social relationships. (Irwin et al., 2006, Ko et al., 2006, Ouslander, 2004)

Definition of incontinence using the definition of the International Continence Society (ICS) from 2002 is as follows: "Any involuntary loss of urine through the urethra." (Abrams et al., 1988)

As per the ICS definition the overactive bladder syndrome is characterised by a compelling desire to pass urine with or without urge incontinence and is associated with frequent daytime and night urinations (>8 at daytime, >2 during night). (Abrams et al., 1988) Concluding to the definition two variants of overactive bladder syndrome exist: the so-called "dry" (without incontinence) and the "wet" (associated with incontinence) variants. Hence, the syndrome covers a larger patient group than incontinence does. (Stewart et al., 2003)

Epidemiology of overactive bladder syndrome

Review of international data

Several multinational studies were conducted to assess the prevalence of overactive bladder syndrome, however the results can be used for comparative analysis with limitations only due to the differences in the populations studied and the definitions and research methods applied. Based on various international statistics the average prevalence of incontinence is 4.6-58.5 % in women and 1.6-24 % in men. (Agarwal et al., 2006)

Hampel et al. reviewed the results of 48 incontinence prevalence studies published between 1954 and 1995. (Hampel et al., 1997) Results obtained in various epidemiological studies applying three different definitions were compared based on which the average prevalence in women and men were found to be 14.0-40.5% and 4.6-15.0%, respectively. The significant difference can be explained by the different methods applied. In the largest overactive bladder survey, the EPIC study data was collected from 19,165 women and men over 18 in telephone interviews. The study was conducted in five countries (Canada, Germany, Sweden, Italy, United Kingdom). The survey was conducted in 2005 and the terminology introduced by ICS was used for the definition of OAB. As a result of their telephone interview study Hu et al. found the prevalence of OAB to be equal in both sexes, average 11.8% (females: 12.8%, males: 10.8%) and the prevalence increased with age independently of the gender. (Hu et al., 2003)

Epidemiology in Hungary

The epidemiology of overactive bladder syndrome in Hungary is unknown. No exact statistical data are available in Hungary as to the frequency of incontinence, especially urge incontinence an overactive bladder syndrome.

In 2001 a national survey organised by the INKO Panel was conducted in Hungary to evaluate the female urinary incontinence. More than 35 thousands (35,448) women over 18 were interviewed about their incontinence complaints. The questionnaire was planned using the Gaudenz[10] Incontinence Questionnaire which is internationally acknowledged but primarily used in German-speaking countries. (Fader et al., 2007) This questionnaire recognises stress incontinence complaints relatively well, however significantly overestimates urge incontinence. The questionnaire can be used well in the case of stress incontinence, but is of less use in urge incontinence. (Majoros et al. 1998) Fifty-six percent of the subject interviewed had incontinence symptoms, however only 36% considered themselves incontinent. Although the incontinence type cannot be precisely identified based on the answers to the questionnaire, it appears that symptoms of the mixed type are the most frequent followed by those of the stress type and at last the urge symptoms[11]. With increasing age the prevalence of both incontinence and overactive bladder syndrome rises. (Inko Inforum 2002/1[12]), a survey was published also in the Inko Inforum in 2000 in which women over 18 and living in Pápa and the surroundings were interviewed about their urinary incontinence complaints using a questionnaire. Incontinence complaints were mentioned by 40% of the interviewed subjects below 30

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[10] The Gaudenz Incontinence Questionnaire asks about urge and stress symptoms, then scores the symptoms and eventually provides a diagnosis based on the scores: urge, stress or mixed incontinence. Majoros et al. (1998) are of the opinion that the questionnaire significantly overestimates urge incontinence. Its positive predictive value is 21%.
[11] Exact diagnosis cannot be established based on the answers to the questionnaire, that by all means requires a medical examination
[12] Publication of INKO Panel

and 68% of those between 51 and 65 years, respectively. Excluding the occasional instances the prevalence of urinary incontinence was found to be between 4% and 38% in the different age groups. (Matányi et al., 2000)

The prevalence of urinary incontinence was found to be 55-60% when occasional complaints were included and 15-20% when these were excluded, respectively. When comparing these data to those of international studies and extrapolate them to the Hungarian population, the number of symptomatic patients (including those with occasional symptoms) can be calculated as app. 4-500 thousands.

In their survey conducted in Budapest, Mersich et al. asked 1000 randomly selected men and women whether they had ever had difficulty holding urine. Average age of the subjects interviewed was 56.4 years. The response rate was 54.7%. Incontinence symptoms were mentioned by 56% of women and 12% of men, respectively, however only 30% of responders sought medical advice due to their complaints. (Mersich et al., 2000)

Demographic characteristics, risk factors

Overactive bladder syndrome as well as urge incontinence are more prevalent among elderly patients and the prevalence increases with the age. With respect to the incontinence episodes the involvement of men are approximately one third of that of women.

If left untreated the condition worsens, however major complications are not to be expected apart from a few exclusions (urinary tract infection, irritated skin due to persistent contamination with urine, depression). (Madersbacher, 2006) Patients rated the massively impaired quality of life as the most severe burden, which may eventually lead

to complete social isolation, severe depression and rarely to extreme psychotic events (even suicidal intent). (Irwin et al., 2006, Ko et al., 2006)

Screening of the patients affected is hampered by the fact that due to their embarrassment many patients do not seek medical help at all or only with longstanding symptoms. The symptoms affect primarily the patient (due to the frequent, strong urges to urinate he/she is unable to travel, do the shopping, often is unable to work, he/she may need to give up the previous sport and leisure activities, the complaints restrict the family life and sexual behaviour, meeting with friends). The patient is constantly worried about having an unpleasant odour and becomes socially isolated due to wearing a pad. Changes in sexual behaviour and family relationships have a negative impact on the spouse and other members of the family. In the case of patients with permanent immobility the use, management and change of medical devices (pad, condom catheters, indwelling catheters) impose a particularly heavy burden on the relatives.

3. OBJECTIVES

3.1 Assessing social burden and cost of illness in benign prostatic hyperplasia

The detailed objectives of the health economic analysis of benign prostatic hyperplasia were the following:

- reviewing and analysing the international and national literature related to social burden and cost of illness in benign prostatic hyperplasia[13]

- assessing cost of illness[14] and quality of life in Hungarian patients diagnosed with benign prostatic hyperplasia, undergoing treatment.

3.2 Cost of illness of bladder cancer in Hungary

Objective of the health economic analysis of bladder cancer patient data:

- assessing cost of illness in bladder cancer patients, especially the cost of medications[15]

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[13] Kovács Á (2015): Cost of illness in benign prostatic hyperplasia: a review. Society and Economy, 37, 4, pp. 531–542. doi: 10.1556/204.2015.37.4.7 Á, Cost of illness in benign prostatic hyperplasia: a review, Society and Economy 2015, 37, 4, 531–542

[14] Rencz F, Kovács Á, Brodszky V, Gulácsi L, Németh Z, Nagy GJ, Nagy J, Buzogány I, Böszörményi-Nagy G, Majoros A, Nyirády P (2015): Cost of illness of medically treated benign prostatic hyperplasia in Hungary. International Urology and Nephrology, 47, 8, pp. 1241-1249. doi: 10.1007/s11255-015-1028-7.

[15] Kovács Á, Hevér N (2016): A húgyhólyag daganatos betegek költsége Magyarországon. Köz-Gazdaság, XI, 3, pp. 303-317.

3.3 Male and female urinary incontinence and the epidemiology of lower urinary tract symptoms in Hungary

The objective of our research on male and female urinary incontinence was to study the following attributes:

- studying the epidemiology of female urinary incontinence[16,17,18]

- studying the epidemiology of male incontinence and the prevalence of lower urinary tract symptoms[19]

3.4 Health economic analysis of the treatment of overactive bladder syndrome

In our overactive bladder syndrome research we set the following objectives:

- cost-utility analysis of the treatment of overactive bladder syndrome[20] [21]

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[16] Kovács Á, Vártokné Hevér N, Tóth A, Pálffi B (2012): A női vizeletinkontinencia epidemiológiája Magyarországon; kérdőíves vizsgálat. Magyar Urológia, XXIV, 4, pp. 15-22.

[17] Majoros A, Sipos A, Kovács Á, Nyirády P (2014): A női vizeletinkontinencia és urogenitális prolapsusok sebészi kezelésének hazai gyakorlata. Magyar Urológia, XVI, 3, pp. 132-133.

[18] Sipos A, Kovács Á, Nyirády P, Majoros A (2015): A női vizeletinkontinencia és urogenitális prolapszusok sebészi kezelésének hazai gyakorlata. Magyar Nőorvosok Lapja, 78, 1, pp. 38-45.

[19] Kovács Á, Vártokné Hevér N, Tóth A, Pálffy B (2013): Férfiak alsó húgyúti tüneteinek gyakorisága Magyarországon - egy nyílt kérdőíves vizsgálat eredményei. Magyar Urológia, XXV, 1, pp. 22-26.

[20] Brodszky V, Ecseki A, Gulácsi L, Kovács Á, Romics I, Majoros A, Rubliczky L, Simon Zs (2008): A solifenacin (Vesicare®) magyarországi alkalmazása hiperaktív hólyag szindrómában; egészség-gazdaságtani elemzés. IME, VII, 9, pp. 30-36.

[21] Domján Zs, Kovács Á, Buzogány I (2015): A hiperaktív hólyag kezelése kismedencei prolapsusok esetében. Magyar Urológia, XXVII, p. 119.

4. HYPOTHESES

In our research the following hypotheses were formulated:

4.1 Assessing social burden and cost of illness in benign prostatic hyperplasia

Hypothesis 1. Benign prostatic hyperplasia significantly lowers quality of life.

Hypothesis 2. The direct medical costs are increasing with age and the severity of illness. Due the postponement of retirement age the active cohort is increasingly involved; the costs resulting from their lowering of productivity are significant.

4.2 Cost of illness of bladder cancer in Hungary

Hypothesis 3. Changes in the social security support of drugs significantly influence treatment practices and together they influence healthcare expenditures.

4.3 Male and female urinary incontinence and the epidemiology of lower urinary tract symptoms in Hungary

Hypothesis 4. The illness is more common in women and its prevalence increases with age.

Hypothesis 5. The number of "hidden" cases are significant in both sexes, especially in the younger cohort.

4.4 Health economic analysis of the treatment of overactive bladder syndrome

Hypothesis 6. When the cost-benefit analysis — taken from a societal perspective, also including indirect costs — of overactive bladder syndrome (also affecting people at working age) and the concomitant illnesses are both taken into account, they significantly influence the results and thereby the health policy and funding decisions.

5. METHODS

After searching for journals, we identified and analysed all the relevant publications.

5.1 Assessing social burden, cost of illness and quality of life in benign prostatic hyperplasia

5.1.1 Literature review

We performed a systematic literature research for the 2005—2015 interval in Medline PubMed, which is the most comprehensive medical literature database. Our strategy was to search for the free text appearances of phrases like "cost analysis related to benign prostatic hyperplasia" and "cost analysis of illnesses related to benign prostatic hyperplasia" in the articles.

We used the following keywords: ((bph[Title/Abstract]) OR prostatic hyperplasia [MeSH Terms]OR prostatic hyperplasia[Title/Abstract])) AND ((((costs or cost analysis [MeSH Terms] OR health expenditures[MeSH Terms]) OR health care costs [MeSH Terms]) OR cost of illness[MeSH Terms]) OR cost [Title/Abstract] OR economic burden [Title/Abstract]) NOT review[publication type][22].

The requirements for inclusion in the study were the following: (1) original article (except reviews and letters), (2) publications about the cost analysis of BPH (except where BPH were studied as an associated illness to another disease).

Studies evaluating only some selected treatments — only surgeries or only specific medications — were excluded.

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[22] Kovács Á (2015): Cost of illness in benign prostatic hyperplasia: a review. Society and Economy, 37, 4, 531–542.

The following data were collected from all included study: study design, year of publication, geographic location, perspective of cost analysis, number of patients, evaluated cost categories, year of cost and cost results.

5.1.2 Cross-sectional questionnaire survey (2014)

We conducted a non-interventional, multicenter cross-sectional study between June and October 2014. Six urology centres participated in the study, one university clinic and the outpatient clinics of four hospitals and one national institute[23].

Out of patients diagnosed with BPH, our study included only those who did not have a prostate surgery in their anamnesis. Data collection (the filling of questionnaires) were conducted when patients visited their urology specialists at outpatient clinics. The ethical approval for the study was given by the Medical Research Council, reference number: 24197-2/2014/EKU. Every patient signed the informed consent confirming their participation in the study.

The first part of the questionnaire was completed by the patients: this included questions about demography and job, the clinical attributes related to the condition of patients, the severity of illness based on self-assessment, quality of life questionnaires related to health and questions about availing health services 12 months before the filling of the questionnaire. The second part of the questionnaire was completed by urology specialists. The filling of this part was done partly based on patient documentation in which related data on how long the illness has been present and what kind of diagnostic tests and treatments were used were present. The questionnaire collected data from the last 12

month before completing the survey. The second part completed by specialists included more data on the actual status of the patients, the results of their test and the treatment applied. We used the following measures.

Measuring quality of life

We measured the patients' general, health-related quality of life with the EQ-5D-3L questionnaire (hereinafter EQ-5D). (EuroQol Group, 1990) The EQ-5D questionnaire was created to measure the general health status. It contains a descriptive part and a 20 cm long, vertical "health thermometer" (visual analogue scale, EQ VAS). EQ-5D was primarily created to be used as a self-filling questionnaire. The descriptive part of the questionnaire explores 5 dimensions of health (mobility, self-sufficiency, usual activities, pain/discomfort and anxiety/depression). In every dimension the subjects have to choose the most appropriate answer on the actual day from 3 options. 1 means "no problem", 2 means "some problems" and 3 means "extreme problems/inability". (Gulácsi, 2012, Péntek, 2014)

A so-called utility value can be calculated from the descriptive part of the questionnaire (EQ-5D index), which reflects the actually preferred health status from a societal view. Lacking national health status utility values in Hungary, values used in the United Kingdom are applied. (Dolan, 1997)

For measuring the severity of illnesses, the International Prostate Symptom Score test (I-PSS) was used. (Barry et al., 1992) I-PSS contains 7 elements related to urination and urinary continence covering a 1 month period. It also contains a question about the quality of life. Every question gets a value from 1 to 5 except the question about the quality of life which is rated on a 0 to 6 point scale. The score of I-PSS can be calculated by the first seven questions and can be rated from 0 to 35 where higher scores reflect a more severe illness. Based on the I-PSS score, patients can be categorized into 3 groups: mild (I-PSS

score: 0-7), moderate (I-PSS score: 8-19) and severe (I-PSS score: 20-35) disease. Alongside the usage of I-PSS, urologist also valued the severity of illness on a 10 point visual analogue scale.

The effect of BPH on work productivity was measured with The Work Productivity and Activity Impairment (WPAI) questionnaire. (Reilly et al., 1993) In the WPAI questionnaire patients gave the actual hours spent with work, missed work hours because of BPH or other reasons, and also gave information about the effect of BPH on their work on an 11 point scale.

Cost calculation

Cost calculation was done from a societal view, based on data collected from patients and specialists. Costs were classified into three categories: direct medical costs, direct non-medical costs and indirect costs (productivity loss). Co-payment was considered as direct medical cost. Only those resource expenditures were taken into account that emerged in the last 12 month because of BPH. Every cost was converted to Euros using the 1 € = 308.71 HUF exchange rate.

Direct medical costs

To assess the direct medical costs of benign prostatic hyperplasia we collected the following data on financed medical services: Doctor visits on account of BPH (general practitioner or urology specialist), hospital admission on account of BPH, usage of diagnostic tests and medications, availing ambulance transportation or home nursing. Furthermore we collected data on the utilization and costs medical services not financed by social insurance, for example the costs of visiting a private urology specialist. We also

considered the utilization of medicinal and pharmaceutical products, appliances related to BPH. In cases of services financed by social insurance, official costs and prices of the National Health Insurance Fund of Hungary (OEP) were used. Patients gave information about the number of their doctor visits during the last 3 months (general practitioners and urology specialists separately). A conservative approach was applied where 4 visits were calculated for each patient who noted ≥4 visits per year at the urology specialist and 12 visits for those who noted ≥12 visits per year at the general practitioner.

The number of doctor visits were multiplied with the following unit prices (except tests): family doctor: 4.2 €, urologist: 3.6 €. The cost of inpatient care was calculated by multiplying the number of days spent in a hospital in the last 12 months with the hospital costs (67.8 €/day) (OEP, 2014). Diagnostic tests were evaluated using the official outpatient care prices, for example PSA testing: 8.1 €, uroflowmetry: 1 €, urodynamic test: 75.4 €, abdominal ultrasound: 4.6 €, transrectal ultrasound: 3.7 € and the examination of the bladder with ultrasound to measure urine volume after urination: 1.6 €. (OEP, 2014b)

Costs of medicines were estimated by the national official price list. (OEP 2014b) Costs of phytotherapy (pharmaceutical plants) and other products not financed by social insurance were estimated by the patients' answers on their monthly expenditures.

Patients gave information about the quantity of appliances used by them in the last month (for example: permanent and disposable catheters, urine collecting bags and tampons). Unit costs of these were requested from the official appliances price list of the National Health Insurance Fund of Hungary (OEP). (OEP 2014b)

To estimate the costs of ambulance transportation we multiplied the distance between the patient's home and the clinic, the number of transportations in the last 12 months and the cost of transportation per one kilometre (0.7 €). Costs of home nursing — cases financed by social insurance, catheter replacement (9.7 €/occasion) for example — were provided by the OEP database.

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Direct non-medical costs

Informal care provided by family members and relatives was estimated by patient answers on the amount of help received weekly, multiplied with the average net hourly wage. (3.1 € in 2014). (KSH 2014) Furthermore, direct non-medical costs also included the travel expenses of doctor visits except the costs of ambulance transportation, which were calculated as part of the direct medical costs. Patients' travel expenses and the accompanying person were also estimated.

Indirect costs

Costs emerging from reduced work capacity were calculated by using a human capital approach based upon patient answers on the WPAI questionnaire. (Braakman-Jansen et al., 2012) Absenteeism (absence from work because of benign prostatic hyperplasia) and presenteeism (reduced productivity at work because of BPH) were taken into account.

For the calculation of indirect costs the average gross hourly wage were used (6 € in 2014), which included the net salary, the personal income tax, the pension contributions, the health contribution tax and the annuities paid by the employer. (KSH 2014)

Statistical processing

Statistical analysis were performed with SPSS 22.0 (Armonk, NY: IBM Corp.) software. First we performed the calculation of descriptive statistics. 2000 replications bootstrap test were used because of the biased distribution of cost data with a 95% confidence interval and with the correction of the bias. The explanatory variables of costs were tested

with an independent patterned t-test, with a one-way ANOVA post hoc TamhaneT2 test and with Pearson correlation. Every statistical test was two sided, the p-value was considered statistically significant when it was lower than 0.05 ($p < 0.05$).

5.2 Cost of illness of bladder cancer in Hungary

5.2.1 Analysis of the National Health Insurance Fund's drug and patient flow database

For the study of Hungarian bladder cancer patient care international and national statistical data along with the National Health Insurance Fund's drug and patient flow database were used[24].

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[24] Kovács Á, Hevér N (2016): A húgyhólyag daganatos betegek költsége Magyarországon. Köz-Gazdaság, XI, 3, pp. 303-317.

5.3 Male and female urinary incontinence and the epidemiology of lower urinary tract symptoms in Hungary

5.3.1 Epidemiology and the surgical treatment practice of female urinary incontinence in Hungary

The chapter is based on earlier publications[25,26,27,28.]

Patients and method

I studied the epidemiology of female urinary incontinence with questionnaire survey in 2011. (Kovács Á et al., 2012)

The questionnaire survey discussed here was conducted in 2011 as part of the "Comprehensive Hungarian Health Promotion Screening Programme 2010-2020". Anyone could fill out the survey who wanted to participate voluntarily. No data allowing personal identification of participants were collected during the questionnaire survey. Questions were compiled based on the professional proposal of the Hungarian Society of Urology and the Incontinence Patient Association.

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[25] Kovács Á, Vártokné Hevér N, Tóth A, Pálffi B (2012): A női vizeletinkontinencia epidemiológiája Magyarországon; kérdőíves vizsgálat. Magyar Urológia, XXIV, 4, pp. 15-22.

[26] Majoros A, Sipos A, Kovács Á, Nyirády P (2014): A női vizeletinkontinencia és urogenitális prolapsusok sebészi kezelésének hazai gyakorlata. Magyar Urológia, XVI, 3, 132-133.

[27] Majoros A, Sipos A, Kovács Á, Nyirády P (2015): A női vizeletinkontinencia és urogenitális prolapszusok sebészi kezelésének hazai gyakorlata. Magyar Nőorvosok Lapja, 78, 1, 38-45.

[28] Kovács Á, Vártokné Hevér N, Tóth A, Pálffy B (2013): Férfiak alsó húgyúti tüneteinek gyakorisága Magyarországon - egy nyílt kérdőíves vizsgálat eredményei. Hungarian Urology, 2013;25,1, 22-26

The questionnaire (see Annex 3) contained 13 questions about urinating habits and the possible problems with urinary continence and urination. The study of the Hungarian surgical practice of female incontinence and urogenital prolapse was conducted at around the same time. The questionnaire was compiled by the leaders of the Hungarian Continence Society's working group. The aim of this was to study Hungarian surgical treatments quantitatively and qualitatively. We requested head physicians leading Hungarian Urology and Gynecology Departments to fill the survey titled "Questionnaire about the surgical treatment of female urinary incontinence and genital prolapse" in a postal letter between August 2011 and February 2012.

5.3.2   The prevalence of lower urinary tract symptoms in Hungarian men

To evaluate men's symptoms in the screening programme the International Prostate Symptom Score (I-PSS, hereinafter I-PSS questionnaire) were used. We processed the results of these questionnaires in our study. Anyone could fill out the I-PSS questionnaire who visited any of the study sites and wanted to participate voluntarily. The completing of the test sheets were taking place at 191 sites in the country. A total of 7888 men participated in answering the questions. 7713 adults (at least 18 years old) informed us about their age — we analysed their data. This proportion is equal to 0.2 percent of adult men living in Hungary. Men's average age was 39.9 (SD 12.2) in the studied adult men sample.

SPSS (Statistical Package for the Social Sciences) software package was used for the statistical processing of the data.

5.4 Health economic analysis of the treatment of overactive bladder syndrome

The clinical efficacy and cost-utility of solifenacin were studied in overactive bladder syndrome. Other medicines also can be given in this indication: currently Detrusitol® (tolterodin IR), Ditropan® – Uroxal® (oxybutynin IR) and Emselex® (darifenacin CR) are marketed in Hungary. Because of similar indications, we also evaluated the cost-effectiveness of oxybutynin and darifenacin in our study. The objective of our study was to compare the effectiveness and costs of different treatment strategies currently marketed and financed by social insurance in Hungary. Detrusitol® (containing tolterodin) is free-pricing, so we did not include it in our study.

Cost-effectiveness analysis was conducted with a decision tree model; to build this model, we used the TreeAge Pro software (TreeAge Software, Inc, Williamstown, Mass). The decision tree built by us is an adaptation of the modified version of the decision tree built by Ko et al.. (Brodszky et al., 2008)

Aided by this model, we conducted the comparison of the costs and clinical efficacy of solifenacin, darifenacin and oxybutynin IR therapies.

6. RESULTS, DISCUSSION AND CONCLUSIONS

Since I report more research conducted in different fields, different objectives and methods in The Thesis, results, discussion and conclusions were discussed in one chapter by subject areas for reasons of clarity.

6.1 Assessing social burden, cost of illness and quality of life in benign prostatic hyperplasia

6.1.1 Literature review

6.1.1.1 Literature research

Literature research yielded 159 matches. 148 of these were excluded from the study for reasons listed below: BPH was not included or the costs were not reported in 84 studies; 12 studies was not an original article; 16 studies used another type of evaluation (for example cost-effectivenes or cost-minimization analysis) and 36 studies only analysed some types of treatment or did not mention the costs per patient, just the costs of the whole cohort or the whole patient population of the country[29].

Finally we included 11 publications in our review which both met the inclusion and exclusion criteria (Table 1). (Bellinger et al., 2012, Cozar&Huerta, 2013, Disantostefano

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[29] Kovács Á (2015): Cost of illness in benign prostatic hyperplasia: a review. Society and Economy, 37, 4, pp. 531–542. doi: 10.1556/204.2015.37.4.7

et al., 2006, Johansen&Istad, 2007, Kirby et al., 2010, Litwin et al., 2005, Saigal&Joyce, 2005, Saigal et al., 2007, Strope et al., 2011, Van Exel et al., 2006, Wei et al., 2005)

Four studies were conducted in European countries and seven in The United States. There was a multinational research involving six European countries (France, Germany, Italy, Poland, Spain, and UK). Two studies were cross-sectional, two were Markov-models and seven were retrospective insurance claims database analysis. Phone interviews and questionnaire surveys were used in the cross-sectional studies. Sample size varied from 1000 to 40,253 capita, but two studies did not mention the number of patients included. Nine studies applied payer perspective for cost calculation, one study used societal perspective and one study used both.

The time horizon of the studies ranged between 1 month and 20 years (average expected lifetime for a BPH patient at the time of diagnosis) while the most commonly used time horizon was 1 year. Year of costs in the studies varied from 1998 to 2012.

6.1.1.2 Costs

8 studies reported costs per patient (Table 1) and 5 studies reported nationwide costs or the cost of a bigger cohort (Table 2). Regarding cost categories, 10 studies considered only direct medical costs and one study considered both direct and indirect costs. The study of Disantostefano et al. only evaluated treatment costs. Besides direct costs, Johansen et al also included the loss of productivity and free time as indirect costs.

Direct medical costs of BPH showed a big difference in individual studies. Direct annual medical costs per patient fluctuated between 255 USD and 5729 USD in the United States, while in Europe, the same costs fluctuated between 253 EUR and 1251 EUR. In Norway, costs on the 4-year and on the 15.5 year horizon fluctuated between 1703 and 7638 EUR and 3924 EUR and 8307 EUR respectively, depending on treatment modalities and cost calculation perspective. In the United States, 5-year direct medical costs fluctuated

between 2193 USD and 12,699 USD. Average costs of patients undergoing surgery exceeded the costs of patients receiving pharmaceutical treatment both in the United States and Europe. In the United States, the costs of patients requesting healthcare claims (5729 USD) were higher than those who did not request claims (4193 USD).

Triumph project (Trans European Research into the use of Management Policies for LUTS suggestive of BPH) was a one-year long, prospective, cross-sectional, observational study including 5077 patients with lower urinary tract symptoms implying BPH from France, Germany, Italy, Poland, Spain and the United Kingdom. (van Exel et al., 2006) Here we only evaluated direct medical costs and collected data related to potential complications, like urinary retention, bleeding, disturbed kidney function, urinary tract infections and bladder stones. Although patients enrolled in the six countries were mostly similar to each other, treatment practices varied between countries. For example, the number of annual visits at the urologist varied between 1.0 (France, Italy, United Kingdom) and 2.7 (Germany), the rate of abdominal ultrasounds varied between 11% (United Kingdom) and 83% (Poland), the rate of rectal ultrasound varied between 1% (United Kingdom) and 26% (France), the testing of prostate-specific antigen (PSA) varied between 41% (Germany) and 88% (Spain) and the rate of urine flow test varied between 4% (Italy) and 26% (Spain). The rate of watchful waiting (when there is no specific treatment, only controls) was the lowest in Italy and Poland (20%), while it was the highest in the United Kingdom (69%). The rate of patients treated with alpha-blockers varied between 2% (United Kingdom) and 9% (Germany and France), while the rate of patients treated with phytotherapy varied between 1.4% (Poland) and 16.5% (France). The lowest surgical treatment rate was in the United Kingdom (1.7%), while the highest rate was in Poland (6.4%). The total direct medical cost of BPH was 639 EUR in France, 513 EUR in Germany, 633 in Italy, 1337 EUR in Poland, 595 EUR in Spain and 292 EUR in the United Kingdom (2003). The dominant cost drivers were pharmaceuticals since they were accountable for nearly three-quarters of the whole treatment cost (the amount of this varied between 40% in France and 89% in Poland). The costs of surgical treatments

were accountable for 15% of total cost, while the costs of diagnostic tests were accountable for 8% of total cost. More severe illness was accompanied with higher costs both in the cases of urination (mild: 673 USD; moderate: 906 UDS; severe: 960 EUR), and in the cases of continence symptoms (mild: 623 USD; moderate: 865 EUR; severe: 1043 EUR). (van Exel et al., 2006)

Estimated cost amounts spent for the treatment of BPH nationwide were released by the United States of America and by the United Kingdom. In 2008, the annual total direct medical cost related to BPH nationwide was 180.8 million GBP in the United Kingdom. (Kirby et al., 2010) Based on insurance claims related costs, nationwide cost of BPH in the United States was 776 million USD in 1998 (Litwin et al., 2005), and 1.1 billion USD in 2000. (Wei et al., 2005) However, another study concerning 1999 describes that the total cost of BPH treatment (total direct and indirect costs) was 3.9 billion annually in the private sector. (Saigal&Joyce, 2005)

6.1.1.3 Discussion of results

In our study, we summarized BPH related cost of illness results of eleven studies published in the last 10 years. These studies were conducted in 8 countries of Europe and the United States. Direct medical costs per patient fluctuated annually between 255 USD and 5729 USD in the United States and annually between 253 EUR and 1251 EUR in Europe. Despite there were no new data available on the nationwide expenditures from most countries, the estimated total costs based on per patient results were significant in all countries.

Direct medical costs, namely the costs of medical examinations, hospital treatments, diagnostic tests and treatments were responsible for most parts of total costs. According to the publications, only a small proportion of men living with BPH visited a doctor (Rosen et al., 2003), which indicates that the direct costs can be higher than this. Acute urinary retention and other complications can emerge in BPH patients with symptoms,

especially in untreated cases. The risk of having acute urinary retention in the next 5 years of men in their eighties is one to three. (Emberton&Anson, 1999) These complications can significantly increase the direct medical costs of BPH. In 2007/2008, the annual total costs related to the most frequent complications of BPH reached 101.2 million GBP nationwide in the United Kingdom's secondary patient care. (Kirby et al., 2010)

 Most of the recently reviewed studies have taken the direct medical costs related to BPH into account, but we also have to calculate with significant indirect costs. Based on the data of more than 120,000 men of working age owning a private insurance, Saigal and Joyce found that an average employer annually spent an average of 7.3 working hours away from their job due to the presence of BPH (approximately 7.1 hours due to outpatient care and approximately 0.2 hours due to hospital treatment). (Saigal&Joyce, 2005) In this study, only a small proportion of the patients were absent from their place of employment in the last year (10%). Those who reported absence from their job while undergoing BPH treatment, the average time of absenteeism exceeded 9 days annually. The indirect costs of employers owning a private insurance were 500 million USD according to the estimations (1999). None of the studies evaluated the costs related to presenteeism (being present at the place of employment but with a reduced productivity due to BPH). However, BPH has a very negative influence on the quality of life. (Fourcade et al., 2012, Schulz et al., 2002), similarly to symptoms associated with epilepsy, chronic migraine or psoriasis (Heredi et al., 2014, Moradi et al., 2015, Pentek et al., 2013, Rencz et al., 2014a, Rencz et al., 2015b) Urinary tract symptoms can also disturb patients during work, which will lead to reduced productivity ("presenteeism").

Parallelly with aging population, retirement age is also increasing in industrialised countries. In the 34 member states of the OECD, the official retirement age were 64.65 on average in 2012. However, in some countries like Australia, the United States, Norway, Israel and Iceland retirement age is above 65 years. (OECD, 2012) Furthermore, in some developed countries, the real age of retirement can exceed official retirement age with more five years, for example in France, Belgium and Luxemburg. According to

forecasts, retirement age will increase in the next decade, therefore we can expect a rise in the direct costs related to aging, including the costs related to BPH. According to what we found in our review, BPH related presenteeism seems like a poorly observed phenomenon. It is strongly recommended to conduct further studies to find out more about the distribution of the costs arising from absenteeism and presenteeism.

Study limitations can arise from the heterogeneity of studies, sample sizes, the attributes of patient populations, study designs, differences between countries and practiced treatments, costs per units and the methods used to calculate costs. Due to these limitations, direct comparison of the studies can be hard. Cost year marked in the studies was between 1999 and 2012. Since 1999, technological advances and the new pharmaceutical treatments available for BPH changed cost patterns. Furthermore, this review did not evaluated studies that reported the costs of only one or only some chosen treatment types.

6.1.1.4 Conclusions

BPH is an age-related illness which is more and more common over the age of 40. Due to demographic aging, continually increasing life expectancy and the high prevalence of illness, BPH means a high economic burden to the healthcare budget of developed countries. Due to demographic factors and the expected novelties in the field of urologic surgery, costs of BPH will likely rise in the future. Due to the increasing number of patients, more qualified urologist will be needed to provide the proper capacity for the optimal treatment of BPH. According to forecasts, retirement age will increase in the next decade, therefore we can expect a significant rise in the direct costs related to aging, including the costs related to BPH. In order to aid the transparent and cost efficient treatment of BPH, it would be essential to draft the rational clinical guidelines which could result in significant improvements in the quality of treatment and in the decreasing of healthcare expenses.

Table 1 Costs of BPH per patient

Author (year)	Study design	Study year	Countries	Patients (N)	Perspective	Evaluated cost categories	Year of expenses	Time horizon	Results
van Exel, 2006	cross-sectional questionnaire survey	February 2000 - May 2003	France	991	payer perspective	direct medical costs per patient including diagnostics, treatment and complications	EUR, 2003	1 year	639 EUR
			Germany	443					513 EUR
			Italy	671					633 EUR
			Poland	1823					1183 EUR
			Spain	952					595 EUR
			United Kingdom	177					292 EUR
Cozar, 2013	cross-sectional phone interviews (153 general practitioner, 154 urologist)	April—May 2010	Spain	NR	payer perspective	direct medical costs /patient diagnostics and treatment	EUR, 2012	1 year	253 – 1251 EUR
Johansen, 2007	Markov-model	2006	Norway	1000	payer and societal perspective	total cost direct and indirect costs	EUR, 2006	4 years	Drug: 1703 – 2054, TURP: 5655 EUR* Drug: 1938 – 2555, TURP: 7638 EUR**
								15.5 years	Drug: 3924 – 494, TURP: 6164 EUR* Drug: 4315 – 5861, TURP: 8307 EUR**

Author (year)	Study design	Study year	Countries	Patients (N)	Perspective	Evaluated cost categories	Year of expenses	Time horizon	Results
Bellinger, 2012	insurance claim database analysis	2000-2007	United States	40 253	payer perspective	direct medical costs per patient including diagnostics and	USD, 2007	1 year (first year after diagnosis)	2000: 255 USD 2007: 344 USD
Saigal, 2005	insurance claim database analysis	1999	United States	2013	payer perspective	direct medical costs per patient	USD, 1999	1 year	without healthcare claim 4193 USD with healthcare claim: 5729 USD
Saigal, 2007	insurance claim database analysis	1997-2002	United States	1952	payer perspective	direct medical costs per patient	USD, 2002	5 years	Drug, first cohort: 2193 USD Surgery, first cohort 12 699 USD
Strope, 2011	insurance claim database analysis	1999-2007	United States	NR	payer perspective	direct medical costs per patient	USD, 2007	1 month	35 – 527 (median 92 USD)
Disantostefano, 2006	Markov-model	2004	United States	1000	societal perspective	treatment cost per patient	USD, 2004	20 years	*1. year:* 195 USD; AB: 628 USD; 5-ARI: 900 USD; Combined treatment: 1333 USD; TUMT: 4073 USD; TURP: 7201 USD *Following years:* 108 USD; AB 541 USD; 5-ARI: 870 USD; Combined treatment: 1247 USD; TUMT: 54 USD; TURP: 54 USD

5-ARI = 5-alpha reductase inhibitor, AB = alpha-blocker, NR = Not Reported, TUMT = Transurethral microwave therapy, TURP = Transurethral prostatectomy, WW = Watchful Waiting
*Payer perspective
** Societal perspective

Table 2 Costs of larger patient cohorts or total costs at the national level

Author (year)	Study design	Year of study	Countries	Patients	Perspective	Evaluated cost categories	Year of expenses	Time frame	Results
Litwin, 2005	insurance claim database analysis	1998-2000	United States	nationwide	payer perspective	direct medical costs	USD, 1998	1 year	776 million USD
Saigal, 2005	insurance claim database analysis	1999	United States	every patient who owns a private insurance	payer perspective	direct and indirect costs	USD, 1999	1 year	3,9 billion USD
Wei, 2005	insurance claim database analysis	1990-2000	United States	nationwide	payer perspective	direct medical costs except the drug costs of outpatients	USD, 2000	1 year	1.1 billion USD
Kirby, 2010	Hospital Episode Statistics (HES)	2007-2008	United Kingdom	nationwide	payer perspective	direct medical costs	GBP, 2008	1 year	180.8 million GBP
Bellinger, 2012	insurance claim database analysis	2000-2007	United States	Medicare 5% cohort	payer perspective	direct medical costs	USD, 2007	1 year (first year after diagnosis)	32.3 million USD

6.1.2 Cross-sectional questionnaire survey: cost of illness and quality of life of patients diagnosed with benign prostatic hyperplasia

The results presented in this chapter were described in more detail in our Rencz et al (2015) publication[30].

6.1.2.1 Cross-sectional questionnaire survey: cost of illness of patients diagnosed with benign prostatic hyperplasia

Attributes of the patient population

The key demographic and clinical features of the patients are shown in Tables 3 and 7. A total of 246 patients were included in the survey. The average age was 70.6 (SD=8.1 years), the average duration of the disease was 6.5 years (SD 6.2 years). According to the Body Mass Index (BMI), 182 patients (74%) were overweight or obese (BMI>25).

The average of the EQ-5D index and the EQ VAS scores of patients were 0.85 (SD=0.9) and 68.4 (SD=15.5) respectively. For 111 patients (45%), the EQ-5D index was 1. In total, 8%, 19%, 28%, 30% and 31% reported moderate or severe problems in self-care, usual activities, anxiety/depression, pain/discomfort and mobility. The average of the I-PSS scores was 12.8 (SD=6.3) in the sample. According to the I-PSS score, 52 (23%), 136 (61%) and 35 (16%) patients were in the mild, moderate and severe BPH groups, respectively.

Table 3 The demographic and clinical characteristics of the patient population

	N (%)	Mean ± SD	Range (min.-max.)
Demographic characteristics			
Age (year)	246 (100%)	70.59 ± 8.13	49-93
BMI (kg/m^2)	242 (98.4%)	27.68 ± 3.88	18-44
Employment (N=243)			
Full-time job	33 (13.4%)	-	-
Part-time job	4 (1.6%)	-	-
Retired	202 (82.1%)	-	-
Disability pensioner	2 (0.8%)	-	-
Unemployed	1 (0.4%)	-	-
Other	1 (0.4%)	-	-
Clinical characteristics			
disease duration (year)	239 (97.2%)	6.5 ± 6.2	0-27
Symptomatic pts at the time of the survey	125 (50.8%)	-	-
AUR in the last 12 months	45 (18.3%)	-	-
Indwelling catheter at the time of the survey	19 (7.7%)	-	-
Health-related quality of life			
EQ-5D[§] (-0.594-1)	237 (96.3%)	0.85 ± 0.19	-0,23-1
EQ VAS (0-100)	233 (94.7%)	68.37 ± 15.54	10-100
I-PSS (0-35)	223 (90.7%)	12.80 ± 6.34	1-35
I-PSS Q8 (0-6)	227 (92.3%)	2.46 ± 1.62	0-6

BMI = Body Mass Index; AUR = acute urinary retention; I-PSS = International Prostate Symptom Score

The use and costs of health care resources

Out of the 246 patients 244 (99%) received outpatient care, and 25 (10%) were hospitalized because of BPH in the past 12 months. Overall, 211 patients (86%) were treated with medication, and 35 (14%) were under observation/watchful waiting, 7 of

whom had indications for surgery. Table 4 summarises the use of health care services by the patient group. The total annual per-patient cost of BPH was 876 € (SD=1829 €). The costs broke down as follows: direct medical costs 46%, direct non-medical costs 31% and indirect costs 23%. (Table 5) Medication costs amounted to 43% of direct costs (173 €). A major part of the total medication cost (77%) came from phytotherapy (81 €) and alpha-blockers (55 €). In addition, informal care (243 €) and visits to private medical professionals (132 €) also resulted in significant costs. Indirect cost amounted to a total of 204 €, where presenteeism was 41% and absenteeism was 59%

Explanatory variables of the costs

There was no significant correlation between the total cost and either age, or the duration of the disease or BMI. Age, however, had a positive correlation with direct non-medical costs (r=0.268, p<0.001) and was inversely proportionate to indirect costs (r=-0.147, p<0.001). No significant correlation was observed between costs and catheter use in the research period or between costs and acute urinary retention (AUR) in the past 12 months. We found that there was moderately strong correlation between the total cost and the I-PSS score (r=0.429, p <0.001). However, there was only weak correlation with the EQ-5D index ($r = -0.307$, $p <0.001$) and the EQ VAS ($r = -0.229$, $p = 0.001$). Direct medical costs correlated only with the I-PSS score ($r = 0.305$, $p <0.001$), while direct non-medical costs correlated with the I-PSS ($r= 0.374$, $p <0.001$), the EQ-5D ($r=-0.416$, $p <0.001$) and the EQ VAS ($r = -0.368$, $p <0.001$) as well. There was no significant correlation between indirect costs and any of the quality of life measures.

Figure 8 shows the costs broken down by I-PSS severity groups. The average annual per-patient cost for patients in the mild, moderate and severe severity groups were 203 € (SD=141 €), 754 € (SD=1118 €) and 2168 € (SD=2850 €) respectively.

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Direct costs were the highest in the severe I-PSS group, indirect costs, however, were higher in the moderate group. There were significant differences in the costs of the mild and the severe, and the moderate and severe groups ($p = 0.001$, $p = 0.021$). Significantly higher medical costs were associated with patients in the severe I-PSS group than with patients in the mild group (p=0.001), but this was not the case when compared to the moderate group (p=0.928). Direct non-medical costs were significantly higher in the severe group than in the mild group (p=0.005), and the moderate group (p=0.006).

Table 4 Use of health care resources in the past 12 months

	Patients ≥ 1	Average number of
Outpatient care	**244 (99.2%)**	-
Visit to GP	45 (18.6%)	0.9
Visit to urologist	244 (99.2%)	3.3
Hospital admission	**25 (10.4%)**	0.4
Diagnostic tests	**244 (99.2%)**	-
Urine sediment	239 (97.2%)	1.3
Blood test (kidney function)	220 (89.4%)	1.1
Prostate-Specific Antigen (PSA)	243 (98.8%)	1.2
Digital rectal examination	241 (98.0%)	1.5
I-PSS scoring	211 (85.8%)	1.0
Uroflowmetry	159 (64.6%)	1.0
Urodynamic test	35 (14.2%)	0.2
Ultrasound examination of the bladder	165 (67.1%)	0.9
Abdominal ultrasound	240 (97.6%)	1.5
Transrectal ultrasound	110 (44.7%)	0.5
Medication*§	**211 (85.8%)**	-
Alpha-blockers (AB)	158 (64.2%)	234.4
5-alpha-reductase-inhibitors (5-ARI)	15 (6.1%)	22.3
Combination therapy (AB + 5-ARI)	25 (10.2%)	37.1
Antimuscarinics	9 (3.7%)	13.4
Phytotherapy and other medicinal products**	108 (43.9%)	160.2
Other	1 (0.4%)	1.5
Medical devices	**32 (13.0%)**	-
Indwelling catheter	21 (8.5%)	2.2
Disposable catheter	10 (4.1%)	1.0
Incontinence pad	3 (1.2%)	6.2
Urine collection bag	18 (7.3%)	9.8
Other reimbursed services	**6 (2.4%)**	-
At-home nursing care	1 (0.4%)	0.2
Ambulance transport	5 (2.0%)	0.2
Not reimbursed services	**36 (14.7%)**	-
Private physician visit	36 (14.7%)	0.8
not reimbursed medical devices	2 (0.8%)	-
Non-health care services	**166 (67.5%)**	-
Informal care	16 (6.5%)	1.5 hours/week
Travel costs/transportation	165 (67.1%)	-
Productivity loss	**19 (7.7%)**	-
Presenteeism	16 (6.5%)	19.9 hours/year
Absenteeism	7 (2.8%)	14.0 hours/year

* 35 patients were not treated with medication, there was an indication for surgery in 7 cases, while 28 were under observation and watchful waiting

§ Combinations occurred

Table 5 Annual per-patient costs of BPH (€, 2014)

	Mean	SD	BCa 95%*	Median	Minimum	Maximum
TOTAL COST	**876.4**	**1829.1**	**669.5-1123.8**	**296.6**	**0**	**18398.8**
DIRECT MEDICAL COSTS	**405.5**	**497.7**	**349.6-464.7**	**222.1**	**0**	**3426.4**
Medical care	**45.9**	**111.2**	**33.1-59.9**	**14.6**	**0**	**845.1**
Visit to GP	3.9	9.4	2.7-5.1	0	0	50.5
Visit to urologist	11.9	4.7	11.3-12.5	14.6	0	14.6
Hospital admission	30.0	109.3	18.5-42.7	0	0	813.6
Diagnostic tests	**36.1**	**33.6**	**32.1-40.5**	**21.9**	**0**	**178.5**
Urine sediment	0.4	0.3	0.37-0.42	0.3	0	2.5
Blood test (kidney function)	2.1	1.3	1.9-2.2	1.8	0	11.0
Prostate-Specific Antigen (PSA)	9.7	7.3	9.0-10.7	8.1	0	1.4
Digital rectal examination	0.4	0.2	0.38-0.43	0.3	0	4.9
I-PSS scoring	0.5	0.5	0.45-0.57	0.5	0	97.4
Uroflowmetry	0.9	0.9	0.84-1.03	1.0	0	5.8
Urodynamic test	12.0	30.8	8.6-15.3	0	0	150.7
Ultrasound examination of the bladder	1.4	1.4	1.3-1.6	1.6	0	9.7
Abdominal ultrasound	6.9	3.5	6.5-7.4	4.6	0	27.5
Transrectal ultrasound	1.8	2.1	1.5-2.0	0	0	11.1
Medication	**178.4**	**157.7**	**159.6-199.6**	**117.3**	**0**	**1399.4**
Alpha-blockers (AB)	55.2	42.2	49.7-60.5	79.1	0	104.3
5-alpha-reductase-inhibitors (5-ARI)	7.5	33.5	4.1-11.2	0	0	249.7

	Mean	SD	BCa 95%*	Median	Minimum	Maximum
Combination therapy (AB + 5-ARI)	26.9	80.3	18.3-35.6	0	0	265.1
Antimuscarinics	7.0	40.1	2.8-12.0	0	0	252.4
Other	0.5	8.4	0-1.1	0	0	132.4
Medical devices	**6.3**	**25.6**	**3.4-9.9**	**0**	**0**	**212.9**
Indwelling catheter	1.8	6.3	1.1-2.6	0	0	39.0
Disposable catheter	0.2	1.5	0.1-0.4	0	0	14.8
Incontinence pad	1.0	11.1	0.1-2.1	0	0	164.4
Urine collection bag	3.3	19.0	1.3-6.0	0	0	183.5
Other reimbursed medical services	**6.1**	**64.0**	**0.3-15.4**	**0**	**0**	**819.6**
At-home nursing care	2.4	37.2	0-2.4	0	0	582.7
Ambulance transport	3.7	52.3	0.2-10.3	0	0	819.6
Other services not reimbursed	**132.6**	**403.1**	**85.6-183.5**	**0**	**0**	**3109.7**
Private physician visit	132.4	403.1	89.1-180.5	0	0	3,109,7
Other not reimbursed medical devices	0.2	3.7	0.0-0.7	0	0	58.3
TOTAL DIRECT NON-MEDICAL COSTS	**267.3**	**1165.5**	**147.9-401.5**	**16.4**	**0**	**9733.2**
Informal care	243.3	1157.7	117.4-400.6	0	0	9678.8
Travel costs (except ambulance transport)	24.0	40.9	19.4-29.2	12.4	0	394.2
TOTAL INDIRECT COSTS	**203.6**	**1284.4**	**87.8-362.3**	**0**	**0**	**18232.5**
Absenteeism	84.0	1119.9	7.6-225.2	0	0	17528.2
Presenteeism	119.7	538.0	61.4-190.2	0	0	5258.5

*BCa95% = bootstrap 95% CI accelerated percentile method, 2000 replications

** not paid for by social security

Figure 8 Per-patient costs by cost categories in the I-PSS severity groups
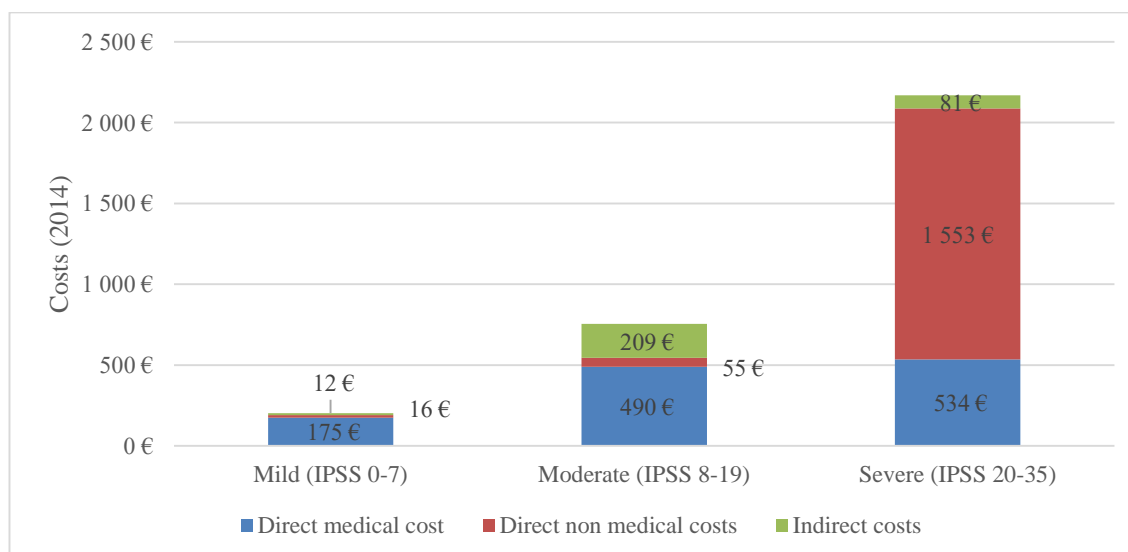
The total annual per-patient cost of BPH was 876 €, 77% of which were direct costs. This is a considerably lower value than in case of other chronic diseases in Hungary (e.g. epilepsy, Parkinson's disease, psoriasis (2421-9254 €) (Balogh et al., 2014, Pentek et al., 2013, Rencz et al., 2014a, Tamas et al., 2014). According to IMS data on the use of medication in relation to BPH in Hungary, the total number of BPH patients receiving medication was approximately 140,000 in 2010. (A jóindulatú prosztata megnagyobbodás (BPH) kezelésének gyógyszerészi és háziorvosi irányelve 2012) By applying our cost calculation estimate to this data, the total burden of disease of BPH is approximately 122.8 million EUR annually in Hungary. Over 198,000 working hours lost annually to absenteeism and presenteeism are included in this amount. Direct medical costs amounted to 56.8 million EUR in the country, which equalled to 0.78% of the total healthcare expenditure in 2013. (OECD, 2015)

As far as we know, the estimate for the costs of presenteeism in BPH provided in this research is the first of its kind in the world. Even though only 15% of the patients in the sample worked full time or part time during the research period, the indirect costs were

rather high, they amounted to 23% of total costs. Our results suggest that presenteeism is the largest cost element in indirect costs.

Decreased labour productivity, a result of the urinary tract symptoms of BPH, caused an average of 120 € / patient loss (average: 20 hours/year). In the US, Saigal et al analysed data of over 120,000 men of working age with private insurance. (Saigal&Joyce, 2005) They found that an average employee missed 7.3 working hours from work annually, which is lower than what we saw in our research (average: 14 hours/year). Our results showed that absenteeism and presenteeism accounted for 10 and 14% of the total costs, respectively. Similarly to the findings of Saigal et al (10%) a smaller group of patients were absent from work in the past year (3%). (Saigal&Joyce, 2005)

Clinical severity expressed with the I-PSS score was the strongest explanatory variable of the costs. The per-patient cost for mild, moderate and severe patients was 203 €, 754 € and 2168 € respectively. The differences of costs among the three groups were statistically significant. (p <0.001). In the past decade, burden of disease studies in other countries mostly focused on the direct medical costs of BPH- (Bellinger et al., 2012, Carballido et al., 2008, Cozar&Huerta, 2013, Disantostefano et al., 2006, Johansen&Istad, 2007, Saigal et al., 2007, Strope et al., 2011, Van Exel et al., 2006) In the US, the average per-patient Medicare expenditure within the first year following diagnosis was 344 $ (2007). (Bellinger et al., 2012) However, if we take into account every possible treatment, the per-patient annual expenditure in the US was probably between 73 and 12,788 $. (Taub&Wei, 2006) In Europe, the TRIUMPH project was a 1-year monitoring, prospective, cross-sectional, observational study with 5077 patients with lower urinary tract symptoms associated with BPH, in 6 European countries between 1999 and 2003. (van Exel et al., 2006) 30% of the patients were observed, 57% were given alpha-blockers, 10% were given finasteride, 10% received phytotherapy, and 4.9% underwent surgery. Direct medical costs in France, Germany, Italy, Poland, Spain and the

UK were 639 €, 513 €, 633 €, 1337 €, 595 € and 292 € respectively (2003). (van Exel et al., 2006)

In 2012 in Spain, the annual per-patient direct medical cost of BPH was between 253 € and 1251 €, depending on the treatment used. (Cozar&Huerta, 2013) In Norway, a model-based cost analysis estimated the total costs – including direct and indirect costs – of BPH treated with medication at 1938–2555 € in 4 years. (Johansen&Istad, 2007) This means that the 406 € direct medical cost of BPH found in the present patient group is in accordance with results from other European countries, but it is significantly lower than in Poland, the other Central-Eastern-European country in the study. It is important to note that 6.4% of Polish patients underwent surgery, and in the cost calculation other complications (e.g. bleeding, renal dysfunction, urinary tract infections, kidney stone) of AUR (acute urinary retention) were also taken into account.

Attention should be paid to certain limitations of our research. Only patients who were treated with medication were included in our research, patients who underwent surgery were excluded. The costs of outpatient care may be underestimated, since, as it was mentioned earlier, where more than 4 urology visits per year were reported, we calculated with 4, and where more than 12 GP visits per year were reported, we calculated with 12. The costs of informal care were estimated based on the patients' responses and the average net wage, but we had no information on the exact employment status of the person providing informal care. In addition, taking into account the average age of 70 in the sample, it is difficult to separate help used because of BPH and help used because of other reasons. Consequently, the costs of informal care may be overestimated in our research.

6.1.2.2. Results

In summary, we can say that the total annual cost of lower urinary tract symptoms associated with BPH can be estimated at 876 € / patient on average. It is a strength of the present research that it involved patients from 6 different centres in the country, and thus the results can be generalised to the whole patient population with BPH receiving medication in Hungary.

The EQ-5D utility scores in the present research (see the next Chapter) and its findings on the cost of illness may be used as country-specific results, which can contribute to the economic analysis of medical interventions used in the treatment of BPH. To our knowledge, this is the first research to analyse indirect costs caused by presenteeism (productivity loss) in BPH, and the second in the world to use social perspective. We were the first to assess the costs of BPH in Hungary. In the Central-Eastern-European region, Poland is the only country where a cost of illness assessment had been performed earlier, but that only examined direct costs. We have found that costs of productivity loss due to BPH exceeded the costs of absenteeism due to BPH. The significance of presenteeism is increasing, especially as we try to achieve sustainable employment, since retirement age is over 65 now in several developed countries, and it is expected to keep increasing.

In the present research, we estimated the annual costs of lower urinary tract symptoms associated with BPH in Hungary. Cost calculation was conducted from a social perspective, and included all direct medical, direct non-medical and indirect costs related to BPH. Costs were significantly different in the I-PSS groups. There is a considerable cost/patient (approx. 270k HUF). There is a significant number of patients, so the social burden is important, and it is important to note that patients bear a major part of the costs.

We were the first in Hungary to publish presenteeism data involving BPH patients - this cost element is already significant today and it is going to increase as the retirement age increases.

Questionnaire based cross-sectional survey; life quality of patients with benign prostatic hyperplasia

We conducted a non-interventional, questionnaire based multicenter cross-sectional study (Kovács) between June and October 2014. Six urology centres participated in the study, one university clinic, the urology departments and outpatient clinics of 4 hospitals, and the specialist practice of an outpatient care centre outside of Budapest[31].

The key demographic, socio-economic and clinical features of the patients selected for the questionnaire based survey are shown in tables 6 and 7. A total of 246 patients were included in the survey, the average age was 70.6 (SD 8.1 years), and the average duration of the disease was 6.5 years (SD 6.2 years). According to the Body Mass Index (BMI), 182 patients (74 %) were overweight or obese (BMI> 25).

64.2% of patients were treated with alpha-blockers, 6.1% with 5-alpha-reductase inhibitors, and 10.2% received combination therapy (5-alpha-reductase inhibitor + alpha-blocker). 3.7% of the patients were treated with antimuscarinics. At the date of completion, almost 50% of the patients had some urinary problems despite the treatment.

In the 12 month before the questionnaire was completed, 10% of patients were admitted to hospital because of urinary problems (90% of such patients once, 10% twice), 18% of the patients visited their GP and 76% visited a urologist because of the symptoms. At the completion of the questionnaire, a total of 42 patients (17%) were waiting for prostate surgery, average age: 70.93 (SD 6.82), the average age of the 194 patients not waiting for surgery was 70.39 (SD 8.42) (for 10 patients age was not provided).

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Table 6 Demographic characteristics of patients (n=246)

Demographic characteristics	n (%) or mean ± SD
Age (year)	70.59 ± 8.13
BMI (kg/m^2)	27.68 ± 3.88
Highest level of education (n=245)	
Elementary school	58 (24%)
Secondary school, vocational school, post-secondary vocational education	113 (46%)
College, university	74 (30%)
Employment (n=243)	
Full time	33 (13%)
Part time	4 (2%)
Retired	202 (82%)
On invalidity pension	2 (0.8%)
Unemployed	1 (0.4%)
Other	1 (0.4%)
Place of residence (n=245)	
Budapest	68 (28%)
County seat	48 (20%)
Other city	66 (27%)
Municipality, village, farm	63 (26%)

Table 7 Clinical characteristics of patients

Clinical characteristics	n (%) or mean± SD
Duration of disease (year) (n=243)	6.5 ± 6.2
Symptoms at the time of the survey	
Urinary urgency (n=238)	119 (50%)
Urinary incontinence (n=240)	21 (9%)
Urinary frequency (n=239)	108 (45%)
No. of urinations during the day (occasions)*	7.5 ± 2.6
No. of urinations at night (occasions)*	3.3 ± 1.7
Indwelling catheter (n=244)	19 (8%)
Established indication for surgery (n=236)	42 (18%)
Symptoms in the past 12 months	
Acute urine retention (n=242)	45 (18%)
Urinary urgency (n=243)	163 (67%)
Urinary incontinence (n=243)	38 (16%)
Urinary frequency (n=241)	119 (49%)
No. of urinations during the day (occasions)*	8.1 ± 1.9
No. of urinations at night (occasions)*	3.1 ± 1.4
Therapy in the past 12 months**	
Alpha-blocker (AB)	158 (64.2%)
5-alfa reductase inhibitor (5-ARI)	15 (6.1%)
Combination therapy (AB+5-ARI)	25 (10.2%)
Antimuscarinics	9 (3.7%)
Phytotherapy	108 (43.9%)
Indication of surgery	42 (18%)
Watchful waiting	28 (11%)
Other	1 (0.4%)
Severity of disease	
I-PSS (0-35) (n=223)	12.80 ± 6.34
Mild (I-PSS 0-7)	52 (23%)
Moderately severe (8-19)	136 (61%)
Severe (20-35)	35 (16%)
Health-related quality of life	
EQ-5D (-0.594-1) (n=237)***	0.85 ± 0.19
EQ VAS (0-100) (n=233)***	68.37 ± 15.54
I-PSS 8th quality of life question (0-6) (n=227)	2.46 ± 1.62
Happiness visual analogue scale (VAS) (0-10) ***(n=235)	6.26 ± 2.19

* From patients with urinary frequency.

** One patient may receive various treatments.

*** Higher scores indicate better health.

The average of the I-PSS scores was 12.8 (SD=6.3) in the sample. According to the I-PSS score, 52 (23%), 136 (61%), and 35 (16%) patients were in the mild, moderate and severe BPH groups, respectively.

The average of the EQ-5D index and the EQ VAS scores of patients were 0.85 (SD=0.19) and 68.4 (SD=15.5) respectively. For 111 patients (45%), the EQ-5D index was 1. In total, 7%, 19%, 28%, 30%, and 31% reported moderate or severe problems in self-care, usual activities, anxiety/depression, pain/discomfort and mobility. (Figure 9)

The general health-related quality of life of BPH patients measured with EQ-5D is shown in Table 8, in subgroups according to symptoms and severity of the disease. Average EQ-5D scores were examined in the I-PSS groups and statistically significant differences were found. We examined correlation between the specific subgroups, and the correlations between continuous variables are shown in Table 9.

Table 8 The general health-related quality of life of BPH patients measured with EQ-5D in subgroups according to symptoms and severity of the disease

Variables		n	EQ-5D index§ ± deviation (-0.594-1)	p	n	EQ VAS§ ± deviation (0-100)	p
Present symptoms							
Urinary urgency	Yes	115	0.85 ± 0.20	0.638	112	67.22 ± 15.75	0.151
	No	116	0.87 ± 0.15		113	70.61 ± 14.76	
Urinary incontinence	Yes	20	0.78 ± 0.27	0.221	21	61.95 ± 16.86	0.041*
	No	214	0.86 ± 0.18		208	69.45 ± 15.0	
Urinary frequency	Yes	103	0.82 ± 0.22	0.024*	102	66.98 ± 15.81	0.166
	No	128	0.88 ± 0.15		124	70.13 ± 14.80	
Indwelling catheter	Yes	17	0.77 ± 0.23	0.100	17	56.24 ± 17.33	0.002*
	No	220	0.86 ± 0.18		216	69.33 ± 15.01	
Established indication for surgery	Yes	40	0.79 ± 0.22	0.029*	40	63.15 ± 16.47	0.016*
	No	197	0.86 ± 0.18		193	69.46 ±	
Severity of disease							
Mild (I-PSS 0-7)		50	0.90 ± 0.12	0.002*	51	72.86 ± 14.65	<0.001*
Moderate (8-19)		134	0.87 ± 0.14		133	69.16 ± 14.63	
Severe (20-35)		34	0.71 ± 0.31		34	59.04 ± 16.02	

* Mann-Whitney U test or Kruskal-Wallis test p<0.05 significant
§ Higher scores indicate better health.

Table 9 Correlation between continuous variables

	EQ VAS	I-PSS	I-PSS 8th quality of life question	Happiness	Age	BMI	No. of urinations during the day	No. of urinations at night
EQ-5D§ (-0.594-1)	0.55***	-0.16*	-0.20**	0.35***	-0.20**	0.69	-0.17	-0.24*
EQ VAS§ (0-100)	-	-0.20**	-0.21**	0.58***	-0.22**	-0.08	-0.05	-0.38***
I-PSS (0-35)	-	-	0.70***	-0.43***	0.14*	-0.01	0.21*	0.34**
I-PSS 8th quality of life question (0-6)	-	-	-	-0.35***	0.11	-0.03	0.09	0.37***
Happiness§ (0-10)	-	-	-	-	-0.20**	0.08	-0.10	-0.26**
Age (year)	-	-	-	-	-	-0.20**	-0.04	-0.01
BMI (kg/m²)	-	-	-	-	-	-	0.09	0.16
No. of urinations during the day (occasions)	-	-		-	-	-	-	-0.22*

* Spearman-correlation $p<0.05$, **$p<0.01$, ***$p<0.001$
§ Higher scores indicate better health.

The comparison of BPH patients and the age- and sex-matched general population in the 5 dimensions of the EQ-5D questionnaire is shown in Figure 9.

Figure 9 Comparison of BPH patients and age- and sex-matched general population in the 5 dimensions of the EQ-5D questionnaire
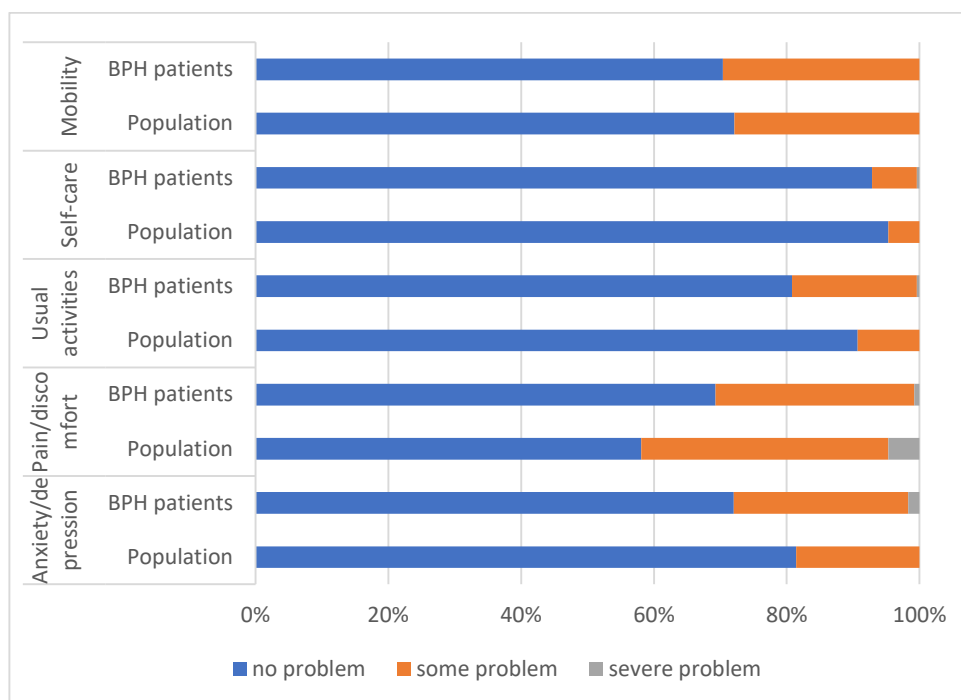
Source: EQ-5D results for males 65 or over in the general population: Baji et al. 2015

The comparison of the EQ-5D index of BPH patients and the age- and sex-matched general population is shown in Figure 10.

Figure 10 Comparison of BPH patients and the age- and sex-matched general population in the EQ-5D index

	45-49	50-54	55-59	60-64	65-74	75+
BPH patients	0,656	0,924	0,961	0,833	0,886	0,788
Genral population	0,855	0,829	0,802	0,826	0,857	0,742

Age (years)

BPH patients   Genral population
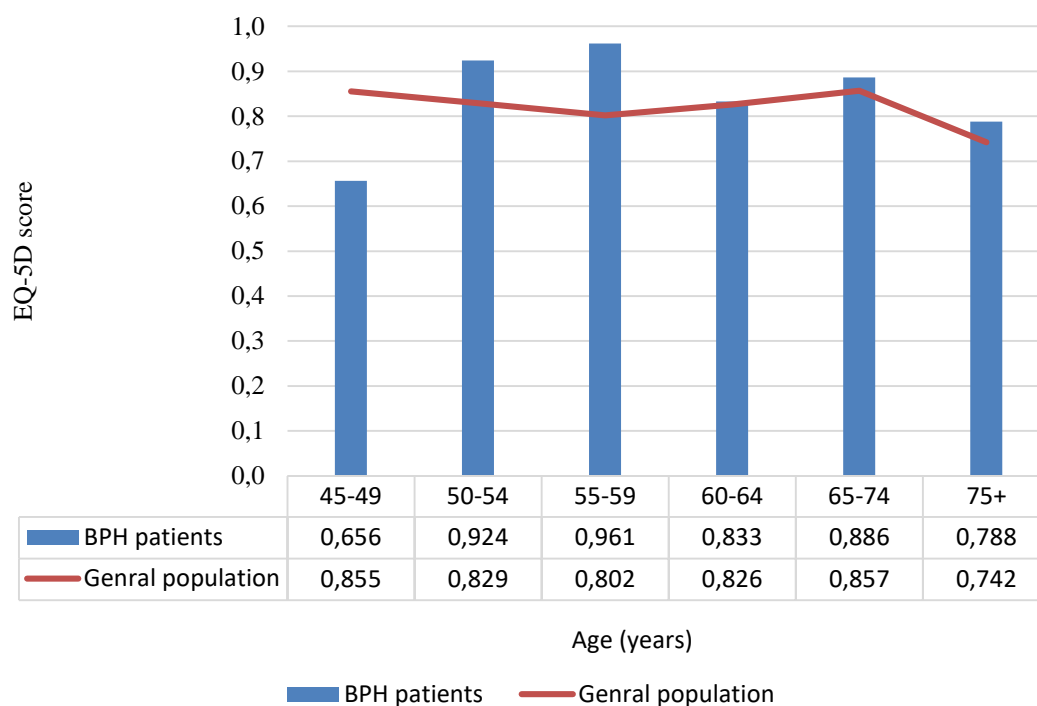
Source: Source of values for the EQ-5D dimensions in the general population: Baji et al. 2015
Note: As the study of the general population in Hungary presented the 65-69 and 70-74 age groups as one, we did the same with BPH patients to ensure comparability.

We have only found significant difference (p<0.05) between BPH patients and the age- and sex-matched general population in the 45-49 and 55-59 age groups.

6.1.2.3 Discussion

In our study, the clinical characteristics and health-related quality of life were examined in BPH patients. We would like to highlight from our results that almost 50% of patients had urinary problems despite the treatment with medication, most of the time urinary frequency and a compelling urge to urinate. The majority of the patients in the sample considered their general health good, according to the EQ-5D, almost half of the patients (45%) reported no problems in any of the 5 dimensions of the questionnaire. The average EQ-5D index of BPH patients in the 45-49 age group was lower than that of the sex and age-matched general population, the results were the same in the 60-64 age group, while in the 50-54, 55-59 and 65-74 age groups it was higher in BPH patients. (Figure 10)

The average of the EQ-5D index in the whole sample was 0.85 (SD=0.19), which was similar to the findings of studies in other countries. The values are the following in the various countries: Spain: 0.90, SD=0.14, average age: 63 years, France: 0.84, SD=0.19, average age: 72 years, Korea: 0.85, SD=0.19, average age: 76 years, and the United Kingdom: 0.71-0.87 depending on severity, average age: 73 years. International comparison is made difficult by the fact that the BPH quality of life studies were partly randomized controlled clinical studies, partly cross-sectional studies related to drug trials (33). The EQ-5D scale were used only in a smaller part of the BPH quality of life surveys, and where it was applied, no comparison with the population average was provided. Inclusion criteria were also different, so international comparison is difficult.

As the total I-PSS score increased, the value of the EQ-5D index significantly decreased, i.e. as the disease became more severe, general health-related quality of life dropped. There was significant, but weak correlation between EQ-5D and the I-PSS score, and also the I-PSS quality of life scale.

Based on our results, it can be established that the health related quality of life of BPH patients who are treated with medication is, on average, not worse than that of the general population, however, in the youngest age group, significantly lower quality of life values were established. When assessing the results, it must be taken into consideration that we used the EQ-5D general health-related quality of life questionnaire in our study, which is less suitable for detecting smaller differences and disease-specific symptoms. In the 50-54, 55-59, 65-74 and 75+ age groups, we had better health related quality of life results for BPH patients, than for the age and sex matched general population, but the difference was only significant in the 55-59 age group. There was no difference in the 60-64 age group. In the 45-49 age group, the quality of life of BPH patients was significantly lower than that of the general population. (Figure 10) The fact that BPH patients in the 45-49 age group reported significantly lower quality of life may partly be due to health-related expectations, as in this age group the acceptance of the presence of the symptoms of BPH is probably low. That the general health-related quality of life values of BPH patients were mostly similar or better than that of the general population, may be due to the fact that these patients were treated in six major urology centres. We suppose that patients with better socio-economic background were admitted to these centres in the first place (the average age of the patient group was 71, and 30% had tertiary level education), whose quality of life is higher than the society's average. Another reason to be mentioned is that patients who had had prostate surgery for any reason were not included in the sample, we might have had different results with them.

With quality of life surveys, several correlations can be revealed that may be used to increase the efficiency of the treatment of such diseases. The present study aims to do so with the survey of the quality of life of BPH patients in Hungary treated with medication.

One limitation of our survey is that only care centres with a large number of patients participated; a survey with randomly selected urology centres might have had different

results. Another limitation is that the underlying causes of symptoms that exist despite the treatment with medication are not revealed; it is not known if the treatment is not sufficiently effective or if patients do not take their medication properly. The present study did not aim to explore this.

6.2 Quality of life and cost of illness in patients with bladder cancer in Hungary

6.2.1 Cost of illness in bladder cancer patients

This chapter uses a publication by Kovács et al (2016)[32].

6.2.1.1 Use of medical care

In the analysis of the cost of illness in patients with bladder cancer, we analyzed the OEP expenditure on care provided in health care institutions (2007-2008) and pharmaceutical sales data (2008-2014).

National Health Insurance Fund (Országos Egészségbiztosítási Pénztár), 2007-2008

A study analysing the years 2007 and 2008, published in 2010, provides an overview of the costs paid by the National Health Insurance Fund (Országos Egészségbiztosítási Pénztár OEP) for bladder cancer (BNO C67). (OEP Elemzési, Orvosszakértői és Szakmai Ellenőrzési Főosztály 2010) According to the report, in 2007 the OEP paid 1.8 bn HUF on the treatment of bladder cancer (BNO C67) 75% of which was provided to inpatient

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[32] Kovács Á, Hevér N (2016): A húgyhólyag daganatos betegek költsége Magyarországon. Köz-Gazdaság, XI, 3, pp. 303-317.

care. In 2008, total costs exceeded 2 bn HUF, 71.5% of which went to inpatient care. Social security expenditure in this diagnosis increased by 33%, by more than 100 million HUF, between 2007 and 2008 (2007: 314,425 million HUF, 2008: 418,193 HUF million). In 2007, Mitomycin-C Kyowa, 20 mg, powder for solution for injection 5x accounted for 19.8% of the total sales of medicinal products (~63 million HUF), and it remained the most significant item (17.2%) in 2008. In outpatient care, the costs of histological tests were the highest (19.8% in 2007, 17% in 2008), followed by the cost of cystoscopy (13.9% in 2007, 16.3% in 2008).

6.2.1.2 Analysis of pharmaceutical sales data by the OEP, 2008-2014

In 2008, OEP provided 58.89 billion HUF social security funding for the oncology medication of cancer patients. (Boncz et al., 2010)

We analysed pharmaceutical sales data by OEP for the 2008-2014 period. For the analysis, we could only take into account the medicinal products that are paid for by the OEP exclusively for the treatment of bladder cancer, based on indication, with special reimbursement, to prevent the recurrence of tumour locally, in the bladder. However, these constitute only a segment of the therapies that may be used for the treatment of the bladder, and do not include the drugs used in systemic chemotherapy, painkillers, antibiotics or other medication, and drugs used during hospital treatments.

Medicinal products used in the treatment of low and medium risk bladder cancer

Medicinal products with the active ingredients epirubicin and mitomycin can be used in the treatment of low and medium risk bladder cancer. In the period analysed (2008-2014) four brands of medicinal products were available with these active ingredients, in

different sizes of packagings. From these, the sales of medicinal products with the active ingredient mitomycin ceased by 2014. (Országos Egészségbiztosítási Pénztár, public sales data)

There may be several reasons for this: 1) The registration of Mitomycin-C Kyowa, 2 mg, powder for solution for injection 10x in glass vials, was cancelled in 2011. 2) There were supply problems with the medicinal product Mitomycin-C Kyowa, 10 mg in December 2012, the National Institute of Pharmacy and Nutrition (Országos Gyógyszerészeti és Élelmezés-egészségügyi Intézet, OGYÉI) was notified. To our knowledge, the problem was not solved until 2014, and after 2015, the product was not marketed in Hungary. (National Institute of Pharmacy and Nutrition) In theory, the product with 20 mg strength is available, and it can be used for substitution, but no product with this strength was sold in 2014. The 10 mg product is available through individual import, but attending physicians did not exploit this opportunity. 3) The reimbursement list published regularly by the OEP providing information on products for "disease groups in the premium and special indication-based reimbursement categories, indication areas and the persons qualified to prescribe them" (Healthcare point) has not contained this active ingredient/medicinal product since January 2013, so it cannot be prescribed with 100% reimbursement. This means that in 2014, epirubicin is the only active ingredient that can be prescribed with a 100% reimbursement from social security. "Epirubicin Accord 2 mg/ml solution for injection or infusion 1x25ml" accounted for 58% of the sales of medicinal products with the active ingredient epirubicin.

Medicinal products used in the treatment of high risk bladder cancer

In high risk cases of bladder cancer, 4 types of medicinal products were available on the market with 100% social security reimbursement or individually granted reimbursement in 2012 for intravesical instillation, all of them with the active ingredient bcg vaccine. (In

intravesical instillation, the active ingredient is put in the bladder through a catheter.) However, the product Immuncyst has not been available on the Hungarian market since 2012, because of a change in an analytical method the manufacturer announced. OGYÉI was notified of this fact in May 2012, a solution and the end of the supply problems are expected by 31 December 2015. (Országos Gyógyszerészeti és Élelmezés-egészségügyi Intézet, National Institute of Pharmacy and Nutrition) So in 2014, there were only two medicinal products on the market available with 100% social security reimbursement. Out of these two, it was BCG-Medac, powder and solvent for suspension for intravesical use 1x50 ml that accounted for most of the sales (99.0%).

Medicinal products used in the treatment of low, medium and high risk bladder cancer

Tables 10 and 11 show the sales of medicinal products with special social security reimbursement only to be prescribed in bladder cancer indication, and the social security expenditure between 2008 and 2014. For the group of these three medicinal products, one indicator of sales, the amount of packages sold expressed in pieces, increased every year at an increasing rate until 2012. On the whole market, sales decreased between 2013 and 2014, the reasons for which were the problems with the supply of medicinal products with the active ingredient mitomycin, and the fact that reimbursement was no longer provided for those products. Even though the sales of medicinal products with the active ingredient epirubicin increased, because of the supply problems of BCG products, there was no medicinal product that could compensate for the shortage. From the medicinal products marketed in the 7 years that were analysed, the share of medicinal products with the active ingredient bcg vaccine, recommended for use in high risk cases, increased until 2010 then it started to decrease. At first, in 2008, their market share was 36.1%, it peaked at 42.8% in 2010, but dropped to 5.9% in 2014. The sales volume of medicinal products with the active ingredient epirubicin increased every year in the period analysed, and now, in terms

of the total number of packages sold, their market share is 94.1%. Starting in 2008, the sales of medicinal products with the active ingredient mitomycin continuously decreased, and it ceased in 2014 for the reasons described above.

Table 10 Sales of medicinal products with special social security reimbursement to be prescribed in bladder cancer indication, number of packages sold, 2008 – 2014

Medicinal product	2008	2009	2010	2011	2012	2013	2014
epirubicin, package	2846	2959	3482	4275	5095	10,728	11,184
mitomycin, package	3653	3096.4	2734.6	2584.8	3278.8	0.4	
bcg vaccine	3678	4130	46,444	4926	4690	335	720

Source: (OEP, 2014a)

Between 2008 and 2012, the number of packages sold increased every year, while in the same period social security reimbursements paid (HUF) decreased every year with the exception of 2011. Between 2012 and 2014, the number of packages sold showed a downwards trend, and so did social security expenditure. From the medicinal products that can be prescribed in bladder cancer with 100% reimbursement, the reimbursements paid for medicinal products with the active ingredient bcg vaccine increased every year from 2008 to 2011, then in 2012 it decreased by almost 5.2 million HUF. In 2013, it further decreased by 93% (94 million HUF), then it rose by 15.6 million HUF in 2014. Social security reimbursements paid for medicinal products with the active ingredient epirubicin increased every year, while reimbursements paid for medicinal products with the active ingredient mitomycin decreased year-on-year every year between 2008 and

2014. (Table 11) Some medicinal products with the active ingredient doxorubicin may also be used in the treatment of bladder cancer for intravesical instillation (Adriblastina, Doxirubicin „EBEWE" and Xorucin) besides other tumours (e.g. breast and advanced ovarian cancer), but between 2008 and 2014 no such medicinal products were sold, so there was no social security expenditure.

Table 11 Social security reimbursement paid between 2008 and 2014, HUF

Medicinal product	2008	2009	2010	2011	2012	2013	2014
epirubicin	481,117,774	49,947,561	58,567,079	72,351,696	847,333,618	128,987,937	89,854,956
mitomycin	104,678,984	88,263,474	59,442,042	52,562,639	31,242,877	14,128	-
bcg vaccine	81,675,209	90,185,214	100,762,907	106,400,590	101,242,908	7,191,196	22,835,358
Total	234,465,966	228,396,249	218,772,028	2,134,314,925	217,219,403	136,193,261	112,690,314

Source: (OEP, 2014a)

The decrease in the social security expenditure on mitomycin between 2008 and 2012 is conspicuous. If we examine sales in mg, we find that the sales of mitomycin decreased and the sales of epirubicin increased between 2008 and 2012. (Figure 11)

Figure 11 Changes of product turnover and sold active agent quantity of epirubicin and mitomycin containing products between 2008 and 2014
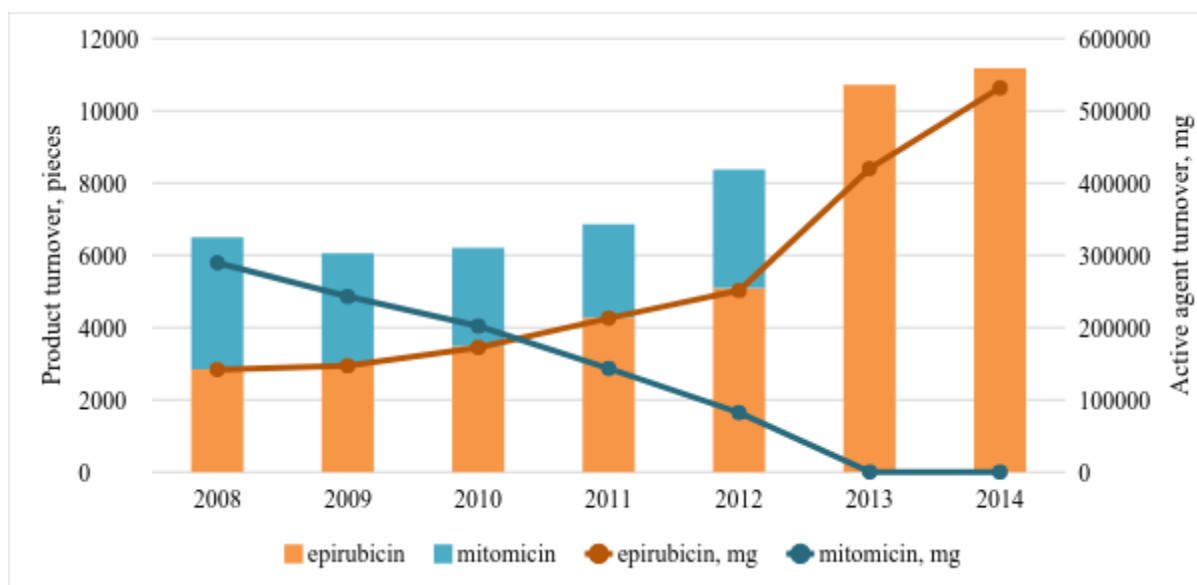
Source: (OEP, 2014a)

Detailed analysis of product turnover serves with further explanation for the decrease in social security funding. Turnover shifted towards the slightly more favourable 20 mg packages in 2011-2012. Also, the turnover of the 1x package was significantly higher in 2012. (Table 12) The wholesale price of mitomycin containing products did not change from 2009 to 2012 (10 mg 5x: 18,000 HUF; 20 mg 1x: 6,300 HUF; 20 mg 5x: 31,500 HUF). The social security charge will be 18,000 HUF for those patients who receive treatment once, calculating with 40 mg per treatment and with the 10 mg package, and additionally one vial will be left with the patient unused. The same will happen with a one-time 40 mg treatment with the 20 mg 1x package will incur a 12,600 HUF charge without leaving any unused medication with the patient. In case of repeated treatments the remaining vial may be used during the next session, e.g. five sessions of 40 mg treatment would cost 72,000 HUF with the 10 mg package and 63,000 HUF with the 20

mg package (no remaining vial). Determining the dosage of mitomycin is patient-specific which means the combination of different packages may be used.

Table 12 Product turnover of Mitomycin-C Kyowa, powder for solution for injection between 2008 and 2012

Doses	2008	2009	2010	2011	2012
10mg, 5x	768	815	191	2011	287
20mg, 1x	2422	1958	1309	959	15449
20mg, 5x	1228	1135	1424	1626	3177

Note: In the years of 2013 and 2014 there was no sale hence it was not indicated.
Source: (OEP, 2014a)

Charges paid by the patients (such as 'packaging price', 300 HUF/packaging) have increased proportionally according to product turnover between 2008 and 2012. It increased roughly from 3 to 4 million Forints (3.061; 3.042; 3.248; 3.526 and 3.916 million HUF each year accordingly).

6.2.1.3 Results

Medication sales information in 2014

Table 13 shows the turnover of medications for low or medium-risk urinary bladder cancer for intravesical instillation with 100% social security funding in 2014. Table 14 shows the turnover of medications for high-risk urinary bladder tumor for intravesical

instillation and for in situ carcinoma (BNO C679) with 100% social security funding in 2014.

According to the above, the total social security funding was 113.04 million HUF for the two active agents (epirubicin and bcg) in 2014. The largest payment is related to EPIRUBICIN ACCORD 2 mg/ml solution for injection or infusion 1x25ml (79.2 million HUF, 70%), on second place came BCG-MEDAC powder and solvent for suspension for intravesical use 1 powder vial for 1x50 ml (22.64 million HUF, 20%).

Table 13 The turnover of medications for low or medium-risk urinary bladder cancer for intravesical instillation with 100% social security funding in 2014

Brand name	Name of medication	Variation	ATC code	Active	Sold	Days of	Social	Gross sales	Patient
EPIRUBICIN ACCORD	EPIRUBICIN ACCORD 2 mg/ml solution for injection or infusion	1x25ml	L01DB03	epirubicin	9 507	475 350	79 202 817	82 054 917	2 852 100
EPIRUBICIN-TEVA	EPIRUBICIN-TEVA 2 MG/ML solution for injection or infusion	1x5 ml injection vial	L01DB03	epirubicin	23	230	36 394	60 375	23 981
EPIRUBICIN-TEVA	EPIRUBICIN-TEVA 2 MG/ML solution for injection or infusion	1x25 ml injection vial	L01DB03	epirubicin	997	49 850	8 306 007	8 605 107	299 100
EPIRUBICIN-TEVA	EPIRUBICIN-TEVA 2 MG/ML solution for injection or infusion	1x100ml injection vial	L01DB03	epirubicin	2	400	65 410	66 010	600
FARMORUBICIN	FARMORUBICIN PFS/RTU 10 MG	1x injection vial	L01DB03	epirubicin	657	6570	2 309 738	2 660 363	350 625
				Epirubicin,	**11 186**	**532 400**	**89 920 366**	**93 446 772**	**3 526 406**

Table 14 Turnover of medications with 100% social security funding which can be used for intravesical instillation in case of high-risk urinary bladder tumor and in situ carcinoma (BNO C679), 2014

Brand name	Name of medication	Variation	ATC code	Active ingredient	Sold amount (pieces)	Days of therapy (DOT)	Social security funding (HUF)	Gross sales price (HUF)	Patient charges (HUF)
BCG – MEDAC	BCG-medac, powder and solvent for suspension for intravesical use	1x powder vial +1x50 ml solvent bag + catheter equipment	L03AX03	bcg vaccine	696	31320	22 640 184	22 848 984	208 800
BCG – MEDAC	BCG-medac, powder and solvent for suspension for intravesical use	1x powder vial +1x50 ml solvent bag + catheter equipment	L03AX03	bcg vaccine	6	270	195 174	196 974	-
BCG - MEDAC	BCG-medac, powder and solvent for suspension for intravesical use	1x powder vial +1x50 ml solvent bag + catheter equipment	L03AX03	bcg vaccine	9	405	290 169	295 461	5292
				Total	**702**	**31 995**	**23 125 527**	**23 341 419**	**214 092**

Source: (OEP, 2014a) DOT: The DOT (Days of Treatment) . The DDD of ATC code L03AX03 is 1,8 mg intravesically. [http://www.whocc.no/atc_ddd_index/]

6.1.2.4 Discussion

By analysing the pharmaceutical turnover data, it is apparent that costs of treating bladder cancer via medication is significant on a national level. Even during a one-year interval (2007 vs 2008), it is clear that the medication costs can significantly rise (with more than 33% meaning 100 million HUF between 2007 and 2008). In the analysis of the 2008-2014 interval, we have focused on the turnover of mitomycin which was the most significant active agent financially in 2008, as well as two other products (epirubicin and bcg vaccine) which can only be used with funding only in case of this disease and incur significant charges. Due to the changes implemented in the social security funding between 2008 and 2014, withdrawals and restrictions, we have found radical restructuring in product turnover for all three products. Mitomycin expenses have been reduced to zero by 2014, although its 20 mg variation gave 33% of the total medication expenses for urinary bladder cancer back in 2008. Meanwhile, the turnover of epirubicin increased while the turnover of bcg vaccine significantly decreased from 2013. In total, the social security funding of these three active agent have been reduced with 112 million HUF between 2008 and 2014 (from 234.5 to 112.7 million HUF). According to the summarizing analysis of the 2017 European clinical policies, mitomycin may decrease the chance of recurrence in certain cases which means that the reasons and consequences behind the absence of mitomycin turnover in Hungary by 2014 require further investigation. (Deng et al., 2017, Roupret et al., 2017),

6.3 Epidemiology of male and female urinary incontinence and lower urinary tract symptoms in Hungary

6.3.1 Surgical treatment practice of female urinary incontinence and urogenital prolapse in Hungary

6.3.1.1 Results

A total of 10,403 women (18 or older) took part in the survey, with the average age of 43.0 (SD 13.8). In the survey, 3506 (33.9%) women answered regarding the incontinence related question that they have experienced leakage - they were included in the incontinence subgroup analysis. Their age distribution is shown in Figure 12. The average age of the adult female incontinence subgroup is 47.0 (SD 12.7).

Figure 12. Did you ever experience any urine leakage?
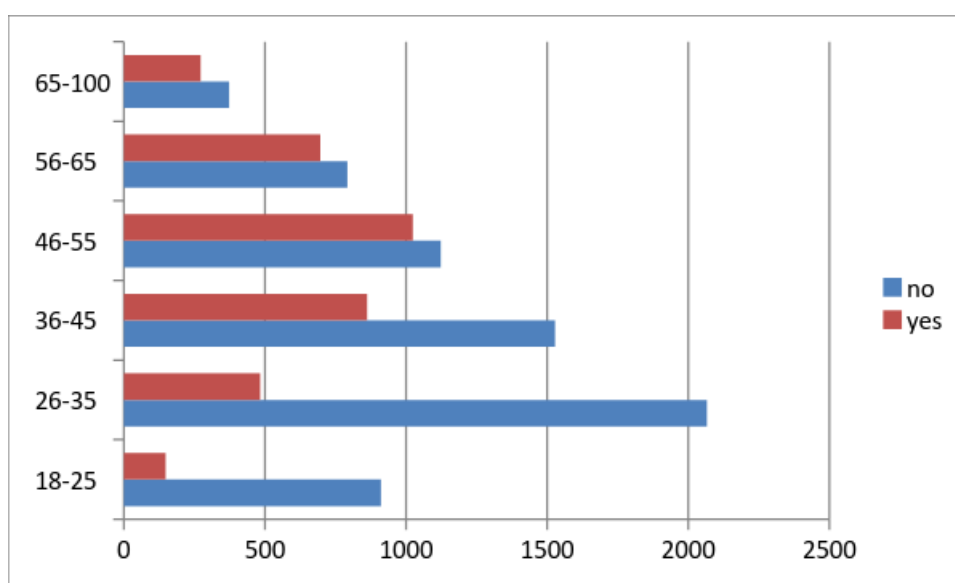
Urine leakage occurred rarely (e.g. during a cold) with 3103 (90.4%) women, and 296 (8.6%) said they experience it more times a day; a total of 33 (1.0%) women said this means a constant issue to them. Detailed questions regarding the occurrence of urine leakage revealed that urine leaks mostly occur during coughing/sneezing (2437 women, 69.5% of the incontinent subgroup; 23.7% of all the participants) or in case of strong urinary urgency (823 women, 23.5% of the incontinent subgroup; 0.9% of all the participants). The amount of leaked urine is only a few drops in case of the majority (3172, 94.1%), a bigger amount for 28 women (0.8%), and 170 women (8.0%) marked the answer as "flowing". As to the question of how much they are irritated by involuntary urine leakage, 1319 (39.9%) women said sometimes, 1170 (35.4%) said very much and 33 (1.0%) said they are being restricted in their daily routine - their age distribution is shown in Figure 13.

Figure 13. How much are you irritated by involuntary urine leakage? - age distribution
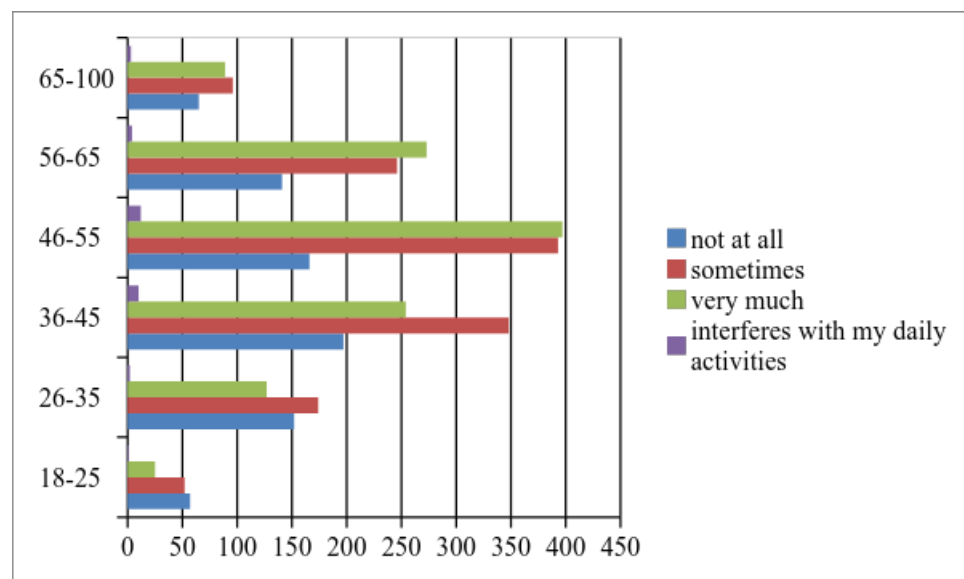
The ladies were also asked if frequent and urgent urinary urgency causes any problems to them. In this specific incontinence subgroup, this is not an issue for 1592 (46.9%) women, while 1418 (41.8%) said they are irritated sometimes, 361 (10.6%) said they are irritated very much and 21 (0.6%) said they are being restricted in everything. 2039 (59.1%) women wake up during the night once or rarely due to urinary urgency while 406 (11,8%) women wake up several times. During the day, 1258 (36.6%) women urinate less than 4-5 times, 1889 (55%) 6-8 times and 290 (8.4%) even more than that.

The majority of the answers for the question of "When do you experience urine leakage?" was aiming at the presence of stress incontinence (sneezing, laughing, running, exercising), but the survey included options for urge incontinence as well - which was selected by 1800 women.

3990 (41%) women said that the frequent and urgent urinary urgency means a problem to them (Q9). They were viewed as a potential overactive bladder syndrome (OAB) group.

The adult female OAB group's average age was 45.8 (SD 14.2). Within this group, 1800 (45,4%) women experienced urine leakage (incontinence). However, to the question of how much they are bothered by their involuntary urine leakage, 2211 (66.1%) replied that they experience some sort of issue: 1133 (33.9%) replied with a no, 1165 (34.8%) said sometimes, 1000 (29.9%) said very much and 46 (1.4%) said they are being restricted in their daily routine.

Of these women we have tried to filter out those who are most probably OAB patients.

Of all the participants, those women have been selected who match the following criteria:

   - 18 or older

- the frequent and urgent urinary urgency causes a problem ("sometimes", "very much" or "being bothered in daily routine")

- urinates more than 10 times a day

Based on the above criteria, a total of 623 (15.8%) women qualified. The average age of these 623 patients is 47.1 (SD=14.8), the youngest being 18 and the oldest 84.

448 (11.6%) women cannot interrupt urination voluntarily, 692 (18%) haven't tried yet and the majority (2713 women, 70.4%) can actually do it.

In case of urinary urgency, 953 (24.1%) cannot wait, they need to go to the toilet immediately. 2312 (58-2%) women wake up during the night once due to urinary urgency, while 570 (14-3%) wake up more times. Urination frequency is 6-8 times a day for 2350 (59.4%) women. 62 answers have been received on the survey measuring surgical treatment practice of female urinary incontinence and urogenital prolapse in Hungary. This is the half of the Hungarian 82 gynecology and 39 urology wards (total of 121). The survey primarily explored the annual surgical numbers with the above indication and the types of the interventions. During data procession, the classification of the departments happened as follows: urology clinic, county urology ward, municipal urology ward, Budapest urology ward, gynecology clinic, county gynecology ward, municipal gynecology ward, Budapest gynecology ward. The proportion of the wards sending back the survey, based on the above order, was the following: 6.4%, 12.9%, 8.1%, 6.5%, 1.6%, 17.7%, 35.5%, 11.3 %. 68% of the replies came from gynecology, 32% came from urology departments.

An average of 29.3 (4-80) incontinence surgeries are performed on urology wards and 44.9 (5-120) on gynecology wards annually. The most common type of surgery in urology practice is the modern suburethral tension-free sling surgery (65% of total surgeries), while this intervention only constitutes 19% of total surgeries on gynecology wards. Colposuspension with open or laparoscopic approach are used in 26% and 13% of the

cases respectively, while Stoeckel and anterior vaginal wall repair are used in 9% and 67% both on urology and gynecology wards.

Figure 14. Distribution of incontinence surgeries on gynecology and urological wards
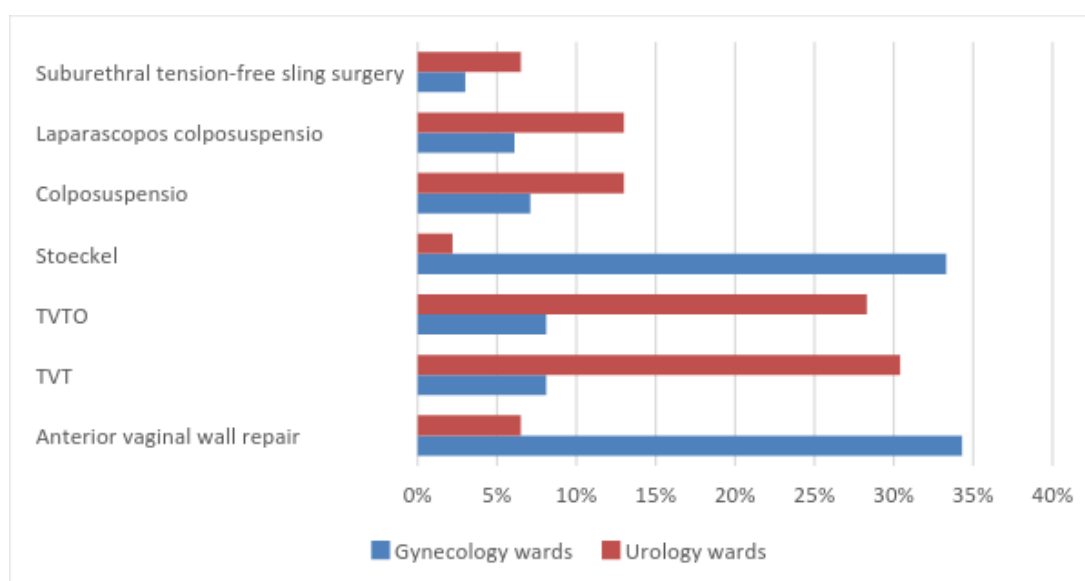
6.3.1.2 Discussion

Following the distribution of incontinence, the answers to certain questions regarding epidemiology given in the survey may refer to the presence of stress or, in case of other types of questions, urge incontinence. Even though the survey has been submitted by more than ten thousand people, not everyone answered all the questions. Due to that reason, the following anomaly occurred: 3500 answered that they had urine leakage and 6700 answered the opposite on Q1. One the next question though (Q2) "How often does

it happen that you cannot hold your urine?" (Figure 14), 8600 participants said rarely (e.g. during a cold), more times a day or constantly. Regarding the amount of urine leakage 6400 women gave some sort of answer (few drops; bigger amount; flowing). The above analysis was carried out with this in mind, after data cleansing.

Figure 15. How often does it happen that you cannot hold your urine?
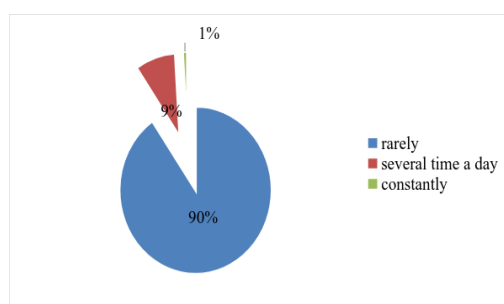
Figure 16. How much are you irritated by involuntary urine leakage?
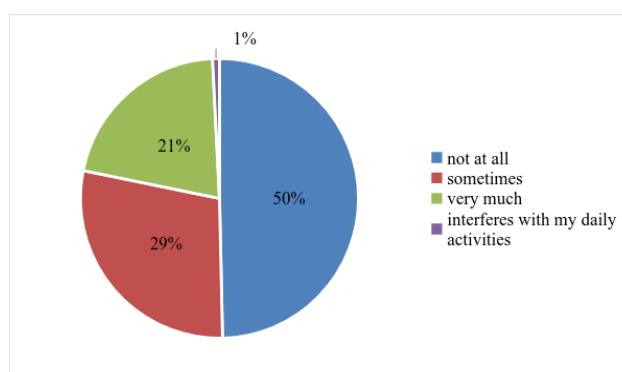
Processing data revealed that almost half of the participants were not bothered by involuntary urine leakage (Figure 15). 9027 can wait but 1093 participants have to go to the toilet as soon as the urinary urges appear. (Figure 16)

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Figure 17. In case of urgency, do you have to go to the toilet immediately or can you wait?
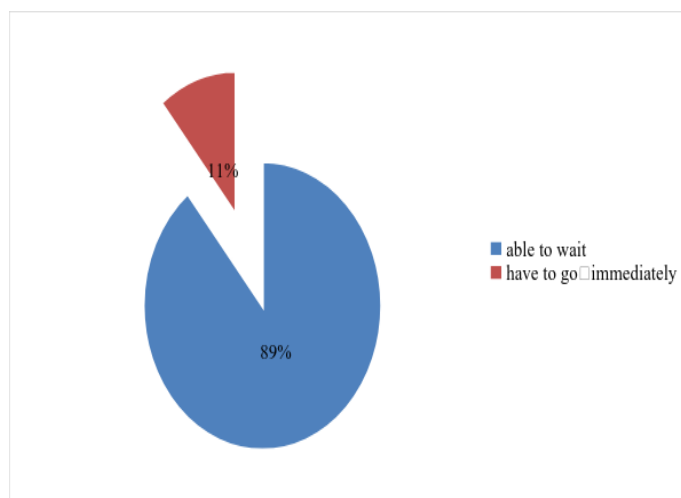
In 2700 cases, the participant said that she experienced urine leakage after feeling urgency, before reaching the toilet (rarely 23.7%; often 3.2%).

A total of 4724 men and 5276 women participated in the web-based studies of Coyne et al. in the United Kingdom and Sweden. The patients have been distributed into two groups based on the prevalence of the OAB symptoms. One group consisted of people who experienced OAB symptoms "sometimes", while the other group experienced them "often". In the group where symptoms are experienced "sometimes", the 22.5% of UK patients are moderately while 11.8% are very much irritated. The same in Sweden is 33.7% and 27% respectively. In the group where symptoms are "often" experienced, the 19.1% of UK patients are moderately while 10.7% are very much irritated. The same in Sweden is 24.7% and 22.4% respectively.

The differences are significant in these countries. Between men and women the difference is significant, in case of men, this number is much lower. Groups with different socio-economic status also feel in different rates that the OAB symptoms irritate them moderately or very much. The rate is also (significantly) higher for those with higher

education, for Caucasian people, for those who live in a family or have a relationship and those who work full time.

The Hungarian studies revealed that 90.4% of women (a total of 10,403 adult female participant, 3506 incontinence and 3103 urine leakage replies) "sometimes" experience OAB symptoms. In case we compare it to the results of United Kingdom and Sweden, that means that 791-1040 women (25.5-33.5%) are irritated moderately and 118-270 are very much irritated by these symptoms. (Projected to 1000 incontinence patients, 76-100 women are moderately irritated by OAB symptoms, while this number is 255-335 women in case of 1000 OAB patients with incontinence.) Third of the participants (33.9%) reported that they experienced urine leakage, meaning they had an incontinent episode. More than third of the participants (41%) reported urgency. It can be assumed of these patients that OAB may be in the background.

Tenth of the participants reported that they are very much irritated or being restricted in their daily routine by their possibly OAB-related symptoms.

It has to be mentioned that one of the limitations of this study was that no medical examination followed the completion of the survey, which means that diagnosing OAB should be done with extreme care.

Due to the structure of the screening programme, completing the survey only took 3-5 minutes, which limited the number and quality of the questions. Simple, understandable questions had to be used. Due to the above reasons, we did not have any data available during the 2011 incontinence survey regarding the participants' BMI score, medication history, smoking habits or if they had any children (if yes, then what were the circumstances when giving birth) or pelvic surgeries.

Health conscious people who participated in the programme received a booklet with the results of the screening, in which the above values (BMI, smoking) were included as part of a different screening programme. With this booklet they may contact their GP's, or they may contact a gynecologist or urologist specifically with the incontinence survey

results in order to plan the appropriate treatment or further examinations. The results of our study provides an overall picture about the current status of incontinence in Hungary, and it may contribute to the development of more efficient national strategies, in order to solve this issue in a reasonable manner.

Studying the Hungarian surgical practice, the results show that the urogynecology treatment is not happening in centres. All the included departments carry out female incontinence surgeries and urogenital prolapse interventions. The preventive, curative and rehabilitation activities are controlled by policies and protocols in every area of modern medicine nowadays. These professional recommendations mostly rely on evidence coming from well-designed examinations. However, there are some areas where the current evidence and results are insufficient or contradictory. In such cases we can rely on the personal opinion of experts. (Atkins et al. 2004) However, there are still many "grey areas" in medicine where no recommendation exists and in such case we may only rely on our own or our colleagues' experiences. The above thoughts apply to the surgical treatment of female incontinence and urogenital prolapse. The policies of the former topic are straightforward, but in the case of prolapse surgeries we may encounter some weaker recommendations. Managing the professional practices and deficiencies detailed above could be assisted by the Hungarian Society of Obstetrics (MNT) and Gynecology and the Hungarian Society of Urology (MUT) by resurrecting their joint Urogynecology Section. One of the most important aim of this section would be to create a urogynecology license exam, which is supported by Gynecology and Urology Department of the Professional Healthcare Society.

6.3.2   The prevalence of male lower urinary tract symptoms in Hungary

The average I-PSS score was 4.2 (SD 3.9) in our study. The distribution between mild, moderate and severe categories happened accordingly: I-PSS=0–7: 6378 men (86.4%) average age was 38.2; I-PSS=8–19: 919 men (12.7%) average age was 46,1; I-PSS=20–35: 85 men (0.9%) average age was 55.2.

The average age was 47.0 (SD 13.7) in the I-PSS >7 - moderate and severe symptoms group (total of 1004 men).

The participants were distributed to seven age groups. The distribution of participant age groups and the respective average I-PSS score is shown in Table 15.

Table 15 The age distribution of participants

Age groups	20 - 29	30 – 39	40 - 49	50 – 59	60 - 69	70 - 79	80 -	total / mean
Number of participants	1549	2564	1610	1169	349	88	8	7337
Mean I-PSS score	3.26	3.52	4.01	5.38	8.28	8,55	7.88	4,16

Most of the participants were in age group 30-39, their average I-PSS score was 3.52. They were followed by age group 40-49 with average I-PSS score of 4.01 then age group 20-29 with average I-PSS score of 3.26. The number of participants above the age of 50 was 1614. Moving on to higher age groups, the participants' average I-PSS score was increasing. We have studied the proportion of participants reporting mild, moderate or severe symptoms in each age group. The results of our analysis are shown in Figure 18.

Figure 18. Distribution of symptoms in each age group according to I-PSS categories

	20 - 29	30 - 39	40 - 49	50 - 59	60 - 69	70 - 79	80 -
■ Mild symtomps (0-7)	1445	2334	1409	897	201	48	4
■ Moderate symptoms (8-19)	102	217	194	245	120	32	4
■ Severe symptopms (20-35)	2	13	7	27	28	8	0
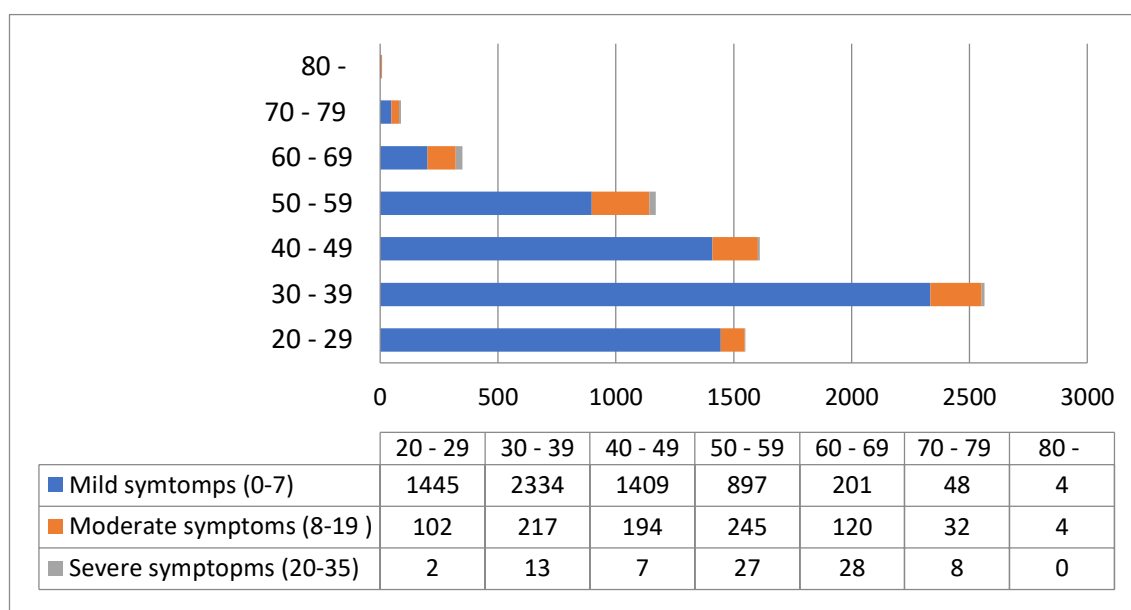
13.6% of the participants reported moderate or severe symptoms (I-PSS=8–35).

Surprisingly, there were some participants who were in age group 20-29 but still got an I-PSS score that relates to moderate or severe symptoms (2 men had a score for severe and 102 men had a score for moderate symptoms). Most of the participants reporting moderate symptoms belonged to age group 50-59 (245 men), whereas most of the participants reporting severe symptoms were from age group 50-69 (total of 55 men).

Table 16 Questions of the I-PSS survey relating to storage symptoms

Frequency
Question 2 - During the last month how often **How often have you had to urinate less than every two hours?**
Urgency
Question 4 - During the last month how often **have you found itdifficult to postpone urination?**
Nocturia
Question 7 - How many times did you have to wake up during a night to urinate?

We have further investigated the received I-PSS surveys and checked the ratio of the "rather voiding" and "rather storage" questions in each age group. Table 16 and 17 shows the voiding and storage symptom related quesions from the I-PSS survey.

Table 17 Questions from the I-PSS survey relating to voiding symptoms

Incomplete emptying
Question 1 – During the last month **How often have you had the sensation of not emptying your bladder?**
Intermittency
Question 3 – During the last month **How often have you found you stopped and started again several times when you urinated?**
Weak stream
Question 5 – During the last month **How often have you had a weak urinary stream**
Straining
Question 6 - During the last month **How often have you had to strain to start urination?**

Figure 19 shows the results of our studies relating to the distribution of symptoms

Figure 19. Distribution of patients showing "rather voiding" and "rather storage" symptoms by age groups based on the I-PSS survey.

	20 - 29	30 - 39	40 - 49	50 - 59	60 - 69	70 - 79	80 -
■ Rather storage	1172	1892	1106	800	234	65	6
■ Rather voiding	232	421	339	267	92	15	1
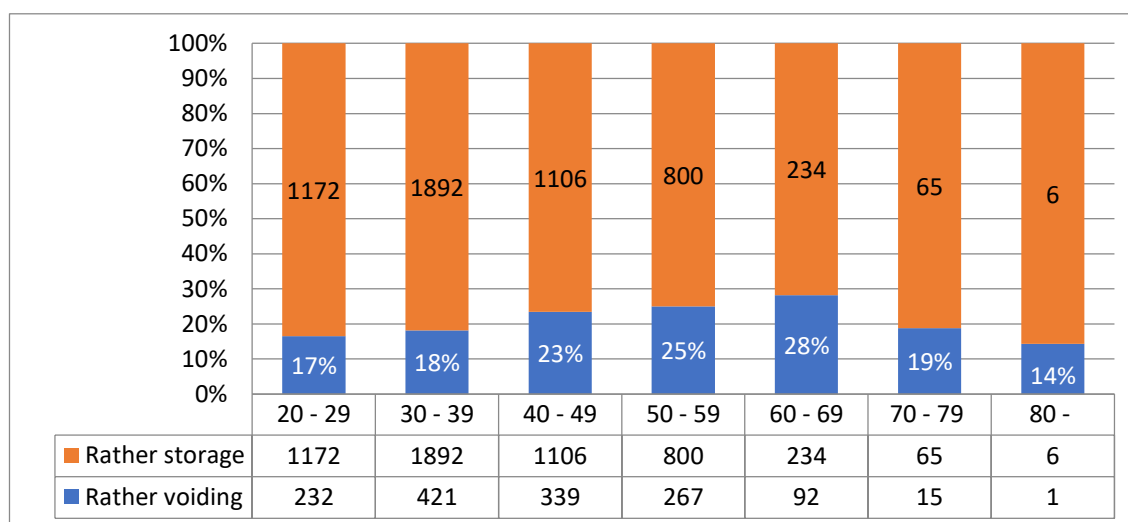
With the help of statistical methods we have been able to differentiate whether the applicant has rather voiding or storage related symptoms in 6642 cases. In case of 5275 patients we have found that their symptoms mainly relate to a voiding issue, and the number of patients with a storage issue is 1367. In the remaining 695 cases there was no significant difference between the nature of the complaints.

6.3.2.2 Discussion

More surveys have been conducted worldwide within the adult male population in order to get a better knowledge on the epidemiologic background of BPH and the patients'

urinary symptoms. A part of these studies used the I-PSS or the American Urological Association Symptom Index (AUASI) surveys. (Guess, 2005) The number, age, examined parameters and the involvement criteria have been different, so comparing results should be sone with great care.

Table 18 shows the number and age of the international participants. These studies proved that mild urinary complaints are very common amongst men over 50. (Guess, 2005)

Table 18 Number and age of the international participants

Name of study	Number of participants	Age of participants	I-PSS	Other surveys studying symptoms and quality of life	Other examined parameters
French National Survey	12 525	50-80 years	yes	no	any previous prostate-related surgery or knowledge about BPH diagnosis
	2011	50-80 years	no	yes	AUASI
Copenhagen, Denmark study	200	above 50 years	no	yes	urinary flow rate
Olmsted County study	2115	40-79 years	no	yes	size of prostate - urinary complaints
Shimamaki-mura, Japan study	274	40-79 years	no	yes	size of prostate - PSA - urinary complaints
Washtenaw County Study	802	above 60 years	no	yes	prostate surgery in medical history

Source: (Guess, 2005, Sexton et al., 2009)

Sexton et al. had the following results based on an Internet survey where the data of 14 139 male participants has been processed (Sexton et al., 2009):

- 29% of the participants have no lower urinary tract symptoms

- the number of purely voiding or storage issues ranged between 9-13%

- every other men with a complaint reported both types of symptoms

Our own results show that a smaller proportion of the participants reported "rather voiding" symptoms in all the age groups. This ratio ranges between 14-28%. The distribution of "rather voiding" and "rather storage" related complaint is 38% vs 60% in favour of "rather storage" amongst patients with moderate and severe symptoms. However, the study conducted by Sexton et al. used a different type of survey in order to measure the symptoms, which means the results of the two studies cannot be compared and no comparison should be made with other studies as well. (Sexton et al., 2009) The I-PSS score of the participants increases with age. The average score was 8.28 with patients above 60, which translates to moderate symptoms/complaints and may require medication or surgical therapy depending on the nature of the symptoms. (Péntek&Gulácsi, 2011) One of the deficiencies of this study is that the surveys do not provide any data on BMI scores, medical history, medications, any treatments that relate to prostate or bladder, surgeries and other important factors. (Péntek&Gulácsi, 2011)

As there was no similar survey conducted in Hungary amongst men with such a high number of cases, there were no publications and results meaning the importance of this study is high. The I-PSS score is an essential part of the risk analysis and treatment planning of BPH patients. (Braun et al., 2003) Which also makes this study more important is that the end results of the I-PSS survey are implemented in the health booklet which contains all the results of the other screening examinations with which the patients can contact their GP or urologist to get further examinations or therapy advice. With the early diagnosis and treatment planning of prostate disorders, the disease progression, the physical burden of the patient and the economic burden of society can be greatly decreased.

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6.4 Health economic evaluation of the treatment of overactive bladder syndrome

6.4.1 Results

6.4.1.1 Cost-effectiveness

During the cost-effectiveness analysis, we have compared each active agent to find out which would be the first one picked to apply. The quality adjusted life years (QALY) are different for each active agent. The lowest score within a three-month interval belongs to oxybutynin: 0.17283 QALY. The score is somewhat higher in case of darifenacin: 0.17379 QALY. The highest score belongs to solifencin: 0.17486 QALY. We have studied the changes of the incremental cost effectiveness rate in the cost factors comparing solifenacin to the two other active agents in three different cases. It can be seen in Table 19 that the highest incremental cost effectiveness rate was estimated when only the medication costs were involved in the calculation. The reason behind it is that the amount of further expenses (diapers, accompanying diseases) is lower due to the more effective therapy, as less diapers are needed and the frequency of accompanying diseases is lower as well. As the amount of other expenses is more favourable in case of an effective therapy, the incremental costs are decreasing considering a higher number of cost factors. Therefore the incremental cost-effectiveness rate is also decreasing. Our estimated expenses are most likely higher than the actual expenses in case of each therapy, thus it can be assumed that the cost effectiveness values would improve if the estimation would be more precise.

Table 19 Results of the cost-effectiveness analysis, costs of one continent patient

Treatment	Costs (HUF)	Incremental costs (HUF)	Ratio of continent patients (%)	Difference of continent ratios (%)	Costs/ continent patients (HUF)	Incremen-tal costs of one continent patient (HUF)
1) only medication costs						
Oxybutynin	5738		16.32		35,150	
Solifenacin	31,136	25,398	47.08	30.76	66,132	**82,575**
Darifenacin	28,997		19.53		148,441	
Solifenacin	31,136	2139	47.08	27.55	66,132	**7765**
2) without the costs of accompanying diseases						
Oxybutynin	16,468		16.32		100,885	
Solifenacin	39,004	22,535	47.08	30.76	82,844	**73,269**
Darifenacin	38,651		19.53		197,865	
Solifenacin	39,004	352	47.08	27.55	82,844	**1280**
3) all cost factors included						
Oxybutynin	19,687		16.32		120,602	
Solifenacin	41,749	22,062	47.08	30.76	88,674	**71,729**
Darifenacin	41,674		19.53		213,334	
Solifenacin	41,749	76	47.08	27.55	88,674	**275**

6.4.1.2 Cost-effetiveness

The number of patients turning continent during therapy is highest in case of solifenacin, 47%. This value is 20% in case of darifenacin and 16% with oxybutynin. We have summarized the results of the cost-effectiveness analysis in Table 19. In case we only consider medication costs, the extra expenses for a continent patient during a three-month interval is 82,575 HUF compared to oxybutynin and 7765 HUF compared to darifenacin. This value shows a decreasing trend if we take other expenses into consideration, as it happened with the ICER rate as well. In case we do not calculate with the costs of the accompanying diseases, the additional costs of treating the continent patients is 71,729 HUF compared with oxybutynin and 275 HUF compared with darifenacin, and if we consider all the cost factors, the differences decrease further.

The horizontal axis of the adoption curve shows the marginal propensity while the vertical axis shows the so-called efficiency ratio. This shows that the incremental cost-effectiveness rate of solifenacin compared to darifenacin and oxybutynin is lower than the marginal propensity in a certain percentage of all the cases (Figure 19). Based on the adoption curve, we can state that the ICER rate of solifenacin compared to oxybutynin goes below the threshold more often than the ICER rate of darifenacin compared to oxybutynin. Therefore, with the increase of marginal propensity per 1 QALY, the solifenacin is much more acceptable than darifenacin. As shown in the figure, we can see the rate of the costs per one continent patient is lower than the marginal propensity shown on the horizontal axis based on the probability of choosing one of the therapies. As seen in Figure 19, initially choosing the oxybutynin therapy was at a 100% rate compared to the other two active agents. However, roughly above a 80,000 HUF threshold, the adoption rate of solifenacin changes to 100% as opposed to the other two types of therapy. In this case, considering the uncertain factors, the incremental costs per continent patient are below the threshold in 100% and in the case of solifenacin patients turn to continent with a better rate, the efficiency is higher.

Figure 20. Adoption curve

Adoption curve

Marginal propensity
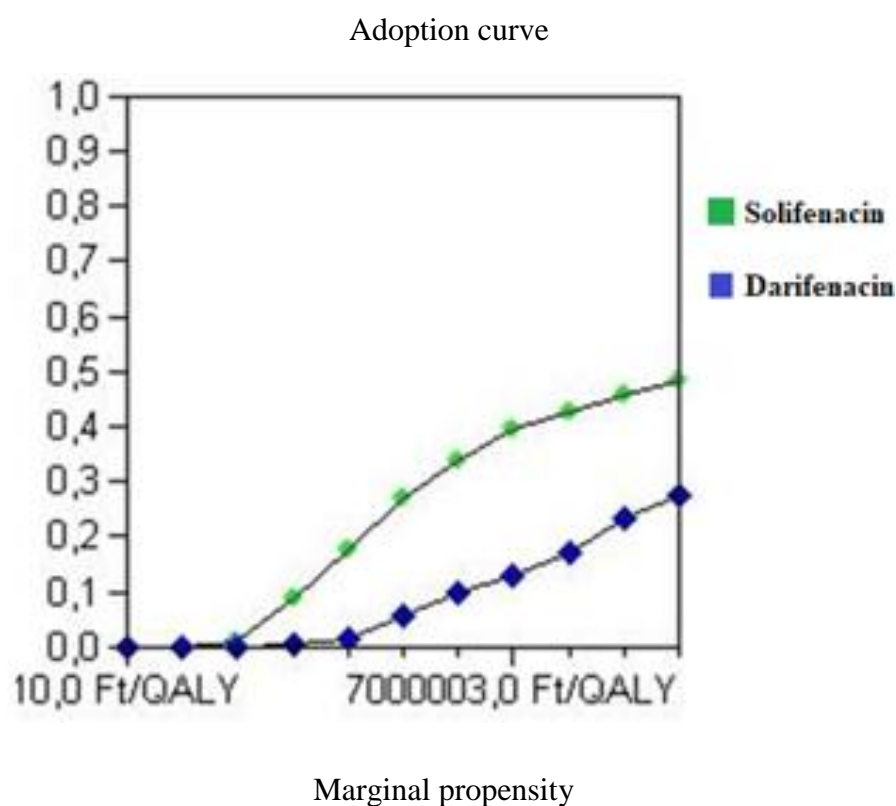
6.4.1.3 Discussion

We have studied the cost effectiveness and cost-effectiveness of solifenacin, oxybutynin and darifenacin therapies with a decision making tree. The quality-adjusted life years are very similar for all of these active agents. The total costs during a three-month interval, is different for each type of therapy based on the distribution of medication costs and other costs. The lowest of the total costs is for oxybutynin (19,687 HUF), but the medication costs constitute only the 29%. The same rate for darifenacin and solifenacin is significantly higher, more than 70%. The related costs of darifenacin and solifenacin

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therapy are almost the same (41,674 HUF, 41,749 HUF). However, the highest QALY of the three therapies belongs to solifenacin (0.17486 QALY). Even though there are some cost-effectiveness studies available for these active agents, those cannot be directly compared to our results due to the different utility measurements used. A similar study conducted by Ko et al. also came to the conclusion that solifenacin is the most effective therapy albeit with the highest costs (Ko et al., 2006).

We have used multiple simplifications in our model. The costs are probably an underestimation of the actual costs, as we have not included the costs of depression that usually accompanies this disease for instance. Our situation was also made more difficult by the limited number of studies relating to other accompanying diseases and the utility of treatments.

7. ANSWERS GIVEN TO THE HYPOTHESES

The followings answers can be given to the hypotheses suggested in this study.

7.1 Studying the costs and social burden of benign prostatic hyperplasia

Hypothesis 1 Benign prostatic hyperplasia significantly lowers quality of life

I accept the hypothesis.

With the increase of the IPSS score (obstructive symptoms) the quality of life significantly declines. 30% of the patients reported problems in the EQ-5D pain/malaise and 28% in the anxiety/depression dimension. The most irritating symptoms are urinary urgency (35%) and nocturia (26%). Therefore the treated patients (with an ongoing disease for 6.5 years) are also not asymptomatic.

We have only found significant difference ($p<0.05$) between BPH patients and the age and gender-matched general population in the 45-49 and 55-59 age groups. Based on our results, the effects of BPH below the age of 50 on the quality of life should be treated with special attention.

Despite the above I accept the hypothesis because there may be methodological reasons behind the not-so significant difference of quality of life in some age groups. Below the age of 45 the number of patients is low, while above 60, where patient numbers are high, the case numbers of the EQ-5D standard are still low. Due to that, the results of the comparison are less likely to be valid within these age groups. It also has to be mentioned that we have involved BPH patients in the study who receive medication treatment, and

those who received appropriate treatment do not have any worse quality of life than the age and gender-matched general population. These are methodological questions that require further research.

Hypothesis 2 The direct medical costs are increasing with age and the severity of illness. Due to the postponement of retirement age, the active age group is increasingly involved; the costs resulting from their productivity decrease are significant.

I accept the hypothesis.

The average costs for mild, moderate and severe cases were €203 (SD=€141)[33], €754 (SD=€1118)[34] and €2168 (SD=€2850)[35] respectively. The differences are significant. An important connection has been found between the healthcare costs and the severity of the disease. That means that with the progression of BPH the costs also rise accordingly, while age correlated directly with the non-healthcare related costs (informal treatment and travel costs). The indirect costs coming from the productivity decrease of patients from the active age group is significant. The indirect costs are €204[36] and within that the rate of costs caused by absenteeism and presenteeism is 41% compared to 59%. The indirect costs will also increase according to the changes in retirement age. Based on that, a confirming answer can be given to the hypothesis in the future as well.

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[33] 63,000 HUF, (SD 44,000)
[34] 233,000 HUF (SD 345,000)
[35] 669,000 HUF (SD 880,000)
[36] 63,000 HUF

7.2 Costs of bladder cancer in Hungary

Hypothesis 3 Changes in the social security support of drugs significantly influence treatment practices and together they influence healthcare expenditures.

I accept the hypothesis.

Analysing the medication turnover data proved a significant, more than 100 million HUF, rise in medication expenses within a one-year period (2007-2008) for treating urinary bladder cancer in Hungary. Our detailed analysis has shown a significant decrease of expenses of similar magnitude (112 million HUF) and the complete reconstruction of medication therapy for the three main medications between 2008 and 2014. Withdrawals, restrictions and changes in social security funding are all behind this phenomenon. Such a big change in treatment practice cannot be completely explained with clinical reasons. Therefore, further investigations are recommended to explore the reasons and consequences of the changes in product turnover. The changes in social security funding may make the therapy cheaper or more expensive, it may also cause changes with the distributors, and these together significantly affect healthcare expenses of the service providers and treatment practices.

7.3 Epidemiology of male and female urinary incontinence and lower urinary tract symptoms in Hungary

Hypothesis 4 This disease is more common in women and its prevalence increases with age.

Based on our study, we accept this hypothesis. This disease is more common in women and its prevalence increases with age. Nearly third of the women (33,9%) reported that

they have experienced urine leakage, an incontinent episode. More than third of the women (41%) reported urinary urgency.

Results of our study show that patients reporting moderate symptoms belong to the 50-59 age group, those who reported severe symptoms belong to the 50-69 age group.

Hypothesis 5 The number of "hidden" cases is significant in both genders, especially in the younger age group.

I accept the hypothesis. Our research has shown a much higher prevalence than the statistical data. The patients probably feel ashamed of their symptoms and they do not turn to their doctors for help, though they reported these complaints via an anonymous survey.

7.4 Health economic evaluation of the treatment of overactive bladder syndrome

Hypothesis 6 The cost-effectiveness analysis of overactive bladder syndrome affecting people at working age (taken from a social perspective, also including indirect costs) and considering accompanying diseases significantly influence the results and thereby the health policy and funding decisions.

I accept the hypothesis. The results of the study demonstrate well that it may lead to different results if only the medication costs are considered, and if we consider the accompanying diseases and efficiency. The result greatly depends on the method, which may lead to significantly different funding decisions.

8. NEW SCIENTIFIC RESULTS IN THE DISSERTATION

8.1 Assessing social burden and costs of disease in patients with benign prostatic hyperplasia

This marks the first time when healthcare economic research results have been published about 'presenteeism' which belongs to indirect costs. (Kovács, 2015)[37] We have found that this cost factor exceeds the costs of "absenteeism" and assume that this cost will only increase with the increase of retirement age. This also marks the first time of publishing a disease expense analysis regarding BPH in the Central Eastern European region.

We were also the first in Hungary to conduct a study regarding the quality of life of BPH patients with the help of EQ-5D survey, of which the QALY can be calculated.[38]

8.2 Costs of bladder cancer in Hungary

This marks the first time in Hungary and in the region, that someone analyzed and published the medication costs and changes of therapeutic methods of urinary bladder cancer during a long interval (7 years). [39]

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[37] Rencz F, Kovács Á, Brodszky V, Gulácsi L, Németh Z, Nagy GJ, Nagy J, Buzogány I, Böszörményi-Nagy G, Majoros A, Nyirády P (2015): Cost of illness of medically treated benign prostatic hyperplasia in Hungary. International Urology and Nephrology, 47, 8, 1241-1249. doi: 10.1007/s11255-015-1028-7.

[38] Kovács Ágnes : The quality of life of BPH patients treated with medications in Hungary; cross-section survey in six urology centres, Urology Journal, submitted for publication

[39] Kovács Á, Hevér N (2016): A húgyhólyag daganatos betegek költsége Magyarországon. Köz-Gazdaság, XI, 3, 303-317

8.3 Epidemiology of male and female urinary incontinence and lower urinary tract symptoms in Hungary

We have studied and analyzed the epidemiology of male and female incontinence and lower urinary tract symptoms with involving the highest number of surveys in Hungary. (Kovács Á et al., 2012, Kovács Á et al., 2013, Majoros et al., 2014, Sipos et al., 2015)

8.4 Health economic evaluation of the treatment of overactive bladder syndrome

This marks the first time of studying the cost-effectiveness of the therapy of overactive bladder syndrome in the Central Eastern European region. (Brodszky et al., 2008)

9. SUMMARY

Our health economic research is the first, which provides information about the personal and social burdens of chronic urologic disorders in Hungary; moreover we have reported some results for the first time in the international dimension.

Based on a systematic review and analysis of the international literature on benign prostatic hyperplasia (BPH), it can be concluded that the disease burden is significant, but the data related to the costs associated with the disease originated mainly from Western European countries and the United States. Such survey in the Central Eastern European region has been conducted only in Poland in the course of a multicenter study. From the methodological point of view it is important to note that the majority of the studies include only the direct medical costs, and disregard the burden resulting from the reduced working capacity of the patients, thus they give only an incomplete picture of the social costs related to the disease.

We evaluated Hungarian patients with benign prostatic hyperplasia, taking into account the results of our review of international publications. Our evaluation included the patients' health-related quality of life, usage of health care services, capacity to work, and the disease costs. According to the results of the multicenter questionnaire, the costs related to BPH are €876/patient/year in Hungary, 23% of which arises as a result of reduced working capacity. A strong correlation exists between the costs and the I-PSS score (an index of the severity of the disease).

As far as we know, we have been internationally the first to evaluate and analyse the decrease of productivity of patients continuing to work, and we have found that this is the largest indirect cost item.

BPH is a major public health problem related to the ageing society. As the disease is dependent on age, the number of BPH patients is expected to increase significantly. There

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is an increasing number of available, but expensive therapies that, patients may need for years or decades, thus the costs are significant and on the rise. In Hungary, there are no previous data on health policy and financing decisions.

Our result on quality of life that can be used for calculating quality-adjusted life year (QALY) required for cost-effectiveness analyses, as well as our data on disease costs can serve as essential country-specific input data for health economic analyses.

Based on health insurance data, we analysed the costs of medicinal products used for treating the malignant bladder cancer out of the malignant urological diseases in Hungarian. There was a significant increase in medication in Hungary between 2008 and 2014, however the total outflow of Social Security decreased, partly due to the withdrawal of certain medications from the market, shortage of stocks, and shift to the use of cheaper products. The main specific pharmaceutical spending on malignant bladder cancer was HUF 234.5 M in 2008, HUF 136.2 M in 2013, and it dropped further in 2014. On the one hand, these data demonstrate the social burden of the disease and, on the other hand, it is a good example of cost changes resulting from the dynamics of access to medicines and changes in financing techniques. This disease is also related to the ageing of the population, therefore costs are expected to increase in the near and distant future.

Diseases related to urinary retention (i.e. incontinence) are significant also at the social and personal level, however, the prevalence is little known in many cases because in the course of a routine doctor-patient meeting does not come to light. During our research, urine incontinence was surveyed in men and in women on a large number of samples. Based on our results it can be noted that this symptom affects middle-aged (older than 35 years) women in large numbers - in mild or in severe degree, intermittently or regularly. Most of the women are disturbed by urine leakage, and also a lot of them (especially women of working age) are being restricted in their daily routine. It also needs to be highlighted that according to our results young male patients (20-29 years) have moderate severe/severe symptoms as well. Although our research was not representative and is

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based on the information provided voluntarily by the responders, we consider it to be of outstanding importance, because it throws light on a concealed but serious disease which is a huge problem for the individuals and represents a public health problem for the society. We believe, our results might be a precious base point for further researches, which helps to identify patients suffering from incontinence and to reveal the disease's effects on the quality of life, the possibilities and limits of access to therapies, and to improve the healthcare. As in the case of the above mentioned two diseases, the prevalence of urinary incontinence is increasing with the aging population. The disease related costs have been already significant and expected to increase rapidly in the next years.

In the course of the health economic analysis, we evaluated the cost-benefit and cost-effectiveness of three types of medical therapy in a specific incontinence subgroup, the overactive bladder syndrome (OAB) disease. The analysis provides relevant and important information to the decision-maker about the Social Security financing of medicines. I think, it is also an important methodological issue, that the arising uncertainty of the results was the lack of the appropriate input data. This research also highlights the importance of high quality, country-specific (if possible) data collection, including epidemiology of the diseases, effects on the quality of life and cost. It also highlights the importance of performing an analysis of the transferability of international data if the above mentioned data are missing. This disease affects the elderly as well as the young employees, and the negative effect of the disease on the quality of life is significant. As this disorder is chronic, patients might need medical therapy for decades. The disease related costs are significant nowadays, and the tendency is rapidly growing.

Pharmaceutical, health policy and financial consequences of the research.

In Hungary, like in other European countries, in case of health services financed by the Social Security or public finance, funding decision depends on the financial impact and cost-effectiveness of the service (e.g. medicine) in question. This obligation has been laid down by law in all countries.

There are other important aspects, e.g. access, equity, ethical considerations, but these aspects were not part of the research presented in this dissertation.

The budget impact depends on the potential number of patients (epidemiology) receiving the health service (e.g. drug therapy), the unit cost of the health service, and the quantity of the health service have been used. Accordingly, data resulted from the researches related to epidemiology and costs are essential in preparing decisions.

In cost-effectiveness studies, health economics research deals with the clinical efficacy of health services (such as medicines) and the measurable efficiency in reality of the services. To analyse cost-effectiveness (or cost-utility), we have to examine the patient's quality of life, impaired quality of life due to the disease and quality of life improvements due to the therapy. The latter is compared to the costs in order to assess the cost-effectiveness of the therapies.

In all European (and other) countries, the legislation on health financing includes that the budget effect and the cost-effectiveness of the different diseases and therapies should be comparable in each sector.

This means that we need to have such economic information with respect to many (in good case several) diseases, because ranking is part of the financial decision making. In the course of ranking, many factors are taken into account, for example the social burden of the disease, epidemiology, the budget impact, and cost-effectiveness.

This explains that in this dissertation several disease field were analysed by health economic aspect, such as benign prostatic hyperplasia, bladder cancer, female and male urinary incontinence, lower urinary tract symptoms and overactive bladder syndrome - which all belong to chronic urological diseases. The results of our research cover a wild range of chronic urological diseases, so they are suitable for use in health policy and financing decision-making.

Our results are essential for planning of medical care and financing in the case of such diseases, which affect a significant part of the population and result in personal and social burden.

The results of this research are useful and can be well utilized in the everyday medical practice, as well as in the preparatory analyses of health policy and financial decision-making, thus the evaluation may help to improve the medical care of patients suffering from chronic urological disease, it may reduce the social burdens and improve the patients' life expectancy and quality of life, while it enables to evolve a social insurance with sustainable financing.

We would like to contribute in this with our research.

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12. ANNEXES

ANNEX 1.

Ha az adott terület pontszáma
= 0-7 nincs probléma   ZÖLD SZÍN (szűrő kamion kiskönyvbe kerül)
= 8-18 enyhe tünetek   SÁRGA SZÍN (szűrő kamion kiskönyvbe kerül)
= 19-30 súlyos tünetek   PIROS SZÍN (szűrőkamion kiskönyvbe kerül)
FÉRFI VIZELÉSI ZAVAR KÉRDŐÍV
Nemzetközi Prosztata tünetértékelő lap (I-PSS)

Kora:…………….év

Az elmúlt egy hónap során	Soha	Nagyon ritkán	Az esetek kevesebb, mint felében	Az esetek felében	Az esetek több, mint felében	Csaknem mindig
1) Hányszor érezte úgy, hogy nem sikerült teljesen kiürítenie a hólyagját?	**0**	**1**	**2**	**3**	**4**	**5**
2) Milyen gyakran fordul elő, hogy vizelés után 2 órán belül ismét vizelnie kell?	**0**	**1**	**2**	**3**	**4**	**5**
3) Milyen gyakran fordul elő, hogy vizelés közben vizelete többször elakadt, majd újraindult?	**0**	**1**	**2**	**3**	**4**	**5**
4) Milyen gyakran érezte, hogy nem tudja tovább visszatartani a vizeletét?	**0**	**1**	**2**	**3**	**4**	**5**
5) Milyen gyakran észlelt gyenge vizeletsugarat vizelés közben?	**0**	**1**	**2**	**3**	**4**	~~**5**~~
6) Milyen gyakran fordult elő, hogy préseléssel vagy nyomással kellett elindítania a vizelést?	**0**	**1**	**2**	**3**	**4**	**5**

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	Egyszer sem	Egyszer	Kétszer	Három-szor	Négyszer	Legalább ötször
7) Éjszakánként hányszor kellett felkelnie vizelni?	0	1	2	3	4	5

Összesített I-PSS pontszám	

	Boldo-gan	Öröm-mel	Általá-ban elégedet ten	Vegyes érze-lemmel	Inkább csaló-dottan	Boldog-talan lennék	Borzasz tónak találná m
8) Hogyan fogadná, ha élete hátralevő szakaszában vizeletürítési képessége a jelenleginek megfelelő maradna?	0	1	2	3	4	5	6

International Prostate Symptom Score (I-PSS)

Patient Name: _____ Date of birth: _____ Date completed _____

In the past month:	Not at All	Less than 1 in 5 Times	Less than Half the Time	About Half the Time	More than Half the Time	Almost Always	Your score
1. Incomplete Emptying How often have you had the sensation of not emptying your bladder?	0	1	2	3	4	5	
2. Frequency How often have you had to urinate less than every two hours?	0	1	2	3	4	5	
3. Intermittency How often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5	
4. Urgency How often have you found it difficult to postpone urination?	0	1	2	3	4	5	
5. Weak Stream How often have you had a weak urinary stream?	0	1	2	3	4	5	
6. Straining How often have you had to strain to start urination?	0	1	2	3	4	5	
	None	**1 Time**	**2 Times**	**3 Times**	**4 Times**	**5 Times**	
7. Nocturia How many times did you typically get up at night to urinate?	0	1	2	3	4	5	
Total I-PSS Score							

Score: 1-7: *Mild*   8-19: *Moderate*   20-35: *Severe*

Quality of Life Due to Urinary Symptoms	Delighted	Pleased	Mostly Satisfied	Mixed	Mostly Dissatisfied	Unhappy	Terrible
If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?	0	1	2	3	4	5	6

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ANNEX 2.

Patient Perception of Bladder Condition Questionnaire[40]

Which of the following statements describes your bladder condition best at the moment?
(Please mark ''X'' in one box only.)

☐   My bladder condition does not cause me **any problems** at all.

☐   My bladder condition causes me some **very minor problems**.

☐   My bladder condition causes me some **minor** problems.

☐   My bladder condition causes me (some) **moderate** problems.

☐   My bladder condition causes me **severe** problems.

☐   My bladder condition causes me **many severe** problems.

.

Severity of urgency scale for patients with symptomatic overactive bladder [41]

Please mark the urinary urgency on a scale of 0-4.

0. **No urgency**, I felt no need to empty my bladder, but did so for other reasons.

1. **Mild urgency**, I could postpone voiding as long as necessary, without fear of wetting myself.

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[40] Patient Perception of Bladder Condition (PPBC)

[41] Severity of urgency scale for patients with symptomatic overactive bladder (PPIUS)

2. **<u>Moderate urgency</u>**, I could postpone voiding for a short while, without fear of wetting myself.

3. **<u>Severe urgency</u>**, I could not postpone voiding, but had to rush to the toilet in order not to wet myself.

4. **<u>Urge incontinence</u>**, I leaked before arriving to the toilet.

ANNEX 3.

FEMALE INCONTINENCE QUESTIONNAIRE

Age: years

1. Have you ever experienced urine leakage (incontinence)? 4 ? Yes 0 ? No

2. How often does it happen that you cannot hold your urine? 0 ? Rarely (e.g. during cold)   2 ? more times a day   5 ?always

3. How much are you bothered by involuntary urine leakage?

   0 ? not bothered 1 ? sometimes 3 ? very much bothered 5 ? I am restricted in my daily routine

4.   When you urinate, can you stop your stream of urine? 0 ? yes 2 ? no 1 ? I have not tried yet

5.   When do you experience urine leakage? During:
   1 ? coughing, sneezing   1 ? laughing   1 ? jolt (stairs, jumping)   1 ? running, exercising 1 ? standing   1 ? getting up (from bed)   1 ? sex   1 ? sitting, lying   1 ? in case of strong urinary urgency

6.   How much urine you think leaks?

   1 ? few drops 3 ? flowing 5 ? large amount

   Accumulated stress incontinence score

7.   Do you experience burning sensation while urinate?
   3 ? Yes 0 ? No

8.   How often do you urinate during the day?

   0 ? less than 4-5 times 2 ? 6-8 times   5 ? more than 10 times

9.   Overall how much does frequent, urgent urinary urgency interfere with your life? 0 ? Does not 1 ? sometimes 3 ? I am bothered very much 5 ? I am restricted in every way

10.   Do you have an urge to go to the toilet immediately after the urinary urgency or can you wait for it? 0 ? I can wait   5 ? I need to go immediately

11.   Did you experience urine leakage after feeling urinary urgency before reaching the toilet?

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0 ? no   2 ? rarely 4 ? regularly

12.   Do you wake up during the night due to urinary urgency? 0 ? no 2 ? once, rarely 4 ? several times

13.   Do you experience urine leakage at night while sleeping? 0 ? no 2 ? sometimes 4 ? regularly

Accumulated urge incontinence score

Total score

ANNEX 4.

Types of incontinence

These are the conventional types of incontinence.

- Urge incontinence

- Stress incontinence

- Mixed incontinence

- Reflex incontinence

- Overflow incontinence

Urge incontinence is urine leakage related to imperative urge to urinate due to uncontrollable, involuntary bladder muscle contraction in the motor form (overactive bladder). Involuntary muscle contraction could be a result of a neurogenic disease (e.g. elderly uninhibited neurogenic bladder), or lower urinary tract obstruction as well as idiopathy. In case of sensory form, imperative urge to urinate associated with urine leakage doesn't linked to detectable bladder muscle contraction. Cause: disease of the bladder (stone, inflammation, tumour) or psychovegetative factors.

Stress incontinence: involuntary urine leakage due to physical (not mental) activity (coughing, sneezing, lifting, climbing stairs, etc.). The bladder pressure increases due to the physical activity and exceeds the pressure of the sphincter, so the patient has urine leakage without any urge to urinate and involuntary bladder contraction.

Mixed incontinence: A combination of the two above mentioned incontinence types.

Reflex incontinence: It causes by abnormal functioning of the spinal reflex circuit or confusion of the reflex circuit's conscious brain control. In case of reflex incontinence it is essential, that the patient does not feel the stimulus for the urinary flow (complete injury) or does not able to suppress the urge to urinate, so the involuntary bladder contraction (incomplete injury). Thus, the lack of the sensation of the urge to urinate or the inability of suppressing the urge to urinate which differentiate this incontinence type from the motor urge incontinence.

Overflow incontinence: Involuntary urine leakage with full bladder. Cause: obstacle of urine outflow (obstructive form) or weak or tired bladder muscle (functional form).